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Biennial Report of the Director

# National Institutes of Health

FISCAL YEARS

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**Biennial Report of the Director,  
National Institutes of Health**

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**Fiscal Years 2006 & 2007**



## PREFACE

When Congress passed and the President subsequently signed into law the National Institutes of Health (NIH) Reform Act of 2006, it was only the third NIH omnibus reauthorization in NIH's history and it signaled renewed confidence in the NIH mission, its employees, and its leadership. NIH hopes that the information in this report—the first submitted under the new requirement established by Section 104 of the NIH Reform Act (Pub. L. No. 109-482)—justifies that confidence.

By amending Section 403 of the Public Health Service Act—to require the Director of NIH to submit, on a biennial basis, a report to Congress—Congress revived, but reinvented, a prior NIH reporting mandate. Instead of an Institute- and Center-based report, like those NIH traditionally generated, Congress required the new biennial report to provide an integrated portrait of NIH research activities.

The report represents the work of many NIH staff members, who collaborated in trans-NIH teams, to capture the remarkable array of important NIH research activities presented herein. As this is the first report submitted under the new requirement—Attachment A provides the language in Pub. L. No. 109-482 relevant to the NIH Director's Biennial Report—NIH welcomes feedback from Congress not only on the activities conveyed in this report, but also on the nature of the report and those aspects that improve NIH transparency and accountability as well as those that could be handled better in the next biennial report.

### Chapter Organization

*Chapter 1* opens with a statement from the Director, NIH, providing an assessment of the state of biomedical and behavioral research. It then provides a description of NIH policies and procedures focusing on the operations of the extramural and intramural research programs, mechanisms for strategic planning (including recommendations for the next set of Roadmap initiatives), and various cross-cutting activities not covered in the chapters that follow.

*Chapter 2* addresses NIH research activities from the perspective of diseases, disorders, and adverse health conditions. The topics covered include:

- Cancer
- Neuroscience and Disorders of the Nervous System
- Infectious Diseases and Biodefense
- Autoimmune Diseases
- Chronic Diseases and Organ Systems
- Life Stages, Human Development, and Rehabilitation
- Minority Health and Health Disparities.

These topics, all categories specified in NIH Reform Act of 2006 (see Appendix A), are grouped together in one chapter to address the intent of the statute, in terms of presenting information on diseases, disorders, and adverse health conditions in a standardized format. Each topic is addressed in a separate section. The material in each section is organized as follows:



A brief introduction describes and defines the field or approach and indicates the scope of NIH research activity, provides data on disease burden and related health statistics, and, when available, presents aggregate data on NIH funding for research on the disease or condition.

This introduction is followed by a summary of NIH activity that reflects the breadth and depth of the research and related efforts of Institutes and Centers (ICs) whose missions encompass these diseases and conditions.

The summary is followed by notable examples of research activities, such as key programs, initiatives, studies, and accomplishments. The notable examples provide snapshots and highlights of research and related activities and, in so doing, illustrate the depth and breadth of NIH efforts.

Following the notable examples is a list of strategic plans relevant to the disease/condition. These plans are listed by IC and office within the Office of the Director (OD), with plans most closely aligned to the topic listed first. Whenever possible, links are provided to Web sites where additional information is available. Many ICs and OD program offices have research plans and agenda that, while not specific enough to a topic to be listed in Chapter 2, nonetheless are worth noting because the plans they set forth crosscut and underpin NIH activities specific to diseases, disorders, and adverse health conditions. Such plans include those of the [National Institute of General Medical Sciences](#), [National Institute of Environmental Health Sciences](#), [National Human Genome Research Institute](#), [National Institute of Biomedical Imaging and Bioengineering](#), [National Center for Research Resources](#), [National Library of Medicine](#), [NIH Clinical Center](#), [Office of Behavioral and Social Sciences Research](#), and [Office of Research on Women's Health](#).

The chapter concludes with a table on NIH funding. The funding information is based on the standard table of NIH [Estimates of Funding by Various Diseases, Conditions, Research Areas](#), which presents information NIH routinely collects on agency-wide funding in areas of special interest.

**Chapter 3** addresses NIH research activities from the perspective of key research approaches and resources. The topics covered include:

*Fields and Approaches*

- Epidemiological and Longitudinal Studies
- Genomics
- Molecular Biology and Basic Sciences
- Clinical and Translational Research

*Tools and Training*

- Disease Registries, Databases, and Biomedical Information Systems
- Technology Development
- Research Training and Career Development

*Health Information and Communication*

- Health Communication and Information Campaigns and Clearinghouses

These topics are all categories specified in the NIH Reform Act (see Appendix A).

NIH research spans many disciplines and every stage of inquiry. Those addressed in this report are of particular interest, based on their citation in the statute. *Epidemiological and longitudinal studies* examine the causes, courses, and outcome of health and disease at the population level. *Genomic research* studies an organism's entire genome (the complete assembly of its genes) focusing on the genome as an interrelated network. *Molecular biology and the basic sciences* are providing insights into human health and disease at the most fundamental levels, providing information essential to understanding basic human biology and behavior in their normal and diseased states. Through investments in *clinical and translation research*, NIH is moving basic discoveries into effective treatments and disease preventives as well as uncovering knowledge gaps that require more basic inquiry.

Similarly, research enabling research activities such as *information systems, technology development*, and *training* provide efficient collection, storage, and accessing of critical biomedical and behavioral information; generate the tools, tests, devices, and methods that foster new fields of science and medicine; and prepare and hone the minds that propel discovery. All of these areas of endeavor extend the capacity of the national biomedical and behavioral research enterprise in critical ways.

Ensuring the uptake of the research results by clinical practitioners and the public is another important facet of NIH's mission. Targeted *health communication plans and information campaigns* that reach the public with science-based information are essential to improving people's health and saving lives.

The material on each of these topics is organized as follows:

A brief introduction describes and defines the disease or condition and indicates the scope of NIH research activity.

This introduction is followed by a summary of NIH activity that reflects the breadth and depth of the research and related efforts of ICs whose missions encompass the topic area.

The summary is followed by notable examples of research activities, such as significant programs, initiatives, studies, and accomplishments. The notable examples provide snapshots and highlights of research and related activities and, in so doing, illustrate the depth and breadth of NIH efforts. Whenever possible, links are provided to Web sites where additional information can be found.

The topic sections in Chapters 2 and 3 each provide an overview and highlights; they are representative rather than comprehensive.

In future editions of the Biennial Report, NIH will have the benefit of using the NIH Research, Conditions, and Disease Categorization (RCDC) system, an NIH-wide automated research categorization system currently in development. RCDC is intended to improve the consistency, transparency, and efficiency of NIH reporting on the areas of research captured in the table of

NIH [Estimates of Funding by Various Diseases, Conditions, Research Areas](#). This tool also will enable NIH to catalog research activities for the various areas. Some expansion of RCDC capacity beyond the areas for which NIH currently captures trans-NIH funding information is needed but will be possible.

**Chapter 4** addresses certain NIH Centers of Excellence. Overall, NIH Centers of Excellence are diverse in focus, scope, and origin. The NIH Centers of Excellence described in this report are a subset—those established by statutory mandate. The chapter provides overviews, outcomes (in the form of programmatic and research accomplishments), recommendations, evaluation plans, and future directions for the six congressionally mandated NIH Centers of Excellence programs, described in order of their establishment:

- Alzheimer’s Diseases Centers (1984)
- Claude D. Pepper Older Americans Independence Centers of Excellence (1989)
- Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (2001)
- National Center on Minority Health and Health Disparities Centers of Excellence (2001)
- Rare Diseases Clinical Research Network (2002)
- New Autism Centers of Excellence (2006) (which merged the previously existing Collaborative Programs of Excellence in Autism and Studies to Advance Autism Research and Treatment)

**The Appendices** present reference documents and supporting data. *Appendix A* provides a copy of the sections of the NIH Reform Act of 2006 (Pub. L. No. 109-482) that require this biennial report. *Appendix B* lists and briefly describes the missions of the NIH ICs and the program offices in the Office of the NIH Director. It also supplies links to IC and Office strategies plans. *Appendix C* supplies a copy of the Common Fund Strategic Planning Report, FY 2008. *Appendix D* consists of data on the primary NIH research training program, the National Research Service Award program, National Library of Medicine training programs, and graduate medical education. *Appendix E* excerpts all but the appendices of *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, in order to identify clinical research study populations by demographic variables. *Appendix F* excerpts sections of the *Report of the Advisory Committee on Research on Women’s Health*, in order to include, by reference, that biennial report, within this one, as required by Section 486(d)(5) and Section 403 of the Public Health Service Act, 42 U.S.C. 283, which predate the reporting requirement established by the NIH Reform Act of 2006.

# Contents

## 1. Introduction

Statement of the Director, NIH.....	1-9
NIH Overview.....	1-14
Extramural and Intramural Research Programs.....	1-16
Strategic Planning and Roadmap 1.5.....	1-19
Other Crosscutting Activities and Policies.....	1-23

## 2. Summary of Research Activities by Disease Categories

Cancer.....	2-1
Neuroscience and Disorders of the Nervous System.....	2-31
Infectious Diseases and Biodefense.....	2-73
Autoimmune Diseases.....	2-103
Chronic Diseases and Organ Systems.....	2-119
Life Stages, Human Development, and Rehabilitation.....	2-179
Minority Health and Health Disparities.....	2-213
Estimates of Funding.....	2-249

## 3. Summary of Research Activities by Key Approach and Resource

### Fields and Approaches

Epidemiological and Longitudinal Studies.....	3-1
Genomics.....	3-27
Molecular Biology and Basic Research.....	3-55
Clinical and Translational Research.....	3-89

### Tools and Training

Disease Registries, Databases, and Biomedical Information Systems.....	3-145
Technology Development.....	3-165
Research Training and Career Development.....	3-195

### Health Communication and Information

Health Communications and Information Campaigns and Clearinghouses.....	3-221
---	-------

## 4. Centers of Excellence

Introduction.....	4-1
Alzheimer's Disease Centers.....	4-3
Claude D. Pepper Older Americans Independence Centers.....	4-10
Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers.....	4-17
National Center on Minority Health and Health Disparities Centers of Excellence Program.....	4-24
Rare Diseases Clinical Research Network.....	4-32
Autism Centers of Excellence.....	4-36

**5. Appendices**

A. Pub. L. No. 109-482 (excerpts pertaining to NIH Director’s Biennial Report)..... A-1  
B. Priorities and Plans of the Institutes and Centers and the Program Offices in  
the Office of the Director.....B-1  
C. Common Fund Strategic Planning Report, FY 2008.....C-1  
D. Research Training and Graduate Medical Education Data..... D-1  
E. Monitoring Adherence to the NIH Policy on the Inclusion of Women  
and Minorities as Subjects in Clinical Research, (excerpt).. .....E-1  
F. Report of the Advisory Committee on Research on Women’s Health (excerpts)..... F-1

**Index**

# Chapter 1

## Introduction

### STATEMENT OF THE DIRECTOR, NIH

Reflection on the origins of NIH aptly frames assessment of the current state of biomedical and behavioral research. After World War I, scientists sought funding to establish an institute that would apply their rapidly growing knowledge of chemistry to the field of medicine. When no philanthropic money materialized, the visionary Senator from Louisiana, Joseph E. Ransdell, led Congress to pass a bill in 1930 that would transform the Nation's small Hygienic Laboratory into the "National Institute of Health" (singular). The change in title underscored a much more significant change—toward public support for medical research. This was a defining moment in the history of biomedical research and health care for our country and for the world. Years later, in 1945, the noted scientist and intellect Vannevar Bush recognized the importance of research to the Nation when he said that "*scientific progress is one essential key to our security as a Nation, to our better health, to more jobs, to a higher standard of living, and to our cultural progress.*"

#### ***Transformation! The payoff of the investment in NIH***

In the over 70 years since the Ransdell Act, NIH transformed modern research and medicine in countless ways—some well known, others so much a part of daily life that their scientific origin is forgotten. We made tremendous improvements in the recovery from heart disease and stroke. For patients with clogged arteries, NIH scientists developed a stent imbedded with the cancer drug Taxol®, which prevents scars from forming during its slow release. This revolutionary drug-device combination dramatically reduced artery reclosing rates to 3-6 percent and is expected to substantially reduce the number of open-heart bypass surgeries—previously the only alternative for some patients. What seems obvious today—for example, knowing about the importance of a healthy diet and the benefits of exercising—are the results of research studies pioneered by NIH. Pregnant women get the most detailed advice available about what foods to eat and what environmental exposures to avoid—again, the result of NIH research. In another example, prostheses known as cochlear implants now allow hearing-impaired children to hear and speak. Worldwide, nearly 100,000 individuals are fitted with cochlear implants, and, in the United States, roughly 22,000 adults and 15,000 children have them. NIH-supported scientists showed that profoundly deaf children who receive cochlear implants at an early age develop language skills at a rate comparable to children with normal hearing.

Our research breakthroughs extend to vision-impaired patients. Eight million older Americans are at high risk for advanced age-related macular degeneration (AMD), with 1.3 million developing AMD within 5 years if untreated. However, a large NIH-sponsored clinical trial established that a daily regimen of antioxidant vitamins and minerals delays the onset of advanced AMD by 25 percent. New drugs (Macugen and Lucentis) that block abnormal blood vessel growth, a hallmark of AMD, also are now available to stave off and, in some cases, reverse vision loss. We possess more effective drugs for treating diseases affecting bones and joints; for example, for patients with moderate to severe knee pain, injections of hyaluronic acid lubricate the damaged joint and may slow progression of disease. We developed new virus-like

particle technology that formed the basis for new commercial vaccines that target specific cancers. In June 2006, the U.S. Food and Drug Administration approved the vaccine Gardasil, which is highly effective in preventing infections with the human papillomavirus types that cause the majority of cervical cancers. Worldwide use of this vaccine could save the lives of 200,000 women each year. We funded research that led to the discovery and development of antiretroviral therapies to treat people with HIV infection. As of today, antiretroviral therapies are the most effective means of treating HIV infections, resulting in improved quality of life and life expectancy for those with access to these drugs. A recent study indicates that highly active antiretroviral therapy has saved approximately 3 million years of life in the United States alone.

An important public health success story is the reduction in tobacco use and related diseases. In the last decade, overall cancer death rates dropped for the first time in a century, driven largely by the dramatic reduction in male smoking from 47 percent in the 1960s to less than 23 percent today. This success has been a trans-HHS victory, with significant research investments over the last 50 years made by many Institutes and Centers.

These are just a few examples by which NIH research laid the foundation for modern medicine, generating enormously better health for the population worldwide. Partly as a result of research, the disability rate in our elderly population has declined by 30 percent since 1982.

NIH research also is a key driver for the private sector, as predicted by Vannevar Bush in 1945. As an example, between 1998 and 2004 alone, a total of 3,114 new technologies were brought to market by 185 universities, hospitals, and private research institutions. From 1980 to 2004, a total of 4,543 new companies were formed around technologies developed by research institutions, many of them directly funded by the NIH. NIH is, indeed, a tremendous asset for America.

### ***Imagine! Where are we going?***

We still have a long road in front of us. But thanks to a steady flow of basic research discoveries, NIH is well-positioned to find new treatments and prevention strategies for a host of our most debilitating diseases. These research breakthroughs of the future will more quickly feed into routine medical practice. The health care system itself will undergo a rapid change. It must, since the current trends—surging costs coupled with the rapid rise of chronic diseases such as obesity and diabetes, the increasing mental health needs in our modern society, the aging population, the emergence and reemergence of infectious diseases—are unsustainable. Science needs to tell us how to strike these diseases before they strike us.

Our goal at NIH is to provide the scientific evidence base that will usher in an era where medicine is ***predictive, personalized, preemptive, and participatory***. This will be a profound transformation from the current model of late-stage “curative” interventions, and one that this Nation must undergo in the coming decades if we are to succeed in providing access to care for all Americans at reasonable costs.

To reach this long-term goal, NIH is strategically investing in research to further our understanding of the fundamental causes of diseases at their earliest molecular stages so that we

can reliably *predict* how and when disease will develop and in whom. Because we now know that individuals respond differently to environmental conditions according to their genetic endowment and their own behavioral responses, we can envision the ability to precisely target treatment or other interventions on a *personalized* basis. Ultimately, this individualized approach will allow us to *preempt* disease before it occurs, utilizing the *participation* of individuals, communities, and health care providers as early as possible in, and throughout, the natural cycle of a disease process. The discoveries we are making today are paving the way to make this future a reality.

Consider how more predictive and personalized treatments could improve the safety and effectiveness of medications. We know that drugs are not in the “one size fits all” category. The same medication can help one patient and be ineffective for, or even toxic to, another. With the emergence of a field of research called pharmacogenetics, we will be increasingly able to know which patients will likely benefit from treatment and which patients will not.

### *What are the roadblocks en route?*

Major speed bumps confront NIH on the road to success. While we have made progress in discovering specific aspects of disease and generated numerous treatments that deliver desirable outcomes, large gaps remain in our fundamental understanding of health and disease. Disease and injury are constant threats to humankind. For example, military casualties suffering from blast injury pose an immediate challenge and highlight how the gaps in our knowledge on these and other traumatic brain injuries hinder medical researchers who are striving to optimize regenerative treatments. Infectious diseases remain among the leading causes of death worldwide. More than 30 newly recognized infectious diseases and syndromes emerged in the last two decades alone, including HIV/AIDS and SARS. Infectious diseases that once seemed to be fading, such as tuberculosis and malaria, have resurged, and the emergence of antibiotic-resistant bacteria is making many common infections increasingly difficult to treat. There is concern that a new influenza virus will emerge with the capacity for sustained human-to-human transmission. Because the new strain would be unrecognized by the human immune system, it could lead to widespread infection, illness, and death, similar to what occurred in three such 20th century pandemics in 1918, 1957, and 1968.

The tragic events of September 11, 2001, and the deliberate release of anthrax spores in the Nation’s capital drove home the realization that certain deadly pathogens, such as smallpox or anthrax, have the potential to be used deliberately as agents of bioterrorism against the civilian population. Similar potential exists for radiological, nuclear, and chemical threats.

To unravel the intricacies of the human body, we must find out what is happening at several levels—molecules, cells, organs—and how a dizzying number of interactions at each of these levels contribute to the health of the whole system. Efforts to prevent, detect, and treat disease require that we understand the complexity of the many biosystems of the human body. As the questions become more complex, and even as knowledge grows, science itself grows more multifaceted. We recognize that to effectively push science/new knowledge forward, researchers and scientists must begin to work more collaboratively to develop unifying principles that link apparently disparate diseases through common biological pathways and therapeutic approaches.



Today, and in the future, NIH research must reflect this new reality. Advanced technologies, including the sophisticated computational tools and burgeoning databases, likewise span diseases and disciplines. The scale and intricacy of today's biomedical research problems increasingly demand that scientists move beyond the borders of their own discipline and apply new organizational models for science. One of NIH's most pressing challenges is to generate and maintain the biomedical workforce necessary to tackle the converging research questions of this century.

Adding to the level of complexity, many of the public health problems NIH confronts have a behavioral component. To confront the escalation in obesity, for example, NIH must address a multitude of intersecting factors, from inherent biological traits that differ among individuals; to environmental and socioeconomic factors; to behavioral factors—which may have both molecular and environmental influences. The obstacles of today's obesity epidemic are daunting, yet the discoveries emanating from previous research investments offer unprecedented opportunities for new scientific research efforts to help meet these challenges.

***Innovate! That's the path to a healthy state.***

With the NIH Reform Act of 2006 (Pub. L. No. 109-482), Congress provided a statutory foundation for the centerpiece of the NIH Roadmap for Medical Research—a Common Fund that provides “incubator space” to spur innovation. The Common Fund supplies a centralized source of funding for trans-NIH initiatives to meet the research and training needs of the 21<sup>st</sup> century and stimulate innovation. To garner support from the Common Fund, research initiatives must not only be trans-NIH and fill a gap in our knowledge base, but also be potentially transformative. The Human Microbiome project, launched in 2007, is one such initiative, promising to reveal how bacteria and other microorganisms that are found naturally in the human body (the “microbiome”) influence a range of biological processes, including development, immunity, and nutrition. This effort will not only improve our understanding of how one biosystem (an individual's microbiome) relates to disease, but will also generate resources and support the development of new technologies and computational approaches—all crosscutting outputs that can be applied to investigations of other biosystems. Another new initiative at the biomedical research frontier is the NIH Roadmap Epigenomics Program, which will scan the human genome to study heritable features that do not involve changes to the underlying DNA sequence, but significantly affect gene expression and are important for informing us about how DNA is regulated. This global analysis of epigenetic changes should reveal new cellular pathways and mechanisms that influence disease progression.

The Common Fund also enables NIH to continue building research teams of the future; growing the Clinical and Translational Science Award Program; sustaining the transformation of the clinical research enterprise, in order to speed new discoveries from bench to bedside; investing strategically at the boundaries between the life and physical sciences, where so much transformative science, such as nanomedicine (the control of matter on the atomic and molecular scale), is taking place; and, through the Pioneer Award Program, nurturing bold ideas that, although they may have more than the usual degree of risk, if successful, will have unusually high scientific impact.

Nurturing a new generation of innovators is critical to our future research endeavors. NIH makes strategic investments at every level of the pipeline to improve the flow of talent drawn from every part and population of America. We produce teaching supplements that help educators from grades 2 through 12 convey difficult concepts through engaging activities, improving health literacy, and hopefully sparking children's interests in careers in research. We have programs that give undergraduate students research experiences, especially geared toward harvesting the vast potential of young people from groups that have been historically underrepresented in the sciences. NIH grants fund graduate students and post-doctoral fellows who go on to fill most every niche in the American biomedical research enterprise—from academic research to private industry, and from venture capitalists to policy makers. To support our new investigators and our most creative scientists, NIH recently established a series of new grants, including the "Pathway to Independence Award" and the "New Innovator Award." Through these programs, nearly 200 of the most promising postdoctoral scientists will be chosen annually to receive 5-year bridging funds during their transition to research independence, while nearly 40 of the Nation's exceptionally creative scientists will be annually selected to receive 5 years of support while taking unconventional approaches to tackling our most vexing biomedical problems.

We are in an era of unprecedented scientific opportunity. In the past year alone, a deluge of genetic discoveries—the outcome of NIH's Human Genome and HapMap projects—promises to usher in a new epoch of biomedical research. To capitalize on recent research insights and technological advances, with partners from the various sectors of the Nation's health enterprise, NIH will build on past successes in basic, translational, and clinical research to keep America on the road to health through the new millennium. We need to sustain this momentum, as progress in the life sciences in this century will be a major determinant of our Nation's health, competitiveness, and standing in the world.

**Elias A. Zerhouni, M.D.**  
**Director, National Institutes of Health**  
**January 15, 2008**

## NIH OVERVIEW

The NIH mission is to uncover new knowledge that will lead to better health for everyone.

To many Americans, the names of one or more of the 27 ICs that comprise NIH may be more familiar than NIH as a whole. The name of an IC generally reflects its focus on a specific disease (e.g., cancer, diabetes), an organ system (e.g., heart, eye), life stage (e.g., children, the aging population), an overarching field of science (e.g., human genome, nursing), or a technology (e.g., biomedical imaging, information technology). It is the strength of each IC's expertise that provides the firm foundation enabling NIH to address the remarkable breadth and complexity of the biomedical and behavioral research it supports and conducts in the interest of improving public health. The ICs *support* research and training through extramural activities and most also *conduct* research and training through intramural activities. (See information below regarding the intramural and extramural research programs.)

The Office of the Director (OD), NIH, provides leadership, oversight, and coordination for the entire NIH research enterprise. The Division of Program Coordination, Planning and Strategic Initiatives, a new structure within the NIH OD, mandated by the NIH Reform Act of 2006, incorporates functions of the Office of Portfolio Analysis and Strategic Initiatives (which has primary responsibility for trans-NIH research initiatives based on NIH-wide portfolio assessment, strategic planning, evaluation, and assessment) and the research coordination functions of the four OD Program Offices. These OD program offices fund research using IC award-making authorities. Often, ICs partner with an office, supplementing its funding on a specific program or project.

Also within OD, many offices develop NIH policy and provide essential NIH-wide oversight and coordination in the areas of Science Policy, Science Education, Biotechnology Activities, Legislative Policy, Communications and Public Liaison, Ethics, Equal Opportunity and Diversity Management, Administrative Management, Budget, Financial Management, Human Resources, Research Services, Technology Transfer, Management Assessment, Management Planning, and Legal Counsel. The policies and activities of some of these offices are highlighted throughout the sections that follow as they relate to NIH research activities and policies. Also within OD are the Office of Extramural Research, which coordinates and oversees NIH policy on research supported by NIH and performed under grants and other award mechanisms by non-NIH institutions, and the Office of Intramural Research, which coordinates and oversees research conducted in NIH laboratories. These offices are discussed in some detail in the sections below.

Following is a list of NIH ICs and OD Program Offices linked to the home page on their Web sites. The ICs are presented in the order in which they appear on the appropriation table in the Congressional Justification. (See Appendix B for brief descriptions of the missions of the ICs and OD program offices and for links to IC and office strategic plans. The set of mission statements and strategic plans in Appendix B both classifies and justifies NIH priorities.)

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## Institutes and Centers

- [National Cancer Institute](#) (NCI)
- [National Heart, Lung, and Blood Institute](#) (NHLBI)
- [National Institute of Dental and Craniofacial Research](#) (NIDCR)
- [National Institute of Diabetes and Digestive and Kidney Diseases](#) (NIDDK)
- [National Institute of Neurological Disorders and Stroke](#) (NINDS)
- [National Institute of Allergy and Infectious Diseases](#) (NIAID)
- [National Institute of General Medical Sciences](#) (NIGMS)
- [National Institute of Child Health and Human Development](#) (NICHD)
- [National Eye Institute](#) (NEI)
- [National Institute of Environmental Health Sciences](#) (NIEHS)
- [National Institute on Aging](#) (NIA).
- [National Institute of Arthritis and Musculoskeletal and Skin Diseases](#) (NIAMS)
- [National Institute on Deafness and Other Communication Disorders](#) (NIDCD)
- [National Institute of Mental Health](#) (NIMH)
- [National Institute on Drug Abuse](#) (NIDA)
- [National Institute on Alcohol Abuse and Alcoholism](#) (NIAAA)
- [National Institute of Nursing Research](#) (NINR)
- [National Human Genome Research Institute](#) (NHGRI)
- [National Institute of Biomedical Imaging and Bioengineering](#) (NIBIB)
- [National Center for Research Resources](#) (NCRR)
- [National Center for Complementary and Alternative Medicine](#) (NCCAM)
- [National Center on Minority Health and Health Disparities](#) (NCMHD)
- [John E. Fogarty International Center](#) (FIC)
- [National Library of Medicine](#) (NLM)
- [NIH Clinical Center](#)
- [Center for Information Technology](#) (CIT)
- [Center for Scientific Review](#) (CSR)

## Office of the Director, Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI)

- [Office of Portfolio Analysis and Strategic Initiatives](#) (OPASI)
- [Office of Disease Prevention](#) (ODP)
  - [Office of Rare Diseases](#) (ORD)
  - [Office of Dietary Supplements](#) (ODS)
  - [Office of Medical Applications of Research](#) (OMAR)
- [Office of Behavioral and Social Sciences Research](#) (OBSSR)
- [Office of Research on Women's Health](#) (ORWH)
- [Office of AIDS Research](#) (OAR)

## EXTRAMURAL AND INTRAMURAL RESEARCH PROGRAMS

### Extramural Research Program

More than \$8 of every \$10 appropriated to NIH is awarded by the ICs through grants and contracts to the extramural community. The extramural community is composed of scientists at universities, medical centers, hospitals, and research institutions throughout the United States and abroad. The extramural research community comprises scientists and research personnel affiliated with over 3,100 organizations, including universities, medical schools, hospitals, and other research facilities located in all 50 States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, and points abroad. With NIH support, these investigators and their institutions conduct the vast majority of research that leads to improvements in the prevention, detection, diagnosis, and treatment of disease and disability; contributes to training the next generation of researchers; and enhances the skills and abilities of established investigators. The NIH OD Office of Extramural Research (OER) provides leadership, oversight, tools, and guidance to administer the NIH grants management operations carried out through the ICs. OER is where [grants policy](#), program coordination, compliance, and electronic Research Administration (eRA) converge. The Deputy Director for Extramural Research executes program coordination through counterparts in each of the grant-awarding ICs.

**NIH Peer Review Process.** All grant applications and contract proposals for research funding undergo evaluation through [peer review](#), in which external expert panels determine which applications or proposals are the most scientifically and technically meritorious and should be considered for funding. NIH policy requires that peer review be carried out in a manner that ensures objectivity, fairness, and maximum competition. The NIH dual (two-level) peer review system is mandated by the Public Health Service Act and Federal regulations (42 CFR 52).

CSR is the portal for NIH grant applications and their review for scientific merit. The NIH grant peer review process begins with assignment. Applications relevant to the NIH mission receive two types of assignment. One assignment is to a CSR Scientific Review Group (SRG) or, if the application is in response to a solicitation, to an IC special emphasis panel, for evaluation of scientific and technical merit. The second assignment is to an IC that has a mission encompassing the aims and objectives of the application. NIH uses established referral criteria (called Referral Guidelines) to determine the appropriate SRG to carry out review and the IC most suitable to potentially fund the project.

At the first level of review, peer reviewers evaluate and judge the *overall* scientific and technical merit of the research proposed in the application. SRGs conducting the first level of review are composed primarily of non-Federal researchers who are actively involved in the area of the proposed research and qualified to review the applications by virtue of their research experience and training. These peer reviewers are consultants to NIH and they provide advice about the potential of the research to advance scientific knowledge and discovery, using standardized criteria for determining the scientific and technical merit of an application, specifically:

1. **Significance:** Does the study address an important problem?
2. **Approach:** Are the concepts and methods well thought out and appropriate to the aim?

3. **Innovation:** Does the project develop or use novel concepts?
4. **Investigators:** Are the investigators appropriately trained and well suited to carry out the work?
5. **Environment:** Will the setting for the research (facilities, resources, institutional support) contribute to probability of success?

All of these criteria are necessary factors in determining the overall scientific and technical merit of an application and the final evaluation score or “priority score” of an application. Additional review criteria may be added for applications in response to solicitations (e.g., a Request for Applications, or RFA).

The second level of peer review is performed by the National Advisory Councils or Boards (Advisory Councils) of each IC, which are composed of scientific and nonscientific public members chosen for their expertise, interest, or activity in matters related to a specific area of health and disease. The vast majority of SRG-scored applications assigned to an IC go to the appropriate Council,<sup>1</sup> which then recommends those applications that should be considered for funding. Identifying applications that further specific program priorities is a particularly important function of this second level of peer review. However, like SRGs, Advisory Councils recommend, but do not make, funding decisions.

An ongoing trans-NIH effort to examine the two-level NIH peer review system with the goal of optimizing its efficiency and effectiveness is discussed in “Enhancing Peer Review,” under the section below on “Improving Research Management.”

**Funding Decisions.** Only applications that are scientifically meritorious, based on SRG review, and favorably recommended by the National Advisory Council may be considered for funding. The priority score given to an application during the peer review process is important, but not the sole factor determining an IC’s funding decision. Other considerations are programmatic relevance, IC priorities, contribution to balance in light of the existing IC research portfolio, and amount of the award.

Many ICs establish a “payline”— a percentile-based<sup>2</sup> funding cutoff point determined at the beginning of the fiscal year by balancing the projected number of applications coming to an IC with the amount of funds determined by NIH and the IC to be devoted to such projects. Because the significance of the proposed research is a critical factor in determining the priority score, applications that score within the payline are most likely to be funded. However, Advisory Councils consider, evaluate, and make recommendations on specific applications that score both within and beyond the payline.

In addition to setting paylines, many ICs establish procedures for funding applications that scored beyond the payline. Terms used for this category of awards vary by IC, but include “select pay,” “exception pools,” “high program-priority,” and “special emphasis.” What is

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<sup>1</sup> Councils do not receive unscored applications (these are applications deemed “not recommended for further consideration [NRFC]”) at the first level of peer review. Also, until enactment of the NIH Reform Act of 2006, Councils were not obligated to review applications for less than \$50,000. Moreover, of applications sent to Council, many IC Councils evaluate only those scoring over a prescribed threshold of success at the first level of peer review.

<sup>2</sup> Percentile represents the relative position or rank of each priority score (from 1 to 100).

consistent is the use of these funds, with strong justification, to support highly innovative or high program priority applications that score beyond the payline.

**Post-Award Administration.** NIH policies extend into the post-award phase of research as well, so that NIH can monitor research progress and ensure responsible conduct of research. Scientific monitoring includes reviewing yearly progress reports, financial reports submitted by grantees, the publications generated by the research, and any invention reports. NIH also monitors compliance with Federal rules on protection of animals used in research and on human subjects (see “Ensuring Responsible Research Conduct” below). In addition, oversight of clinical research may involve data safety monitoring.

Oversight of initiatives involves another level review. NIH staff track what is funded under each initiative and may hold follow-up advisory group meetings, workshops, and/or formal program evaluations. This type of information becomes yet another source of input for the IC as it evaluates priorities and considers midcourse adjustments to initiatives and strategic plans.

## **Intramural Research Program**

Approximately 10 percent of NIH funds support research activities carried out by NIH scientists in NIH laboratories on its campuses in the Bethesda (including the NIH Clinical Center), Rockville, Frederick, and Baltimore, Maryland, areas; Research Triangle Park, North Carolina; Phoenix, Arizona; and the Rocky Mountain Laboratories, Montana. The NIH Intramural Research Program, or IRP, conducts basic, translational, and clinical research. Most ICs have an intramural program; the exceptions are NIGMS, CSR, FIC, NCRR, and NCMHD.<sup>3</sup> Organizationally, the individual laboratories and clinics answer to their respective IC, and generally are responsible for conducting original research consonant with the goals of their IC. Approximately 1,150 principal investigators lead intramural research projects. The NIH Office of Intramural Research (OIR) is responsible for trans-NIH oversight and coordination of intramural research, human subjects protections, animal welfare, training, policy development, laboratory safety, and technology transfer conducted within NIH laboratories and clinics. OIR is led by the NIH Deputy Director for Intramural Research and its oversight responsibilities are carried out in conjunction with the IC Scientific Directors. A summary of policies governing intramural research can be found in the [Intramural Research Sourcebook](#).

As with the extramural program, intramural research proposals are generated by scientists. In the intramural research program, however, program directions and priorities are not generally shaped through grant awards,<sup>4</sup> but rather through professional hiring and promotion decisions, external reviews, and the allocation of resources to laboratories and branches.

Each intramural research program has a promotion and tenure committee that evaluates all recommendations for professional appointment or promotion. In addition, there is a central

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<sup>3</sup> Although NCMHD does not have an intramural program per se, some NCMHD funds are applied to intramural activities in partnership with other ICs.

<sup>4</sup> In July 2007, NIH issued NOT-RM-07-011 notifying members of the NIH IRP that Roadmap requests for allocations from the IRP will be considered on a competitive basis along with Roadmap applications from members of the extramural scientific community. CSR will be responsible for initial peer review involving competition among members of the IRP and the extramural scientific community.

tenure committee that reviews all candidates for tenure at the NIH. Through a competitive process, only approximately 60 percent of the individuals who enter the tenure track at the NIH, after a national search, eventually become permanent tenured staff.

Although tenure guarantees a base salary, research resources are competitive. Tenured and tenure-track scientists undergo formal, annual, internal reviews. Resource allocation and promotions are determined from these reviews. In addition, at least every 4 years, an external expert Board of Scientific Counselors (BSC) reviews the work of each tenured/tenure-track scientist and makes recommendations regarding continuation or modification of projects and adjustment of resources (budget, space, personnel). The IC Director or Scientific Director reports the results of BSC reviews to the IC National Advisory Council.

Each IC intramural research program is led by a Scientific Director. Scientific Directors are evaluated for performance by an external committee every 5 years. The reviewing committee reports to the IC National Advisory Council through the IC Director and to the NIH Deputy Director for Intramural Research.

Moreover, each IC intramural research program is reviewed in its entirety by a “blue ribbon” panel approximately every 10 years. These panels assess and make recommendations concerning the impact of the research program, program balance, and other significant matters that play a role in the success of the program.

## STRATEGIC PLANNING AND ROADMAP 1.5

Strategic planning at NIH takes place at many levels. The U.S. Congress, through the NIH authorization and appropriations processes, sets IC funding levels, establishes the missions for some ICs, and directs NIH attention to particular areas of research interest or emphasis.<sup>5</sup> The Administration also establishes priorities for improving the health of the Nation that must be addressed by NIH. An example is *Healthy People 2010*, a comprehensive set of disease prevention and health promotion objectives for the Nation to achieve by 2010.<sup>6</sup> *Healthy People 2010* has two overarching goals—“Increase Quality and Years of Healthy Life” and “Eliminate Health Disparities”—and NIH is understandably the lead or co-lead for many of the specific topic areas. In addition, NIH establishes its goals and priorities fully cognizant of the framework of the *HHS Strategic Plan Goals and Objectives —FY 2007-2012*,<sup>7</sup> which sets the stage for individual performance plans and outcome measures across NIH.

Some strategic plans pertain to the whole agency, for example, the NIH Roadmap for Medical Research. NIH initiated the Roadmap planning process in 2002 by consulting broadly with stakeholders to identify and prioritize the most pressing problems (roadblocks) facing medical research that could be uniquely addressed by NIH as a whole. Ideas for Roadmap initiatives were formulated from those initial consultations and then vetted based on whether the initiative has high potential to transform the way health research is conducted, synergizes with but cuts across the individual missions of the Institutes and Centers, is not redundant with activities conducted

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<sup>5</sup> For more information, see <http://officeofbudget.od.nih.gov/PDF/Significant%20Items-2008.pdf>

<sup>6</sup> For more information, see <http://www.healthypeople.gov/>

<sup>7</sup> For more information, see [http://www.hhs.gov/strategic\\_plan/](http://www.hhs.gov/strategic_plan/)



by other agencies or entities, and is expected to have an impact on public health such that results should be broadly disseminated and in the public domain. This novel NIH-wide planning process launched a set of over 30 initiatives under three broad themes in 2003. The first set of Roadmap initiatives already is deepening our understanding of molecular biology and its role in health and disease; creating tools for 21st century biomedical research; stimulating interdisciplinary research teams; promoting high-risk breakthrough science; and reengineering the clinical research enterprise. NIH institutionalized this NIH-wide planning process when it established the Office of Portfolio Analysis and Strategic Initiatives (OPASI) in spring 2006. That summer, OPASI began soliciting ideas for the next generation of Roadmap initiatives. When NIH established OPASI, it also enhanced NIH's systems for gathering and analyzing information in support of strategic planning (see sections on "OPASI" and on "Roadmap 1.5," below).

Although the Roadmap process is novel, NIH has a significant tradition of NIH-wide and trans-NIH strategic planning. The *NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities* is a prominent example of an NIH-wide plan. Trans-NIH strategic plans focus on areas that are best addressed by involving multiple ICs in identifying research goals and priorities; for example, the Strategic Plan for NIH Obesity Research was developed by the NIH Obesity Research Task Force, led by NIDDK and NHLBI. The Plan seeks to maximize collaboration among the ICs and OD Offices to capitalize on their respective capabilities. Recent initiatives (FY 2006 and 2007) relate to translational research for the prevention and control of diabetes and obesity (NIDDK and OBSSR); bioengineering and obesity (NHLBI, NCI, NIA, NIBIB, and NIDDK); and identifying and reducing diabetes and obesity-related health disparities within health care systems (NIDDK), among others. Other trans-NIH research plans address goals and objectives in areas that include neuroscience research, HIV/AIDS, liver disease, diabetes, health disparities, muscular dystrophies, autoimmune diseases, and more.

Naturally, however, the majority of strategic planning at NIH is IC-based. IC strategic plans function as guideposts to the investigative and NIH communities. Each NIH IC has unique processes for developing and disseminating its strategic plans, but by developing and articulating consensus on today's most pressing health needs and research questions, all IC strategic plans influence the research directions and methods proposed by investigators in their applications. By the same token, strategic plans inform IC decisions about areas of research that require stimulation—achieved through a variety of means including meetings, workshops, conferences, Program Announcements, and Requests for Applications and Requests for Proposals—to move science planning into the implementation stage. Finally, strategic plans influence IC decisions on which applications to fund.

While each of the 24 grant-making ICs has a broad Strategic Plan that clearly states its mission and priorities, many of the ICs also have disease- and program-specific strategic plans and research agendas as well as reports from workshops, "blue ribbon" panels, and other expert panels that contain recommendations for research goals or priorities within the IC mission.

Strategic planning at NIH is a highly consultative process involving many constituencies that generate and provide input on public health needs and research gaps, opportunities, and priorities. Importantly, strategic plans also serve as a means for ICs to measure and report on portfolio balance and progress relative to their missions. NIH stays constantly tuned to the twin

touchstones for priority-setting—public health need and state of the science. In Chapter 2, at the end of each disease topic section, there is a list of relevant strategic plans.

## **Division for Planning and Strategic Initiatives**

As noted above, the NIH Reform Act of 2006, signed into law in January 2007, created the new Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within the NIH/OD. The purpose of DPCPSI is to identify and report on research that represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that deserve special emphasis and would benefit from the conduct or support of additional trans-NIH research (research that involves collaboration between two or more ICs), or would otherwise benefit from strategic coordination and planning. As specified in the NIH Reform Act of 2006, a Council of Councils, which met for the first time in November 2007, advises the NIH Director on matters related to the policies and activities of DPCPSI. To a large extent, the legislative mandate for DPCPSI confirms the administrative action that NIH took when it established OPASI. As such, OPASI will continue its role in developing and managing Roadmap initiatives as an integral part of DPCPSI.

## **Office of Portfolio Analysis and Strategic Initiatives**

When NIH established OPASI in spring 2006, the aim went beyond institutionalizing the Roadmap planning and investment process. OPASI's full role is to provide NIH and the ICs with the methods and information necessary to manage their large and complex scientific portfolios; to lead trans-NIH efforts in identifying new and shifting public health challenges and important areas of emerging scientific opportunity; and to assist in accelerating trans-NIH investments in these areas, focusing on those involving multiple ICs.

OPASI develops and employs databases, analytic tools, and methodologies to conduct key assessments and portfolio analyses and integrates these analyses with information from multiple other sources for use in identifying and recommending concepts for trans-NIH initiatives. Since evaluation is an integral part of strategic planning and priority-setting, OPASI also is responsible for planning, coordinating, and conducting program and initiative evaluations. As part of its evaluation agenda, OPASI subjects each Roadmap initiative to rigorous review, with outcome tracking, an annual review of progress, and a major review not later than the fourth year of the initiative. In addition, OPASI is responsible for overseeing and coordinating IC use of evaluation set-aside funds and the systematic assessments required by the Government Performance and Results Act (Pub. L. No. 103-62) and the OMB Program Assessment Rating Tool.

## **Roadmap 1.5 and the Common Fund Strategic Initiative Process**

Roadmap initiatives are a collective NIH-wide resource supported through the NIH Common Fund. They were previously funded through IC and OD contributions, but since FY 2007 have been funded within the OD appropriation level. While OPASI does not have direct grant-making authority, the Common Fund provides an “incubator space” for Roadmap and other initiatives on a time-limited basis (5 to 10 years). Current and future initiatives either transition out to the ICs

after this 5- or 10-year period or are concluded. In this way, NIH can remain nimble in responding to newly identified emerging research needs that have the potential to transform biomedical or behavioral research.

To perpetuate the Roadmap, OPASI manages the [process by which recommendations for trans-NIH strategic initiatives are selected and developed](#), and provides the information needed for NIH leadership to allocate resources effectively for these trans-NIH efforts.

The process is exemplified by the steps OPASI took in 2006 and early 2007 to select and plan the next generation of Roadmap initiatives—Roadmap 1.5—which will be funded in FY 2008.

Through summer and fall 2006, NIH solicited ideas for new initiatives from the intramural and extramural scientific community, patient advocates, and the general public to help senior NIH staff identify crosscutting challenges in biomedical research that meet special criteria established for Common Fund (Roadmap) initiatives. One of the important steps in this process was issuance of a Request for Information published in the NIH Guide<sup>8</sup> in October 2006. The respondents were invited to submit up to three ideas that met predetermined criteria to be considered for a Roadmap initiative.

To facilitate the prioritization of ideas, OPASI coordinated a programmatic review of the submitted ideas assessing their responsiveness to the criteria. To further inform the decision-making process, OPASI and ICs worked together to provide a preliminary assessment of the currently funded portfolio of research related to several of the broad areas highlighted by the ideas. OPASI efforts to develop portfolio analysis tools will enhance NIH capacity for these analyses. Informed by this analysis and following extensive scientific discussion, the IC Directors selected broad areas that were to be pursued either as major Roadmap initiatives, pilot studies, coordination areas, or strategic planning areas.

Next, Trans-NIH Working Groups, led by IC Directors, developed specific proposals in the identified broad areas. Then, in May, the IC Directors and NIH Director met to review and prioritize the proposals. They selected two topics, the Microbiome and Epigenetics, for immediate implementation as 5-year Major Roadmap Initiatives. Although the Reform Act was not enacted in time for NIH to establish and convene the Council of Councils during consideration of concepts for Roadmap 1.5, in the future the Council will act as an external advisory panel to the IC Directors during the concept approval stage of Roadmap initiatives.

#### Criteria for Major Roadmap Initiatives

- ▷ Is the proposed initiative truly transforming – could it dramatically affect how biomedical and/or behavioral research is conducted over the next decade?
- ▷ Will the outcomes from the proposed initiatives synergistically promote and advance the individual missions of the ICs to benefit health?
- ▷ Does the proposed initiative require participation from NIH as a whole and/or does it address an area(s) of science that does not clearly fall within the mission of any one IC or OD program office?
- ▷ Is the proposed initiative something that no other entity is likely or able to do, and is there a public health benefit to having the results of the research in the public domain?

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<sup>8</sup> For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-011.html>

- **Microbiome.** The Microbiome is the full collection of microbes (e.g., bacteria, fungi, viruses) that naturally exist within and on the human body. In a healthy adult, microbial cells are estimated to outnumber human cells by a factor of 10 to 1. These communities, however, remain largely unstudied, leaving almost entirely unknown their influence on human development, physiology, immunity, and nutrition. The NIH Human Microbiome Project (HMP) will generate the tools and resources necessary for comprehensive characterization of the human microbiota and analysis of their relationship to human health and disease.
- **Epigenetics/Epigenomics.** Epigenetics is the study of changes in gene expression or function that are caused by factors other than change in DNA sequence. Epigenetic changes allow cells to have different characteristics despite containing the same genomic material. Curiously, some epigenetic features are inherited from one generation to the next. This subject is of such current scientific interest that the prominent journal *Cell* recently devoted an entire special review issue to the subject.<sup>9</sup> The overall hypothesis of the NIH Epigenomics Program is that the origins of health and susceptibility to disease are, in part, the result of epigenetic regulation of the genetic blueprint. Initiatives in this area would develop a “toolbox” to better measure these genetic modifications; collect data and develop algorithms to build the infrastructure needed to model epigenetic processes; and incorporate epigenetic information in genetic studies to increase our understanding of the relationship to human health and disease.

Other topics were approved as pilot studies, coordination areas, and strategic planning areas (see Appendix C, the “Common Fund Strategic Planning Report, FY 2008,” for further information on plans for use of the Common Fund).

## OTHER CROSSCUTTING ACTIVITIES AND POLICIES

Chapters 2 and 3 of this Report summarize NIH research activities on the topics specified in the statute mandating this report. Chapter 2 summarizes research activities on topics that are disease-specific (e.g., those regarding cancer and chronic diseases). Chapter 3 summarizes activities from the perspective of key research approaches and resources (e.g., genomics, clinical and translational research, research training, and health communications. Other activities essential to the mission of the NIH—technology transfer, science education, providing a platform for discovery, enhancing the management of research, and ensuring responsible research and development—are summarized below.

### Technology Transfer and Sharing

Federal and NIH policy requires that the outcomes of NIH research be made available to the public. Provisions of the Bayh-Dole Act (35 U.S.C. 200 et seq.) and the Federal Technology Transfer Act (15 U.S.C. 1501 et seq.) are intended to stimulate the commercialization of

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<sup>9</sup> *Cell*, 128, February 23, 2007.

federally funded inventions by ensuring the transfer of federally funded technology to the private sector.

The NIH Office of Technology Transfer (OTT) develops technology transfer policies that are approved by the PHS Technology Transfer Board. Technology transfer and sharing policies, as they apply to extramural research, are developed with and administered by OER. These policies include principles, guidelines, and regulations related to publication, invention reporting, and intellectual property policy matters. [OER policies](#) are designed to enhance access to publications resulting from NIH-funded research; ensure appropriate sharing of data, tools, and research resources; and promote the transfer of technology (in the form of licenses and patents). All recipients of Federal grants or contracts must report details of inventions and patents that have been made through such awards. NIH developed an online Extramural Invention Information Management System (Edison) in 1995 for Bayh-Dole reporting compliance, and now administers the Interagency Edison system (iEdison) through which inventions supported by any of 18 Federal research agencies can be reported.

Intramural [policies](#) and activities are managed by the Office of Technology Transfer (OTT) in the NIH OIR. As mandated by the Federal Technology Transfer Act and related legislation, OTT evaluates, protects, licenses, monitors, and manages the wide range of intramural NIH and U.S. Food and Drug Administration (FDA) discoveries, inventions, and other intellectual property. A large part of OTT's responsibility for technology transfer is carried out by retaining title to inventions developed in NIH and FDA laboratories and licensing these inventions to the private sector entity best suited to conduct the further research and development needed for potential commercialization and public health benefit. The NIH Pipeline to Partnerships (P2P) searchable database is a new resource developed to encourage the development of technologies licensed from OTT or being developed by NIH SBIR/STTR awardees by showcasing them for an audience of potential strategic partners, investors, and licensees. The P2P database provides an additional avenue by which NIH can facilitate more rapid development of products for the benefit of public health.

## **Science Education and Literacy**

NIH takes an active role in science education and science literacy activities. These activities aim to attract young people to biomedical and behavioral science careers, lay the groundwork for advanced study, enhance public understanding of health science, and empower the public as consumers of science and health information.

[Curriculum supplements](#)—ready-to-use, interactive teaching units—are one of NIH's most popular and effective science education efforts. Crafted through a unique partnering of NIH scientists, teachers, and expert curriculum developers, the supplements are aligned with State education standards and are consistent with the National Science Education Standards. NIH has shipped nearly 300,000 curriculum supplements to K-12 educators across the Nation. Topics covered include “The Science of Healthy Behaviors,” Cell Biology and Cancer,” “Sleep, Sleep Disorders, and Biological Rhythms,” and “The Brain: Understanding Neurobiology through the Study of Addiction.”

NIH aims to engage students and the public in the wonders of biology and biomedical research through other thought-provoking programs as well. For those who are interested in a career in the life sciences, NIH provides resources such as [LifeWorks®](#), a career exploration Web site for middle and high school students, their parents, teachers, and career guidance counselors. LifeWorks® includes in-depth career information on more than 100 health and medical science-related careers. Users can search the site and generate a customized list of careers that match their skills and interests. “SciLife” is an annual health and biomedical career planning workshop for parents and high school students. NIH also sponsors a speakers’ bureau that provides engaging science professionals to talk to school groups and local and national organizations.

NIH’s [Science Education Partnership Awards](#) (SEPA) funds innovative educational programs, such as collaborations among biomedical and clinical researchers and teachers and schools, museums and science centers, media experts, and other educational organizations that generate educational resources such as curricula; exhibits; films; student, teacher, and parent workshops; after-school and summer hands-on science programs; essay contests; and science fairs. A dedicated [SEPA Web site](#) provides access to the educational materials and expertise produced through these efforts. SEPA enables researchers, educators, and community groups to share their knowledge, expertise, and enthusiasm about health and science research with K-12 students and the general public.

## **Providing the Platform for Discovery**

***Buildings and Facilities.*** With more than 18,000 employees and 229 government-owned buildings in six locations, the facilities infrastructure maintained by the OD Office of Research Facilities is the literal foundation for a successful research program. The facilities necessary to support 21st century science are far more sophisticated than yesterday’s bricks, mortar, pipes, and lines. From biosafety to facilitating team science, the requirements of today’s research create greater demands in providing and sustaining a safe, healthy, and functional environment for employees and patients.

***The Clinical Center.*** The Clinical Center is the Nation’s largest hospital devoted entirely to research. Here, NIH scientists work to translate laboratory discoveries into better means to improve the Nation’s health. Comprising two facilities—the Mark O. Hatfield Clinical Research Center, which opened in 2005, and the original Warren Grant Magnuson Clinical Center, which opened in 1953—the Center houses inpatient and outpatient units as well as research laboratories and features a unique design that locates patient care units in close proximity to cutting-edge laboratories doing related research. This facilitates interaction and collaboration among clinicians and researchers. More than 1,600 intramural NIH laboratories use the Center to conduct research. The Center has more than 100,000 outpatient visits a year and 7,000 inpatient admissions. Approximately 1,200 credentialed physicians, dentists, Ph.D. researchers, 660 nurses, and 570 allied health care professionals such as pharmacists, dietitians, and medical technologists work at the Center. As a research facility, only patients with the precise kind or stage of illness under investigation are admitted for treatment under a protocol, but subjects who are enrolled in clinical studies receive the benefit of access to cutting-edge technologies and compassionate care.

**The Library.** Through the National Library of Medicine (NLM), NIH provides the world's largest medical library. The Library collects materials in all areas of biomedicine and health care. The collections stand at more than 9 million items—books, journals, technical reports, manuscripts, microfilms, photographs, and other images. Housed within the Library is one of the world's finest medical history collections of old and rare medical works. Far more than a physical facility, the Library is responsible for MEDLINE<sup>®</sup>, a database freely accessible on the Internet through PubMed<sup>®</sup>, which has more than 16 million journal article references and abstracts going back to the mid-1960s with another 1.5 million references back to the early 1950s. Some 900 million searches of MEDLINE are done each year by health professionals, scientists, librarians, and the public. Links from references to full text articles increasingly are available.

To maintain the currency of its collection, the Library selects, orders, and acquires publications from a wide variety of sources. Each year NLM receives, reviews, and processes approximately 25,000 monographic items for possible addition to the NLM collections, and acquires, licenses, and processes over 22,000 print, non-print, and electronic serial titles.

To manage its collection and maximize accessibility, the Library employs sophisticated cataloging and indexing schemes that in and of themselves are important tools for the Nation's network of medical libraries. These activities include maintaining and developing the online [NLM Classification](#), a scheme for the shelf arrangement of medical literature in libraries, and [MeSH](#), the Library's controlled vocabulary thesaurus. MeSH consists of sets of terms naming descriptors in a hierarchical structure that permits searching at various levels of specificity. The MeSH thesaurus is used for indexing articles from 4,800 of the world's leading biomedical journals for the MEDLINE/PubMED<sup>®</sup> database. It also is used for the NLM-produced database that includes cataloging of books, documents, and audiovisuals acquired by the Library. Each bibliographic reference is associated with a set of MeSH terms that describe the content of the item. Similarly, search queries use MeSH vocabulary to find items on a desired topic.

**Information Technology.** Information technology (IT) and computational science increasingly are essential to deciphering the complexity of biological systems. The NIH Center for Information Technology (CIT) provides core IT infrastructure, system security, and services ranging from cable and server acquisition and management, to video conferencing and Web site development, as well as providing the policy framework for IT activities undertaken by other ICs. In addition, CIT and many ICs provide NIH scientists with access to the sophisticated systems, analytic tools, and databases necessary to advance quantitative investigations in fields such as molecular biology and proteomics (for additional information see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3). From supercomputing to management of an Image Processing Facility, CIT also provides the NIH intramural community with invaluable scientific support tools and resources.

**Public-Private Partnerships.** The NIH Program on [Public-Private Partnerships](#) was established in 2006 within the NIH Office of Science Policy as a Roadmap initiative to facilitate collaborations to improve public health through biomedical research. As the central NIH resource on public-private partnerships, the program provides guidance and advice to NIH and potential partners on the formation of collaborations that leverage NIH and non-NIH resources to



achieve synergy. NIH partnerships can be established directly between NIH (as a whole or through one or more ICs) and any of a wide range of other organizations, including patient advocacy groups, foundations, pharmaceutical or biotechnology companies, academic institutions, and the Foundation for the NIH (FNIH), an independent, private charitable foundation established by Congress. The Program works with the ICs and OD Offices to review existing partnership mechanisms and recommend policies or legal authorities needed to achieve NIH objectives and manage intellectual property, achieve data access and sharing, and address human subjects protections and other concerns. In September 2007, the Program issued, in the *NIH Manual*, a [reference guide](#) to many of the relevant legal authorities, policies, ethics issues, and other considerations in using the various available mechanisms to create public-private partnerships.

## Improving Research Management

**Enhancing Peer Review.** In June 2007, NIH embarked on a [trans-NIH effort](#) to examine the two-level NIH peer review system with the goal of optimizing its efficiency and effectiveness, while ensuring that NIH continues to meet the needs of the research community and public at large. The examination involves leaders from across the scientific community through two working groups—one external and one internal. Both groups are seeking broad input. Information collection efforts included a Request for Information published in the *NIH Guide* seeking comments and creative concrete suggestions on how to enhance the system; an internal NIH staff survey; regional meetings around the country; and consultations with professional societies and advocacy groups. After all of the input has been analyzed, both working groups will meet in January 2008 to develop a set of integrated recommendations for next steps.

In parallel with NIH's examination of the peer review system, CSR launched several peer review pilots and initiatives that will inform this ongoing effort. Based on a two-stage pilot test that began early in 2006, NIH shortened the review cycle for new investigators submitting R01 applications. (The R01 is the most common mechanism of grant support for individual investigators.) Before the pilot, on average, it took 10.3 months from the receipt of an application until NIH made an award to support the proposed research. For new applicants, CSR now posts the conclusions of peer review meetings within 10 days. This acceleration gives new applicants opportunity to revise and resubmit amended applications for the next review cycle—4 months sooner than the previous opportunity for resubmission. Since new investigators, by definition, have had no previous R01 support, any delay in their ability to submit an amended application could have a negative impact on their careers. NIH has great interest in the career development of new scientists and this initiative is just one example of NIH's commitment to supporting new investigators in their efforts to obtain R01 research grant funding. NIH is now working toward shortening the review cycle for all applicants.

CSR also has been developing and testing different modes of conducting peer review to enhance the recruitment of the best reviewers. One experiment involves scheduling some study section meetings in areas outside the Washington, D.C., area so meeting sites and travel are more convenient for reviewers.



**New Investigators.** New investigators are the innovators of the future—they bring fresh ideas and technologies to bear on biomedical and behavioral research problems and they pioneer new areas of investigation. Entry of new investigators into the ranks of NIH-funded researchers is essential to the health of this country's research enterprise. Because of that, NIH interest in the training and funding of new investigators is deep and longstanding. NIH exceeded its target of 1,500 new investigators attaining project grant support in FY 2007. In addition, NIH established two new programs to help new investigators in their quest to become independent research scientists—the [Pathway to Independence Award](#) and [NIH Director's New Innovator Award](#). The Pathway to Independence Program, announced in January 2006, offers a new opportunity for promising postdoctoral scientists to receive both mentored and independent research support from the same award. This new award mechanism is a bridge that will accelerate the transition of new, creative scientists from research dependence to research independence. The NIH Director's New Innovator Award, announced in March 2007 as a component of the NIH Roadmap, supports exceptionally creative scientists who take highly innovative, even unconventional, approaches to major challenges in biomedical or behavioral research. New Innovator Awards are reserved for investigators who have not yet received a regular research (R01) or similar grant.

**Aligning Grant Applications with Team Science.** In February 2006, NIH announced a pilot initiative to alter a longstanding policy and allow more than one principal investigator (PI) on a grant application. This multiple-PI model enables investigators to share the authority, responsibility, and credit for leading and directing a project—intellectually and logistically—and encourages collaboration among equals, when a “team science” approach is the most appropriate way to address a scientific problem. This policy change began as a 2005 Roadmap initiative to stimulate interdisciplinary science. In 2006, NIH and the White House Office of Science and Technology Policy solicited advice and comments on this topic from the scientific community. On the basis of the NIH pilot and received advice, all Federal research agencies are preparing to formally implement policies and procedures allowing multiple PIs on research awards. NIH released its implementation [guidance](#) to the community in November 2006 and most electronic applications were modified to accept multiple PIs beginning with January receipt dates in 2007. On June 25, 2007, NIH released a *Federal Register* [Notice of Proposed Rule Making](#) to solicit input on the change in definition to accommodate multiple PIs. A notice addressing those comments is being prepared.

**Streamlining Grant Management.** NIH constantly strives to make the process of receiving and reviewing grants more efficient. To understand the importance of this streamlining, consider the fact that NIH receives nearly 80,000 applications per year. Moving from a paper-based to an electronic submission process is central to the streamlining effort. NIH recently passed the mark at which over 75 percent of all grant applications are submitted electronically, via the Web portal of Grants.gov. Simultaneously, NIH is phasing out the Public Health Service grant application form and replacing it with a federal-wide application. This represents a significant reduction in burden for applicants who otherwise have to contend with a variety of forms and information requirements depending on the agency to which they apply. The advent of electronic receipt of grant applications has improved the clarity of application materials delivered to reviewers. It also will enable the use of artificial intelligence software to automate referral to NIH Institutes and review committees. The expanded use of Internet Assisted Review allows reviewers to electronically submit critiques and initial priority scores before review meetings as a means of

streamlining the review as well as shortening review meetings. These changes will make the review process more effective and less onerous and eventually will lead to a reduction in the time from receipt to award.

The “[NIH Guide for Grants and Contracts](#)” is NIH’s primary means of communication with the extramural community. The “Guide” publicizes policy changes, research solicitations, and other notices. Because many funding announcements are trans-NIH solicitations, drafting announcements can involve considerable collaboration. NIH is in the process of developing an Automated Guide System to serve as a document/content management system in support of the “Guide” publication process. This solution will supplant the current manual process of collaboration and review that goes into publishing funding announcements. The management system will facilitate communications and the exchange of data between and among ICs and within the Office of the Director. It also will provide a more efficient and cost-effective means of publishing NIH funding opportunity announcements. A pilot of the system was launched during summer 2007 and a final application will be released in spring 2008.

A first-ever NIH Division of Extramural Activities Support (DEAS) started operations in October 2004. This new organization—the largest A-76 activity at NIH—provides support services for grants management, peer review, and scientific program management functions. The reorganization of extramural support services into DEAS represents a major change in NIH business practices, from a decentralized operation to a centrally managed unit using standardized operating procedures. Experience with the new organization demonstrated that improvements are needed in its efficiency and effectiveness to best meet IC needs. NIH reengineered the organization to better align staff skills with required responsibilities, be more cost-effective, enable DEAS staff to achieve career growth, and foster better working relationships between DEAS and its IC customers. A new organizational structure was implemented in September 2007.

## **Ensuring Responsible Research**

NIH is committed to promoting scientific progress in a transparent and responsible manner. Several OD offices have, or share, responsibility for the development and implementation of policies and procedures to ensure that research is conducted safely, ethically, and securely.

**Biotechnology Activities.** The [Office of Biotechnology Activities](#) (OBA) within the OD Office of Science Policy continually monitors scientific research and progress in the areas of recombinant DNA and genetics technologies in order to anticipate future developments, including potential ethical, legal, and social concerns. In accord with these responsibilities, OBA manages the operation of, and provides analytical support to, the NIH Recombinant DNA Advisory Committee (RAC) and the HHS Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). OBA also manages the National Science Advisory Board for Biosecurity, which is addressed in Chapter 2 in the section on Infectious Diseases and Biodefense, and the NIH/FDA Genetic Modification Clinical Research Information System (GeMCRIS), a comprehensive information resource and analytical tool for scientists, research subjects, sponsors, institutional oversight committees, Federal officials, and others with an interest in human gene transfer research.

[RAC](#) reviews all proposals for human, gene-transfer clinical research (often referred to as “gene therapy”) at institutions receiving NIH funds for recombinant DNA research. RAC review occurs before biosafety review at the institution where the research will be conducted. This enables RAC review to inform local review. As a Federal advisory committee, RAC issues recommendations to the NIH Director. RAC proceedings and reports are posted to the OBA Web site to enhance their accessibility to the scientific and lay publics. As new issues are identified, RAC helps NIH develop safety symposia and policy conferences to engage the scientific and public communities in thoughtful dialogue regarding developing issues and concerns. RAC has been a vital national forum promoting critically important scientific progress in a transparent, responsible, and safe manner and enhancing public trust in the science.

SACGHS provides policy advice to the Secretary, HHS, on the broad array of complex medical, ethical, legal, and social issues raised by the development and use of genetic technologies. In 2006, SACGHS began an in-depth fact-finding process on the U.S. system of oversight of genetic testing. The Secretary’s charge for this inquiry is to undertake the development of a comprehensive map of the steps needed for evidence development and oversight for genetic and genomic tests, with improvement of health quality as the primary goal. In November 2007, SACGHS issued a [draft report for public comment](#).

***Human Subjects Protections in Research.*** The HHS [Office for Human Research Protections \(OHRP\)](#) implements the Federal regulations governing the protection of human subjects [45 CFR 46](#) for all HHS agencies, including NIH. OHRP is responsible for (1) negotiating assurances with each institution that conducts HHS-sponsored human subjects research, (2) registering local Institutional Review Boards (IRBs), which assess risk, benefit, and many other matters with respect to proposed and ongoing studies involving human subjects, (3) issuing policy and guidance that clarifies the regulations, and (4) providing educational materials and programs for investigators and IRBs, and overseeing compliance. Because of the clinical research conducted in the NIH intramural program, NIH itself has an assurance with OHRP.

Although 45 CFR 46 is called the “Common Rule” and some 17 Federal agencies, including the National Science Foundation, Department of Defense, and Department of Veterans Affairs are governed by the rule, implementation policies vary and parallel regulations, e.g., for FDA, compound the differences in agency human subject protection practices. In fact, variability exists even across NIH ICs. Recognizing that this variability can hamper the efficiency and effectiveness of the clinical research system (because it requires the research community to understand and fulfill multiple requirements that may be redundant or even conflicting), NIH created a Clinical Research Policy Analysis and Coordination (CRpac) Program to serve as a focal point for harmonizing, streamlining, and optimizing human subjects protection policies and requirements. Launched as an NIH Roadmap initiative, CRpac aims to develop clear, effective, and coordinated rules for clinical research to achieve maximally effective human subjects protections. High on CRpac’s list of problems to tackle is the variation in requirements for reporting adverse events. (An adverse event is an unfavorable medical occurrence associated with the subject’s participation in the research). Investigators and IRBs face multiple requirements regarding the content, format, and timing of adverse event reports that must be made to different agencies and oversight bodies. Working closely with the preexisting Federal Adverse Event Task Force (FAET), CRpac gathered and analyzed adverse event terms,

definitions, and rules contained in a wide array of regulations, policies, and guidance documents across many agencies; documented the workflow for reviewing and using adverse event information; and developed a draft Basal Adverse Event Report (BAER)—a single core report that PIs could send to multiple agencies for consideration. In addition, CRpac formed a Trans-NIH Adverse Event Steering Committee to analyze NIH-specific needs and requirements for adverse event information and propose ways to coordinate and streamline the reporting policies of the ICs. In addition, to launch a dialogue on the characteristics and relative benefits of various models of IRB review, in November 2006, CRpac helped sponsor a National Conference on Alternative IRB Models.

The [Office of Human Subjects Research](#) in the NIH OIR manages human subject protection activities in the intramural program. Functioning under the assurance NIH filed with OHRP, and in cooperation with the ICs, the Office implements [NIH policy](#), establishes and maintains the 14 NIH IRBs, and provides training for researchers and IRB members. In addition, the Office manages the Human Subjects Research Advisory Committee, which advises the Deputy Director for Intramural Research—who is the Institutional Official responsible for human subjects investigations at NIH—on policies and procedures regarding the conduct of human subject research.

Within the NIH Clinical Center, the site of most NIH intramural human subjects research, the [Department of Bioethics](#) provides a center for research, training, and service related to bioethical issues. The Department conducts conceptual, empirical, and policy-related research into bioethical issues; offers comprehensive training and educational programs in bioethics; provides ethics consultation services to clinicians, patients, and families; and is available as a source of advice to the NIH IRBs.

***Animal Care and Use in Research.*** The [Office of Laboratory Animal Welfare \(OLAW\)](#) in the Office of Extramural Research (OER) oversees the use of animals in Public Health Service (PHS)-supported biomedical and behavioral research. OLAW provides guidance and interpretation of the *PHS Policy on Humane Care and Use of Laboratory Animals* ([PHS Policy](#)), monitors compliance with the *PHS Policy*, and supports educational programs that further the humane care and use of research animal subjects. As a condition of receiving PHS support for research involving laboratory animals, institutions must provide a written Animal Welfare Assurance (Assurance) to OLAW describing in detail the means they will use to comply with the *PHS Policy* and Federal statutes and regulations relating to animals. OLAW negotiates and approves these Assurances as required by HHS acquisition regulations and the *PHS Policy*. The assurance commits the institution and its personnel to full compliance with the PHS policy. OLAW holds accountable and depends upon institutional officials, Institutional Animal Care and Use Committees, research investigators, and other agents of the institution to ensure conformance with the institution's Assurance. This includes evaluating all allegations or indications of noncompliance with Federal animal welfare requirements.

OLAW maintains a comprehensive Web site with links to relevant laws, policies and guidance, an online tutorial, and a variety of other training materials and resources regarding laboratory animal welfare. In 2006, when OLAW published "[What Investigators Need to Know About the Use of Animals](#)," it added a significant new brochure to the materials it offers. Humane care and

use of animal subjects in biomedical and behavioral research is monitored by several Federal agencies and regulated by numerous guidelines and regulations. The brochure provides a complete, concise overview of all the regulations that apply to PHS-funded investigators. Response to the brochure from the research community has been overwhelmingly positive and OLAW has distributed more than 60,000 copies.

A new source of information on the need for animals in research is in development by NIH.<sup>10</sup> *Animals in Research* will be a Web-based resource for the public, grantee investigators and institutions, and NIH staff. The OER Web site will provide information on the critical role of this research for improving human and animal health, the latest breakthroughs in animal-based research, new funding opportunities, up-to-the-minute policy and training information, and guidelines for grantee institutions' emergency preparedness and crisis communication.

The [Office of Animal Care and Use](#) (OACU) in the NIH OIR administers the intramural program of animal care and use. OACU develops [guidelines and policies](#) for the responsible care of laboratory animals and the proper operation of NIH animal facilities and offers a variety of training courses and health and safety information for personnel who work with animals. Each NIH component that uses animals in research has an Animal Care and Use Committee that reviews and approves requests to use animals in research. In addition, each component's animal care and use program is directed by a senior veterinarian. An Animal Research Advisory Committee meets monthly to discuss trans-NIH topics and provide advice to the NIH Deputy Director for Intramural Research, who is the NIH institutional official accountable for animal care and use. All components of the intramural NIH animal care and use program are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

***Ethical Conduct.*** The fundamental Federal principles of ethical conduct hold that conscientious performance of duty is placed above private gain, that employees shall not have financial interests that conflict with that duty, and that employees will avoid any actions creating the appearance that they are violating the law or the standards of ethical conduct. It is the responsibility of every NIH employee to abide by the [statutes and regulations, including the supplemental standards of ethical conduct](#) for HHS employees, and the implementation policies and procedures of NIH. Significant ethics training resources at NIH help employees to meet that responsibility. The [NIH Ethics Program](#) consists of a central NIH Ethics Office located organizationally within the NIH OD and an ethics office in each IC, managed by a [Deputy Ethics Counselor](#) and an [Ethics Coordinator](#). Attorneys from the HHS Office of the General Counsel, Ethics Division, maintain an office at NIH to provide legal advice and assist IC ethics counselors and coordinators as needed.

The Ethics in Government Act (5 U.S.C. App.) requires each agency to provide an initial ethics orientation to new employees. NIH provides a Web-based training system for completing this requirement and the mandatory annual training. Also, NIH ethics staff is readily available to answer questions and provide ethics and conflict-of-interest counsel, as needed, and the central Ethics Office provides extensive information and resources on its Web site.

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<sup>10</sup> When the *Animals in Research* Web site goes live in June 2008, the URL will be: <http://grants.nih.gov/grants/policy/air/index.htm>



Prudent stewardship of public funds requires that appropriate steps be taken to ensure objectivity in research and freedom from financial conflicts of interest. Therefore, each institution receiving NIH research funds must have written guidelines on the avoidance of conflicts of interest. These guidelines must cover financial interests, gifts, gratuities and favors, nepotism, and other areas such as political participation and bribery. They also must indicate how outside activities, relationships, and financial interests are reviewed by the responsible and objective institution official(s). Institutions that identify research investigator financial conflicts are required to report the conflicts to the NIH Grants Management Officer at the funding IC.

The most recent edition of the “[Guidelines for the Conduct of Research](#) (2007)” sets forth the general principles governing the conduct of good science as practiced in the NIH IRP, including the responsibilities of research staff in the collection and recording of data, publication practices, authorship determination, mentoring, peer review, confidentiality of information, collaborations, human subjects research, financial conflicts of interest, and animal care and use.

NIH also has established [conflict of interest, confidentiality and nondisclosure rules](#) for reviewers of grant applications and R&D contract proposals. The [rules](#) require reviewers to identify and certify real or apparent conflicts of interest both pre- and post-meeting. Employment, financial benefit, personal relationships, professional relationships, or other interests may be a basis for a conflict of interest, and any one condition may serve to disqualify a reviewer from participating in the review of an application or proposal.

Conflicts of interest are especially problematic in clinical research. For that reason, the [HHS Office for Human Research Protections](#) issued specific guidance on “[Financial Relationships and Interests in Research Involving Human Subjects](#).” Moreover, in February 2007, NIH updated its “[Guide to Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH](#).” The Guide, directed at the intramural community, aims to ensure both the integrity of research and the safety of subjects in the intramural program.



## Chapter 2

# Summary of Research Activities by Disease Categories

## CANCER

*By the late 1970s, it was well known that genes from viruses could rapidly transform normal cells into cancer cells and that the viruses acquired these genes from the genomes of the animals and birds that they infected. In 1982, three separate laboratories all cloned the first human cancer-causing gene, called an “oncogene.” This discovery was the result of the laborious process of testing increasingly smaller pieces of DNA from a cancer cell for the ability to cause cancer. Subsequent studies confirmed that the oncogene was a version of a gene called ras, which had been incorporated into the mouse genome from a mouse virus. The ras gene in the mouse virus had a single genetic change that caused it to induce uncontrolled growth that resulted in cancer. This elegant work confirmed what had previously been just a notion—that cancer was a disease of altered genes. This finding began the era of modern molecular cancer research and treatment.<sup>1</sup>*

### Introduction

Cells are the building blocks of all living things. Normal cells multiply in an orderly way and die when no longer needed. Cancer can be described as uncontrolled growth of abnormal cells from almost any organ or tissue within the body. The process that leads to cell death is often blocked in cancer cells. Cancer cells can invade nearby tissues and spread to other parts of the body. Because it takes so many forms and occurs in so many parts of the body, cancer should be thought of not as a single disease but as a complex set of diseases that must be studied from multiple perspectives.

The National Institutes of Health’s (NIH’s) strategic approach to cancer research focuses on understanding the causes and mechanisms of cancer; accelerating progress in cancer prevention; improving early detection and diagnosis; developing effective and efficient treatments; understanding factors that influence cancer outcomes; improving the quality of cancer care; improving the quality of life for cancer patients, survivors, and their families; and overcoming cancer health disparities.

NIH also coordinates transdisciplinary translational research designed to realize a vision of personalized medicine. As this vision evolves, doctors will be able to use detailed information about an individual’s tumor and employ molecular and clinical data to guide the selection of therapies or preventive measures that are most likely to be safe and effective for that person. Personalized medicine promises to improve quality of life for cancer survivors, minimize adverse side effects of therapy, and reduce disparities among populations currently experiencing an excess burden of cancer.

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<sup>1</sup> For more information, see <http://www.nature.com/milestones/milecancer/full/milecancer17.html>



Several examples illustrate the types of research advances and promising new initiatives achieved by NIH scientists and grantees. For example, Gardasil<sup>®</sup>, the first vaccine to prevent cervical cancer induced by human papillomavirus (HPV), has the potential to save over 200,000 women's lives worldwide each year, including 5,000 U.S. women's lives. In another example, using whole-genome scans, the [Cancer Genetic Markers of Susceptibility](#) project has pinpointed common genetic variants associated with increased risk of breast and prostate cancers. In addition, the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences (NIEHS) have launched the [Breast Cancer and Environment Research Centers](#) to study the impact of prenatal-to-adult environmental exposures that may predispose a woman to breast cancer.

Cancer research is conducted by a number of NIH Institutes and Centers (ICs); most of the research investment is committed to NCI programs. NCI's two intramural divisions conduct basic, translational, clinical, and population research, making fundamental discoveries related to cancer causes and mechanisms, genetics, and host immunological and other responses to cancer and rapidly translating those findings into novel preventive and detection methods and therapies. Five NCI extramural divisions support research carried out at nearly 650 universities, hospitals, cancer centers, specialized networks and research consortia, and other sites throughout the United States and in more than 20 other countries. In addition, NCI provides infrastructure to help the greater cancer research community take advantage of the potential benefits of emerging technologies (e.g., genomics, proteomics, bioinformatics, and molecular imaging).

Cancer research conducted or supported by other NIH ICs is wide ranging and often is coordinated with NCI programs and grantees—for example, the [Surveillance, Epidemiology, and End Results](#) (SEER) program (a source of information on cancer incidence and survival in the United States) and the nationwide network of NCI-funded Comprehensive Cancer Centers. Examples of cancer research within other ICs include:

- National Institute on Aging (NIA) research on prostate and skin cancers and the biology of aging as it relates to cancer
- NIEHS research on the effects of biological, chemical, or physical agents on human health
- National Heart, Lung, and Blood Institute (NHLBI) research on blood-related cancers and support for breast, colorectal, and reproductive cancer as the administrative coordinator of the NIH [Women's Health Initiative](#)
- National Institute of Dental and Craniofacial Research (NIDCR) research on head and neck cancers
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) research on liver, prostate, kidney, colorectal, and bladder cancers
- National Institute of Allergy and Infectious Diseases (NIAID) technology development in support of cancer research, diagnosis, and therapy and studies of the role of viruses in cancer
- National Institute of Neurological Disorders and Stroke (NINDS) research on brain, spinal cord, and pituitary cancers
- National Institute of Nursing Research (NINR) HIV/AIDS and Oncology program

- National Institute of Child Health and Human Development (NICHD) research on breast and reproductive cancers
- National Institute of General Medical Sciences (NIGMS) cancer-related basic biomedical research
- National Institute of Biomedical Imaging and Bioengineering (NIBIB) imaging and bioinformatics technology development in areas that are vital to cancer research
- National Institute on Drug Abuse (NIDA) research on treatments for tobacco addiction serving as cancer prevention

## Burden of Illness and Related Health Statistics

Because cancer is the second leading cause of death in the United States and the economic cost of cancer in 2005 was estimated at over \$200 billion (including \$74 billion in direct health care costs and over \$135 billion in indirect costs associated with lost productivity due to illness and premature death), cancer research is a major NIH priority.<sup>2</sup> Although significant progress has been made toward reducing the burden of cancer in America, cancer remains a leading cause of death, second only to heart disease—one of every four deaths is due to cancer.<sup>3,4</sup> The American Cancer Society estimated that, in 2007, there were about 1,444,920 new diagnoses of invasive cancer and 564,830 Americans died of cancer.<sup>5</sup> Moreover, the World Cancer Report indicates that cancer rates are set to increase at an alarming rate globally – specifically, they could further increase by 50% to 15 million new cases in the year 2020.

One sign of progress is that U.S. death rates for the most common cancers and for all cancers combined have decreased significantly since 1995.<sup>6</sup> However, the annual number of cancer diagnoses is expected to almost double over the next 50 years, from 1.4 million to 2.6 million. Increasing numbers of Americans are surviving cancer. NIH estimated that, on January 1, 2003, 10.5 million living Americans had a history of invasive cancer.<sup>7</sup> These numbers are likely to increase because of the anticipated growth and aging of the U.S. population.<sup>8</sup>

The most common cause of cancer-related death in the United States is lung cancer. The three most common cancers among men are prostate cancer, lung cancer, and colon cancer. For women, the three most frequently occurring cancers are breast cancer, lung cancer, and colon cancer.<sup>9</sup>

Significant disparities in the U.S. burden of cancer have been documented through literature reviews, program reviews, and ongoing research. These disparities are discussed in the section “Minority Health and Health Disparities” later in this chapter.

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<sup>2</sup> For more information, see <http://obf.cancer.gov/financial/attachments/06Factbk.pdf>

<sup>3</sup> For more information, see <http://www.cancer.org>.

<sup>4</sup> CDC, 2004.

<sup>5</sup> American Cancer Society, 2005.

<sup>6</sup> NCI, 2006.

<sup>7</sup> For more information, see [http://seer.cancer.gov/csr/1975\\_2003](http://seer.cancer.gov/csr/1975_2003)

<sup>8</sup> Edwards BK, et al. *Cancer* 2002;94:2766-92, PMID: 12173348

<sup>9</sup> NCI, 2006.

## NIH Funding for Cancer Research

In fiscal years (FYs) 2006 and 2007, NIH funding for cancer research was \$5.575 billion and \$5.643 billion respectively. The table at the end of this chapter indicates some of the research areas involved in this investment (see “Estimates of Funding for Various Diseases, Conditions, and Research Areas”).

### Summary of NIH Activities

Across NIH, cancer research activities are focused on two overarching goals: preempting cancer at every opportunity and ensuring the best outcomes for all. Specific objectives related to these goals include:

Preempting cancer at every opportunity:

- Understanding the causes and mechanisms of cancer
- Accelerating progress in cancer prevention
- Improving early detection and diagnosis
- Developing effective and efficient treatments

Ensuring the best outcomes for all:

- Understanding the factors that influence cancer outcomes
- Improving the quality of cancer care
- Improving quality of life for cancer patients, survivors, and their families
- Overcoming disparities in cancer prevention, diagnosis, treatment, and outcomes

NIH is also exploiting the potential of emerging technologies (e.g., molecular imaging, nanotechnology, and bioinformatics) in cancer research and care and is building the research infrastructure needed to expand knowledge and put new insights into practice.

## Preempting Cancer at Every Opportunity

### *Understanding the Causes and Mechanisms of Cancer*

Research that improves our understanding of the causes and mechanisms of cancer—from identifying novel risk factors to elucidating the processes of metastasis (the spread of cancer from the primary tumor site)—is essential to our ability to develop and apply interventions to preempt cancer’s initiation and progression. NIH’s plan for deciphering the causes and mechanisms of cancer includes studies in molecular epidemiology to define complex risk factors, research on the tumor macroenvironment and microenvironment, understanding the role of altered gene expression in cancer progression and exploring the roles of susceptibility genes in cancer risk and initiation.

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A primary challenge for NIH is dissecting the molecular basis of cancer. [The Cancer Genome Atlas](#) (TCGA) is developing a comprehensive catalogue of the genetic changes that occur in cancers. The genomic information generated by TCGA could fuel rapid advances in cancer research and suggest new therapeutic targets. It could also suggest new ways to categorize tumors, which might allow clinical trials to focus on those patients who are most likely to respond to specific treatments. **The Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments (TARGET)** initiative identifies and validates therapeutic targets for childhood cancers beginning with acute lymphoblastic leukemia and neuroblastoma.

Genetic susceptibility to cancer and cancer risk associated with environmental exposures are also important research topics. Using powerful new technologies to scan the entire human genome, NIH is conducting genome-wide association studies to identify unsuspected genetic variants associated with cancer risk. The [Cancer Genetic Markers of Susceptibility](#) (CGEMS) project, for example, is designed to identify genes that increase the risk of breast and prostate cancers. Similar efforts are directed at cancers of the pancreas, bladder, lung, and other organs. The results of these genome-wide studies promise to provide novel strategies for cancer detection, prevention, and treatment.

Another major NIH initiative is the [Sister Study](#), which is investigating environmental and genetic risk factors for breast cancer. This study involves a cohort of 50,000 sisters of women who have had breast cancer. These unaffected sisters are being followed over time, with periodic health updates. The women who develop breast cancer during the follow-up period will be compared with those who remained healthy to identify factors associated with increased cancer risk. NIH is also supporting a network of [Breast Cancer and Environment Research Centers](#) (BCERCs) to study the impact of prenatal to adult environmental exposures that may predispose a woman to breast cancer. One of the goals of the BCERCs is to develop public health messages to educate young girls and women who are at high risk of breast cancer about the role of specific environmental stressors in breast cancer and how to reduce exposures to those stressors.

Other research into the causes and mechanisms of cancer has revealed that tumors function like organs, comprising many interdependent cell types that contribute to tumor development and progression. The relationship between tumors and their surrounding cellular environment evolves over time, strongly influencing tumor progression, metastatic potential, and responsiveness to treatment. The [Tumor Microenvironment Network](#) is a new NIH program focused on expanding our understanding of the role of the microenvironment in which a tumor originates and the critical role it plays during tumor development, progression, and metastasis.

Furthermore, interest is growing in the scientific community about the relationship between inflammation and cancer. NIH is actively pursuing research on the linkages between carcinogenesis and alterations in the microenvironment induced by inflammation. Inflammation is a response to acute tissue damage, whether resulting from physical injury, infection, exposure to toxins, or other types of trauma. Current research on inflammation suggests that pro-inflammatory conditions contribute to the development of several types of cancer, including lung, stomach, and liver cancers, and may lead to new treatment approaches.

Another area of research focus at NIH is the interface between aging and cancer. As part of an interagency collaborative effort, eight NCI-designated Cancer Centers are conducting [studies on the biology of aging and cancer](#) and addressing questions related to cancer prevention, treatment, and survivorship in older patients. This research will help provide insights into why cancer occurs more frequently in older people, whether cancer behaves differently in older adults than in younger people, whether older patients respond differently to treatment, and how prevention and screening services should be adapted for this population.

Angiogenesis—the growth of new blood vessels—is required at a certain point for tumors to continue to grow beyond a size at which they begin to need their own blood supply. Thus, blockade of angiogenesis can prevent tumor growth. The NIH [Trans-Institute Angiogenesis Research Program](#) funds promising angiogenesis research. The program’s multidisciplinary approach fosters data exchange and resource sharing among vascular biology and angiogenesis researchers from different disease disciplines. A number of new angiogenesis inhibitors are currently being developed, including several in late-stage clinical trials.

Systems biology and systems genetics are also promising new fields of study that will increase our understanding of the causes and mechanisms of cancer. These disciplines focus on biological and genetic networks that can be measured, modeled, and manipulated rather than focusing on the individual components. Because this research requires multidisciplinary teams of experts in biology, medicine, engineering, mathematics, and computer science, NIH launched the [Integrative Cancer Biology Program](#) (ICBP) to develop a framework for these activities. The ICBP has funded nine integrative biology centers around the United States to provide the nucleus for the design and validation of computational and mathematical models of cancer. Networks of genes can be found and their associations with cancer tested and quantified, and parallel association studies can be conducted in relevant human populations.

NIH is expanding its research portfolio related to the [basic biology of tumor stem cells](#) (also referred to as tumor-initiating cells). Tumor stem cells may be responsible for the recurrence of malignancy in some cancers. These cells are often resistant to standard chemotherapeutic agents but may contain unique target molecules that may allow their eradication with novel molecular therapeutics. Progress has been made in identifying tumor stem cells in multiple myeloma, acute myelogenous leukemia, and breast cancer.

### ***Accelerating Progress in Cancer Prevention***

Current research efforts into preventing cancer focus on modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting the cancer process through early medical intervention. Dramatic developments in technology and a more complete understanding of the causes and mechanisms of cancer will enable us to provide more effective ways to prevent the disease. Identifying critical molecular pathways in precancerous lesions will provide new drug targets for preempting cancer. Transdisciplinary research will provide a more complete understanding of the interplay of molecular, behavioral, genetic, and other factors that contribute to cancer susceptibility.

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A major step forward in our efforts to prevent cancer has been the development of vaccines that target [HPV](#). Persistent infection with HPV is recognized as the major cause of cervical cancer. Gardasil<sup>®</sup>, a U.S. Food and Drug Administration (FDA)-approved vaccine against HPV types 6, 11, 16, and 18—the viral types that cause approximately 70 percent of cervical cancers and 90 percent of genital warts—is now available. Other similar vaccines against HPV types 16 and 18 and/or additional subtypes are in development. These vaccines have the potential to save thousands of women’s lives annually in the United States and several hundred thousand more each year worldwide. All of these vaccines resulted directly from epidemiological, basic, and preclinical research discoveries, as well as the development of a prototype HPV vaccine, by NIH scientists.

Another area of focus in cancer prevention is cancer’s relationship with diet and obesity. In its [2006-2007 Annual Report](#), the President’s Cancer Panel cites evidence that as many as one-third of the nearly 600,000 yearly cancer deaths in the United States can be attributed to unhealthy diets and obesity. In an effort to reduce the cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet, NIH has funded the [Transdisciplinary Research on Energetics and Cancer](#) (TREC) research centers, which foster collaboration among transdisciplinary teams of scientists. The TREC research centers are studying factors that lead to obesity and the mechanisms by which obesity increases the risk of cancer. The TREC initiative is connecting with a number of established initiatives in the area of diet, physical activity, and weight and is integrated with the NIH Obesity Research Task Force Strategic Plan.

Because most cases of lung cancer are caused by tobacco use and are, therefore, preventable, multiple NIH Institutes have co-funded seven [Transdisciplinary Tobacco Use Research Centers](#) (TTURCs), which seek to identify familial, early childhood, and lifetime psychosocial pathways associated with smoking initiation, use, cessation, and patterns of dependence. Research on the genetics of addiction, physiological biomarkers, and advanced imaging techniques should allow the development of individualized and community approaches to the prevention and treatment of tobacco-related diseases. The TTURC model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships.

We now know that the environment and behavioral lifestyles can play a critical role in the development of cancer. In fact, it was this discovery that led to a public health success story in the 20th century—the reduction in tobacco use and related diseases. By the mid-1950s, the mysterious and alarming epidemic in lung cancer, a disease that was almost nonexistent in 1900, was linked to smoking behavior. In the last decade, overall cancer death rates have dropped for the first time in a century, driven largely by the dramatic reduction in male smoking from 47 percent in the 1960s to less than 23 percent today. About 40 percent of this drop in overall cancer rates has been credited to the dramatic reduction in male smoking and male lung cancer deaths since 1991 (more than 146,000 fewer deaths during 1991 to 2003 alone). This success has been due to public-private partnerships and is also a trans-DHHS victory, as significant research investments have been made over the last 50 years by NCI, NHLBI, NIDA, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the John E. Fogarty International Center (FIC), the Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ). Without these investments, 40 million Americans might still be smoking



today, hundreds of thousands of them would have died prematurely of a tobacco-related disease, and billions of dollars would have been spent on their treatment.<sup>10</sup>

The NIH-supported [Community Clinical Oncology Program](#) (CCOP) provides a network for greater participation in clinical trials on cancer prevention and treatment. Over the past 23 years, more than 200,000 people have enrolled in clinical trials involving CCOP investigators and institutions. One example is the [Study of Tamoxifen and Raloxifene](#) (STAR), which compared the drug raloxifene with the drug tamoxifen in reducing invasive breast cancer in high-risk postmenopausal women. The initial results from STAR indicate that raloxifene is as effective as tamoxifen with fewer side effects. The FDA Oncology Drug Advisory Committee has recommended approval of raloxifene for breast cancer prevention.

### ***Improving Early Detection and Diagnosis***

Detecting and diagnosing tumors early in the disease process, before the tumor becomes invasive and metastatic, can dramatically improve a patient's odds for successful treatment and survival and prevent a large proportion of cancer deaths. Therefore, NIH seeks to accelerate the translation of basic research findings into sophisticated, minimally invasive procedures that harness imaging, genomic, proteomic, nanotechnology, and other advanced early-detection and diagnostic techniques.

One NIH effort in the area of early detection is the [National Lung Screening Trial](#) (NLST), which is comparing two ways of detecting lung cancer—spiral computed tomography (CT) scans and standard chest X-rays. This study aims to answer the important question whether deaths from lung cancer can be reduced through the use of CT screening. Research has shown that spiral CT is capable of detecting not only smaller lung abnormalities, but also more lung cancers than chest x-ray. However, most of the lung abnormalities seen on screening spiral CTs are not cancer. Moreover, it is not known if finding these lung abnormalities will actually benefit people by lowering deaths from lung cancer. NLST is designed to scientifically answer the question of which screening test will better reduce lung cancer deaths and make meaningful recommendations for public policy.

Molecular profiling is an ongoing effort at NIH, from work at the bench to larger initiatives. In the area of molecular diagnostics, NIH has formed the [Early Detection Research Network](#) to bring a collaborative approach to the discovery, development, and validation of early-detection biomarkers for clinical application. Another NIH program, the [Strategic Partnering to Evaluate Cancer Signatures](#) program, focuses on confirming, evaluating, and refining “signatures” derived from the molecular analysis of tumors (i.e., biomarkers detection) to improve patient management and outcomes. In addition, the [Cancer Genome Anatomy Project](#) (CGAP) focuses on determining the gene expression profiles of normal, precancerous, and cancerous cells to improve detection, diagnosis, and treatment. The CGAP Web site makes tools for genomic analysis available to researchers worldwide.

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<sup>10</sup>[Thun, M.J., Jemal, A. \*Tobacco Control\* 2006;15:345-7](#), PMID: 16998161

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Yet another area of research that holds promise for advancing molecular diagnostics is proteomics—the study of complex arrays of proteins produced by cells and tissues. The completion of the Human Genome Project in 2003 has been a major catalyst for proteomics research, and NIH has taken a leading role in facilitating the translation of proteomics from laboratory research to clinical application through its [Clinical Proteomic Technologies Initiative for Cancer](#). The overall objective of this initiative is to build the foundation of technologies (assessment, optimization, and development), data, reagents and reference materials, computational analysis tools, and the infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate basic science research and the development of clinical applications.

The first product of an NIH-funded research project to integrate new technologies into a reliable clinical protocol to improve oral cancer detection has reached the market. Researchers report success using a customized optical device that allows dentists to visualize in a completely new way whether a patient might have a developing oral cancer. Deviations from the natural fluorescence of healthy tissue may indicate the presence of developing tumor cells. Health care providers can shine a light onto a suspicious sore in the mouth, look through an attached eyepiece, and check for changes in color. The instrument is an effective aid in screening and can guide surgeons when removing tissue for biopsies.

### ***Developing Effective and Efficient Treatments***

Developing more effective, more efficient, and less toxic cancer treatments is at the heart of the NIH cancer research agenda. A strong understanding of the fundamental mechanisms leading to cancer development, progression, and metastasis will dramatically improve our ability to identify key biochemical pathways in the disease process as targets for treatment. Acceleration of target validation and the development of new treatment modalities will be possible through recent advances in biomedical science and technology. Rapid translation from development to delivery will ensure that promising treatments move safely and efficiently from preclinical investigation through late-stage clinical trials and into clinical practice. NIH is taking a multipronged approach to developing new therapies for cancer.

One innovative initiative, the [NCI Experimental Therapeutics Program](#) (NExT), safely shortens the timeline for moving anticancer drugs from the laboratory to the clinic by combining NIH expertise in drug development with state-of-the-art research facilities. This program takes advantage of new FDA guidelines that allow human trials, referred to as “Phase 0” or “Early Phase I” trials, to proceed before traditional, expensive, time-consuming drug development steps have occurred. The first Phase 0 study has been successfully completed, demonstrating that this new approach can reduce the number of patients required for an early clinical study and shorten the time necessary to gather critical drug development information.

Another NIH program, the [Cancer Imaging Program](#) (CIP), supports cancer-related basic, translational, and clinical research in imaging sciences. CIP initiatives include the development and delivery of image-dependent interventions for malignant and premalignant conditions; standardized models for the design of clinical trials that use imaging technologies; development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput



screening; and development of imaging methods for cancer detection and treatment and for monitoring responses to therapy.

In addition, NIH's Radiation Research Program (RRP) evaluates the effectiveness of radiation research conducted by grantees. The RRP coordinates its activities with other radiation research programs at NIH, other Federal agencies, and national and international research organizations. Currently, major clinical trials are evaluating radiation therapy dose escalation, as well as novel combinations of chemotherapy with concomitant boost radiation therapy, in non-small cell lung cancer (NSCLC).

Marshalling the exquisite specificity of the immune system to selectively target cancer cells without harming normal cells is another focus of cancer treatment research at NIH. The [Cancer Vaccine and Immunotherapy Program](#) is evaluating therapeutic cancer vaccines aimed at antigens that are unique to or overexpressed by cancer cells. Other approaches under evaluation include immunotherapy with T lymphocytes that specifically kill cancer cells, monoclonal antibodies and immunotoxins that target cancer cells, and the use of cytokines that boost the body's ability to fight cancer. These approaches may be used in combination with conventional treatments for cancer, such as chemotherapy and radiotherapy.

NIH launched the [Comparative Oncology Program](#) (COP) in an effort to improve the translational research process. Its mission was to provide an integrated mechanism by which naturally occurring cancers in pet dogs could be used to generate new information about cancer, translate biological concepts towards clinical application, and bring novel therapeutic options to the management of human cancers. As part of this effort, COP has established a multi-center collaborative network of extramural comparative oncology programs that have completed three clinical trials this year and plans to initiate five additional trials.

## **Ensuring the Best Outcomes for All**

Research on the quality of cancer care is essential to ensuring the best outcomes for all who may be affected by cancer. Research in this area can include surveillance as well as epidemiological and cost-effectiveness studies. In addition, quality-of-life research increases our understanding of the impact of cancer on patients, survivors, and their family members—many of whom are themselves at increased risk for cancer due to shared cancer-causing genes, life styles, or environmental exposures. Dissemination research helps ensure that the knowledge gained through NIH-supported research is appropriately and effectively communicated to health care providers, policymakers, and the public. An additional goal related to ensuring the best outcomes for all—overcoming health disparities in cancer incidence and outcomes—is described in a later section of this chapter (see “Minority Health and Health Disparities”).

NIH is currently engaged in making cancer a working model for quality-of-care research and the translation of the findings of this research into practice. To this end, several collaborative projects have been initiated: (1) an interagency working committee, [The Quality of Cancer Care Committee](#), which has fostered collaborative projects directly involving the Health Resources

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and Services Administration, the Centers for Medicare and Medicaid Services, and the Department of Veterans Affairs; (2) the National Quality Forum, a major public-private partnership, to identify core measures of cancer care quality; (3) research on outcomes measurement by the Cancer Outcomes Measurement Working Group and the [Cancer Care Outcomes Research and Surveillance Consortium](#); (4) studies on improving the quality of cancer communications; and (5) research to monitor patterns of treatment dissemination and quality of care through [Patterns of Care/Quality of Care Studies](#), the [Prostate Cancer Outcomes Study](#), and studies utilizing the [SEER-Medicare Database](#). In addition, the [NCI Community Cancer Centers Program](#) (NCCCP) is researching how best to bring effective cancer treatments to patients in the communities where they live.

The population of cancer patients surviving more than 5 years continues to grow. NIH continues to support research and education aimed at professionals who deal with cancer patients and survivors. NIH cancer survivorship research addresses the physical, psychosocial, and economic impacts of cancer diagnosis and its treatment and the need for interventions to promote positive outcomes in survivors and their families. Important early findings suggest long latencies for treatment-related effects, highlighting the need for extended follow up, early identification, and intervention before complications become more serious.

To improve the outcomes of cancer patients, advances in knowledge must be effectively disseminated to the public and to health care providers. The [Cancer Control P.L.A.N.E.T.](#) Web portal is a collaborative effort aimed at providing access to data and resources that can help cancer control planners, health educators, program staff, and researchers design, implement, and evaluate evidence-based cancer control programs. P.L.A.N.E.T. assists local programs with resources that help them determine cancer risk and the cancer burden within their State and helps States identify potential partners. P.L.A.N.E.T. also provides online resources for interpreting research findings and recommendations and for accessing products and guidelines for planning and evaluation.

## Infrastructure for Research

NIH places a high priority on technology development (see the section “Technology Development” in this chapter) to support both research and the application of research findings to improve health care delivery, emphasizing the areas of bioinformatics, cancer imaging, proteomics, and nanotechnology. As NIH-supported scientists begin to apply new discoveries to cancer prevention, early detection, and treatment, it will be increasingly important to integrate the tools and insights of research, science, and technology as effectively as possible.

The [Cancer Biomedical Informatics Grid<sup>TM</sup>](#) (caBIG<sup>TM</sup>) is an important initiative that has been launched to accelerate research discoveries and improve patient outcomes by supporting the sharing of data and tools among researchers, physicians, and patients throughout the cancer community. NIH is committed to bringing caBIG<sup>TM</sup> into an enterprise model that can be extended and sustained across a broader community.

Another initiative, the [NCI Alliance for Nanotechnology in Cancer](#), is a comprehensive endeavor that involves both the public and the private sectors and is designed to accelerate the application

of the best capabilities of nanotechnology to cancer research. This initiative supports research on novel nanodevices to detect and pinpoint the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real time whether these drugs are effective in killing those cells.

Given the global burden of cancer and opportunities to identify new approaches in prevention and treatment through international collaborative research, NIH is strengthening health research infrastructure and building global research capacity through the International Tobacco and Health Research and Capacity Building Program. This program promotes transdisciplinary approaches to reduce the global burden of tobacco-related illness and is designed to promote international cooperation between U.S. investigators and scientists in low- and middle-income nations where tobacco consumption is a current or anticipated public health urgency. Because the overwhelming majority of smokers begin tobacco use before they reach adulthood, the program emphasizes research on determinants of youth smoking in diverse cultural and economic settings, as well as effective ways to prevent young people from starting to smoke.

## Personalized Medicine

Advances in these critical aspects of cancer research are being synthesized into a vision of a future approach to health care called “personalized medicine,” which will enable clinicians to use detailed molecular and clinical information about an individual’s health to guide the selection of cancer therapies or preventive measures that are most likely to be safe and effective for that person. The NIH vision of personalized medicine spans the entire cancer continuum, from prevention through survivorship. Investments in risk assessment, treatment, and infrastructure development have already yielded progress toward reaching that vision. Potential benefits of personalized medicine include increased understanding of individual risk factors, earlier detection and more accurate diagnosis of cancer, more effective targeted treatment, increased likelihood of survival with improved quality of life, and implementation of high-quality, patient-centered cancer care through improved communication, informatics, and surveillance.

## Notable Examples of NIH Activity

### Key for Bulleted Items:

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

COE = Supported through a congressionally mandated **C**enter of **E**xcellence program

GPRA = Relates to progress toward a goal tracked under the **G**overnment **P**erformance and **R**esults **A**ct

## Initiatives and Major Programs

**Clinical Proteomic Technologies Initiative for Cancer:** The completion of the Human Genome Project in 2003 has been a major catalyst for proteomics research, and NIH has taken a leading role in facilitating the translation of proteomics from research to clinical application through its Clinical Proteomic Technologies Initiative for Cancer. The overall objective of this Initiative is to build the foundation of technologies (assessment, optimization, and development), data, reagents and reference materials, computational analysis tools, and the infrastructure

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needed to systematically advance our understanding of protein biology in cancer and accelerate discovery research and clinical applications.

- For more information, see <http://proteomics.cancer.gov>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E/I) (NCI)

**NCI Alliance for Nanotechnology in Cancer:** The NCI Alliance for Nanotechnology in Cancer is a comprehensive, systematized initiative that encompasses the public and private sectors and is designed to accelerate the application of the best capabilities of nanotechnology to cancer. The program supports research on novel nanodevices that may detect and pinpoint the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real time whether these drugs are effective in killing malignant cells. Nanotechnology is likely to change the very foundations of cancer diagnosis, treatment, and prevention.

- For more information, see <http://nano.cancer.gov>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*.
- (I/E) (NCI)

**Cancer Imaging Program (CIP):** The CIP's mission is to promote and support cancer-related basic, translational, and clinical research in the imaging sciences. CIP initiatives include (1) development and delivery of image-dependent interventions for cancer and pre-cancer; (2) development of standardized models for the design of clinical trials using imaging; (3) development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening; and (4) development of imaging methods to detect, treat, and monitor response to therapy.

- For more information, see <http://imaging.cancer.gov>
- This example also appears in Chapter 3: *Technology Development*.
- (I/E) (NCI)

**Clinical Trials Networks:** The Clinical Trials Networks are part of the infrastructure that allows patients and community physicians access to national studies, facilitating the ability to put successful regimens into practice:

- ▷ The Community Clinical Oncology Program (CCOP) is a network for conducting cancer prevention and treatment clinical trials. In 23 years of CCOPs, more than 200,000 people have enrolled in treatment and prevention trials. An example is the Study of Tamoxifen and Raloxifene (STAR), which compares the effectiveness of these two drugs for reducing the incidence of breast cancer in postmenopausal women at increased risk of the disease. Initial results indicate that raloxifene is as effective as tamoxifen with fewer side effects. (For more information, visit <http://www.cancer.gov/STAR> and <http://dcp.cancer.gov/programs-resources/programs/ccop>.)
- ▷ Cooperative Group Trials consist of researchers, Cancer Centers, and community doctors who investigate new cancer treatment, prevention, early detection, quality of life, and rehabilitation. They involve more than 1,700 institutions, thousands of individual

investigators, and more than 22,000 patients each year. These trials are testing therapies that demonstrate improvement to overall patient survival. For example, the Bevacizumab with Platin-Based Chemotherapy study showed that when the monoclonal antibody [bevacizumab](#) is added to a paclitaxel-carboplatin chemotherapy regimen for patients with NSCLC, their overall survival, progression-free survival, and response rates significantly increased. (For more information, visit <http://ctep.cancer.gov>.)

- ▷ The NCI Community Cancer Centers Program (NCCCP) is a 3-year pilot program to test the concept of a national network of community cancer centers to alleviate inadequate care delivery. NCCCP will develop and evaluate programs on community-based cancer care and identify ways to facilitate their broader engagement in cancer research. (For more information, visit <http://ncccp.cancer.gov>.)

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCI)

**Community Networks Program (CNP):** The CNP aims to reduce and eliminate cancer disparities among racial minorities through community-based research, education, and training. The goals of the program are to significantly improve access to and utilization of beneficial cancer interventions in communities with cancer disparities. A total of 25 projects across the United States and in American Samoa were launched in May 2005 to address cancer disparities among African Americans, American Indians/Alaska Natives, Hawaiian Natives and other Pacific Islanders, Asians, Hispanics/Latinos, and rural underserved populations. Ten grantees work in local areas, 10 in regional areas, and 5 in national programs. Visit: <http://crchd.cancer.gov/cnp/overview.html>.

- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCI)

**Genome-Wide Association Studies of Cancer Risk:** Beginning with the Cancer Genetic Markers of Susceptibility (CGEMS) initiative for breast and prostate cancer, NIH has capitalized on its long-term investment in intramural and extramural consortia by creating strategic partnerships to accelerate knowledge about the genetic and environmental components of cancer induction and progression. With powerful new technology capable of scanning the entire human genome, these efforts have recently identified unsuspected genetic variants associated with increased risk for developing cancers of the prostate, breast, and colon. Additional scans, either planned or under way, will be directed at cancers of the pancreas, bladder, lung, and other organs. The results of these genome-wide studies, together with the follow-on studies planned to narrow the search for causal gene variants, promise to provide novel clinical strategies for early detection, prevention, and therapy. To expand upon these emerging opportunities, a new Laboratory of Translational Genomics (LTG) has been established to further characterize genetic regions associated with cancer susceptibility and to identify gene-gene and gene-environment interactions. The LTG will create opportunities for collaboration and data sharing to accelerate the translation of genomic findings into clinical interventions.

- For more information, see <http://cgems.cancer.gov/>
- For more information, see <http://epi.grants.cancer.gov/BPC3/cohorts.html>
- For more information, see <http://epi.grants.cancer.gov/PanScan>

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- For more information, see <http://cgems.cancer.gov/index.asp>
  - This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*.
  - (E/I) (NCI)

**NCI Experimental Therapeutics Program (NExT):** The NExT program safely shortens the timeline for taking anticancer drugs from the laboratory to the clinic by combining NIH's expertise in drug development with state-of-the-art research facilities. The program also utilizes new FDA guidelines that allow early Phase I clinical trials to proceed before certain time-consuming and expensive drug development steps occur. The first such study passed the initial stage of clinical examination demonstrating that this new type of trial can reduce the number of patients required for an early clinical study and the time necessary to gather critical drug development information.

- For more information, see <http://dctd.cancer.gov/MajorInitiatives/02NExT.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E/I) (NCI)

**Systems Biology and Systems Genetics:** NIH launched the Integrative Cancer Biology Program to focus on networks that can be measured, modeled, and manipulated rather than individual components. Multidisciplinary teams are critical to integrating the disciplines of biology, medicine, engineering, math, and computer science (e.g., computational biology). Equally important to our understanding of cancer is systems genetic research (systems biology and genetics). Networks of genes can be found and their associations tested and quantified with parallel association studies on relevant human populations.

- For more information, see <http://icbp.nci.nih.gov>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NCI)

**The Cancer Biomedical Informatics Grid<sup>TM</sup>:** The Cancer Biomedical Informatics Grid<sup>TM</sup> (caBIG<sup>TM</sup>) initiative has been launched to accelerate research discoveries and improve patient outcomes by linking researchers, physicians, and patients throughout the cancer community. caBIG<sup>TM</sup> completed its 3-year pilot project in March 2007. This date represents a new phase of evolution, as NIH is committed to bringing caBIG<sup>TM</sup> into an enterprise model that can be extended and sustained across a broader community.

- For more information, see <http://cabig.cancer.gov>
- This example also appears in Chapter 3: *Technology Development*.
- (E/I) (NCI)

**The Sister Study:** The Sister Study is a major NIH initiative to study environmental and genetic risk factors for breast cancer in a cohort of 50,000 sisters of women who have had breast cancer. The asymptomatic women are being followed over time with periodic health updates. The

women who develop breast cancer during the follow-up period will be compared with those who remained healthy to identify factors associated with increased cancer risk.

- For more information, see <http://www.sisterstudy.org>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (NIEHS)

**The Cancer Genome Anatomy Project (CGAP):** The goal of CGAP is to determine the gene expression profiles of normal, precancer, and cancer cells to improve detection, diagnosis, and treatment for the patient. The CGAP Web site makes various tools for genomic analysis available to researchers. Through worldwide collaborations, CGAP seeks to increase its scientific expertise and expand its databases for the benefit of all cancer researchers.

- For more information, see <http://cgap.nci.nih.gov/>
- This example also appears in Chapter 3: *Genomics*.
- (E/I) (NCI)

**The Cancer Imaging Program (CIP):** The mission of CIP is to promote and support cancer-related basic, translational and clinical research in imaging sciences. CIP initiatives include: a) development and delivery of image-dependent interventions for cancer and pre-cancer; b) standardized models for the design of clinical trials using imaging; c) development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening; and d) development of imaging methods to detect, treat and monitor response to therapy.

- For more information, see <http://imaging.cancer.gov/>
- This example also appears in Chapter 3: *Technology Development*.
- (E/I) (NCI)

**The NCI Alliance for Nanotechnology in Cancer:** This is a comprehensive, systematized initiative encompassing the public and private sectors, designed to accelerate the application of the best capabilities of nanotechnology to cancer. The program supports research on novel nanodevices that may detect and pinpoint the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real-time if these drugs are effective in killing malignant cells. Nanotechnology will likely change the very foundations of cancer diagnosis, treatment and prevention.

- For more information, see <http://nano.cancer.gov/>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*.
- (E/I) (NCI)

**The Radiation Research Program (RRP):** The RRP establishes priorities, allocates resources, and evaluates the effectiveness of radiation research and coordinates with other Federal radiation research programs. RRP has established guidelines for studying proton radiation therapy. Major trials are evaluating radiation dose escalation in NSCLC and novel combinations of chemotherapy with concomitant-boost radiation therapy in patients with NSCLC.

- [Bonner JA, et al. \*N Engl J Med\*. 2006;354:567-78, PMID: 16467544](#)
- [Bao S, et al. \*Nature\*. 2006;444:756-60, PMID: 17051156](#)



- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I) (NCI)

**The Tumor Biology and Metastasis Program:** The Tumor Biology and Metastasis Program supports research to delineate the molecular mechanisms and signaling pathways involved in tumor progression, cell migration and invasion, angiogenesis, lymphangiogenesis, and metastasis. Research indicates that the progression of cancer depends on the co-evolution of carcinoma cells in their immediate microenvironment. In 2006, NIH launched the Tumor Microenvironment Network (TMEN) to investigate the composition of the stroma in normal tissues. The goal of this network is to delineate the mechanisms of tumor-stromal interactions in human cancer.

- For more information, see <http://tmen.nci.nih.gov>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCI)

**The NCI Vaccine Program:** NCI's vaccine program develops novel vaccines for cancer immunotherapy and prevention and HIV. The program encourages collaborations, identifies organizational and reagent needs for the community, and develops the optimal infrastructure for vaccine development and novel clinical trial approaches. Gardasil<sup>®</sup>, the first vaccine to prevent cervical cancer induced by HPV, is now available and can potentially save more than 5,000 U.S. women's lives each year. This FDA-approved vaccine resulted from basic research performed at NIH that produced a prototype vaccine and the observation that linked HPV and cervical cancer.

- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NCI)

**Long-Term Cancer Survivors Research Initiatives:** The population of cancer patients surviving more than 5 years continues to grow across life stages, from children through senior adults. These research initiatives focus on the physiological and psychosocial effects of treatment, as well as medical interventions to promote positive outcomes in survivors and their families. Important early findings suggest long latencies for treatment-related effects, highlighting the need for extended follow up, early identification, and intervention before complications become more serious. Implications include the length and quality of survival and the ongoing burden of illness and costs.

- For more information, see [http://cancercontrol.cancer.gov/bb/2006\\_bb.pdf#page=93](http://cancercontrol.cancer.gov/bb/2006_bb.pdf#page=93)
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-04-003.html>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NCI, CDC, NIA)

**International Tobacco and Health Research and Capacity Building Program:** Without a significant shift in worldwide smoking patterns, tobacco is projected to cause roughly 10 million deaths each year by 2025; 70 percent of this increase will occur in developing countries. To address this rising epidemic, NIH reissued the International Tobacco and Health Research and Capacity Building Program for funding in 2007. Grantees are generating a solid evidence base that can inform effective tobacco control strategies and policies. The program focuses on five



critical areas: epidemiology and surveillance, susceptibility and risk for smoking uptake, behavioral and social sciences, effective interventions, and policy-related research. The program also emphasizes research on determinants of youth smoking in diverse cultural and economic settings. A central goal of this program is to strengthen capacity in tobacco research in low- and middle-income nations, which advances the science and permits greater international collaboration.

- For more information, see [http://www.fic.nih.gov/programs/research\\_grants/tobacco/index.htm](http://www.fic.nih.gov/programs/research_grants/tobacco/index.htm)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (FIC, NCI, NIDA, NIDCR, ORWH)

**The Program in HIV/AIDS & Cancer Virology:** The mission of the Program in HIV/AIDS & Cancer Virology is to facilitate and rapidly communicate advances in the discovery, development, and delivery of antiviral and immunologic approaches for the prevention and treatment of HIV infection, AIDS-related malignancies, and cancer-associated viral diseases. This includes basic laboratory, translational, and clinical studies of disease pathogenesis, the development of novel targeted treatment approaches for cancers in HIV-infected individuals and for HIV infection itself, and drug resistance. Recent advances include a new prophylactic vaccine for HPV and promising candidates for prophylactic and therapeutic vaccines against HIV infection.

- For more information, see <http://ccr.nci.nih.gov>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E/I) (NCI)

**Trans-Institute Angiogenesis Research Program (TARP):** TARP encourages and facilitates the study of angiogenesis, the formation of new blood vessels. A number of common disease conditions are angiogenesis dependent, including some cancers, macular degeneration, atherosclerosis, diabetic retinopathy, and many others. Cancers cannot grow beyond a certain size without new blood vessels. According to one estimate, more than 500 million people could benefit from anti- or pro-angiogenesis treatments in the coming decades. TARP funds promising angiogenesis research and provides training and workshops to communicate state-of-the-art preclinical and clinical angiogenesis research. The program's multidisciplinary approach fosters data exchange and resource sharing among vascular biology and angiogenesis researchers from different disease disciplines. A number of new angiogenesis inhibitors are currently being developed, including several in late-stage clinical trials.

- For more information, see <http://www.tarp.nih.gov/funding.html>
- (E) (NCI, NEI, NHLBI, NICHD, NIDDK, NINDS)

**The Sister Study:** The Sister Study is a major NIH initiative to study environmental and genetic risk factors for breast cancer in a cohort of 50,000 sisters of women who have had breast cancer. The asymptomatic women are being followed over time with periodic health updates. The women who develop breast cancer during the follow-up period will be compared with those who remained healthy to identify factors associated with increased cancer risk.

- For more information, see <http://www.sisterstudy.org/English/index1.htm>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIEHS)

**Brain Tumor:** The NIH Brain Tumor Progress Review Group identified many priorities for the field. Research on understanding and preventing brain tumor dispersal was one of the group's highest scientific priorities, and NIH funds a number of projects in this area, many of which were submitted in response to a Program Announcement with set-aside funds issued in 2004. NIH also funds clinical studies investigating therapy delivery to the brain and evaluating the safety and tolerability of various therapies, including immunological therapies, vaccine therapy, monoclonal antibodies, and combination therapies. The Surgical and Molecular Neuro-Oncology Unit within the NIH Division of Intramural Research investigates basic mechanisms of brain tumor development and chemotherapy resistance to find new therapeutic strategies, particularly for malignant gliomas.

- For more information, see [http://www.ninds.nih.gov/find\\_people/groups/brain\\_tumor\\_prg/index.htm](http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NINDS, NCI)

**Cancer Stem Cells:** NIH is expanding its research portfolio related to the basic biology of tumor-initiating cells (i.e., stem cells) within the hematological and solid-tumor malignancies. Tumor stem cells are a minor population of cells thought to be capable of reconstituting an entire tumor. This is extremely important clinically in that these cells may be responsible for the recurrence of malignancy. Progress has been made in identifying such minority populations of tumor stem cells in both multiple myeloma and acute myelogenous leukemia. These tumor-initiating cells are resistant to standard chemotherapeutic agents but may contain “stem cell-unique” target molecules that may allow their eradication with novel small molecular therapeutics. Progress in identifying tumor “stem cells” among solid tumors has also been made in breast cancer, where the minority of “stem cells” have been separated and characterized from the majority of breast cancer cells in the tumor.

- For more information, see <http://stemcells.nih.gov/index.asp>
- (E/I) (NCI)

## Exemplary Current Studies and Projects

**Cancer and Inflammation:** NIH is actively pursuing research on the relationship between alterations in the lung microenvironment caused by inflammation and carcinogenesis. Inflammation is a response to acute tissue damage, whether resulting from physical injury, ischemic injury, infection, exposure to toxins, or other types of trauma. Current research on inflammation suggests pro-inflammatory conditions such as chronic pulmonary irritation contribute to the development of lung cancer and may be strongly correlated with the occurrence of lung cancer in nonsmokers. Ongoing studies are investigating inflammation in stomach, liver, and other cancers.

- (E/I) (NCI)

**Molecular Profiling of Cancer:** The underlying cause of each patient's disease is typically unique to the individual. Because each tumor has its own biological properties, molecular profiling provides advanced analysis and tools to characterize each individuals' disease or tumor so that tailored medical strategies can be given. Several notable examples include:

- ▷ *The Early Detection Research Network (EDRN)* brings together dozens of institutions to help detect cancer in its earliest stages. EDRN was formed to bring a collaborative approach to the discovery, development, and validation of early detection markers by accelerating the translation of biomarker information into clinical applications.
- ▷ *The Strategic Partnering to Evaluate Cancer Signatures (SPECS) Program* establishes strategic partnerships to bring together interdisciplinary teams to evaluate the clinical utility of molecular signatures. SPECS focuses on confirming, evaluating, and refining signatures and/or profiles derived from molecular analysis of tumors (i.e., biomarkers detection) to improve patient management and outcomes.
  - For more information, see <http://edrn.nci.nih.gov/>
  - For more information, see <http://www.cancerdiagnosis.nci.nih.gov/specs/index.htm>
  - This example also appears in Chapter 3: *Clinical and Translational Research*.
  - (E/I) (NCI)

**The Cancer Genome Atlas (TCGA):** TCGA is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. The goal of TCGA is to develop a free, rapidly available, publicly accessible, comprehensive catalog, or atlas, of the many genetic changes that occur in cancers, from chromosome rearrangements to DNA mutations to epigenetic changes—the chemical modifications of DNA that can turn genes on or off without altering the DNA sequence. The overarching goal of TCGA is to improve our ability to diagnose, treat, and prevent cancer.

- For more information, see <http://cancergenome.nih.gov/index.asp>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E/I) (NCI, NHGRI)

**Patient Navigation Research Program (PNRP):** PNRP is an intervention that addresses barriers to quality standard care by providing individualized assistance to cancer patients and survivors and their families. The program’s aim is to decrease the time between a cancer-related abnormal finding, definitive diagnosis, and delivery of quality standard cancer care. PNRP will focus on the four cancers with the greatest disparity in screening and follow-up care: breast, cervical, prostate, and colorectal cancers. Nine PNRPs reach African Americans, American Indians, Asians, Hispanics/Latinos, and rural underserved populations.

- For more information, see <http://crchd.cancer.gov/pnp/pnpr-index.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCI)

**Advances in Oral Cancer Detection:** The first product of a current NIH-funded research project to integrate new technologies into a reliable clinical protocol to improve oral cancer detection and survival has reached the market. Researchers report success using a customized optical device that allows dentists to visualize in a completely new way whether a patient might have a developing oral cancer. The simple, handheld device emits a cone of light into the mouth that excites molecules within our cells, causing them to absorb the light energy and re-emit it as visible fluorescence. When the light is removed, the fluorescence disappears. Changes in the natural fluorescence of healthy tissue can indicate light-scattering changes caused by developing

tumor cells. Health care providers shine a light onto a suspicious sore in the mouth, look through an attached eyepiece, and check for changes in color. Normal oral tissue emits a pale green fluorescence, whereas early tumor cells appear dark green to black. The instrument is an effective screening adjunct and is useful for helping surgeons determine how far to extend the surgical borders when removing tissue for biopsies.

- For more information, see <http://clincancerres.aacrjournals.org/cgi/content/full/12/22/6716>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*.
- (E) (NIDCR)

**Promoting Early Detection of Oral Cancer in African American Men:** NIH is developing a new series of oral cancer education materials specifically for African American men, who have the highest risk of oral cancer and the lowest 5-year survival rate (only 35.6 percent) of any other population in the United States. This is the first national-level effort of its kind. The first piece in the series, “Are You at Risk for Oral Cancer? What African American Men Need to Know,” is now being pre-tested in Washington, DC, Chicago, Los Angeles, and Columbia, South Carolina. The brochure—along with other complimentary education tools, such as fact sheets, posters, and both print and audio public service announcements—will be distributed to African American community groups around the country.

- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (NIDCR, NCI)

**Research May Lead to Blood Test to Predict Cancer Treatment Response:** In 2007, an estimated 34,000 Americans will be diagnosed with cancer of the oral cavity and pharynx (the middle part of the throat that includes the soft palate, tonsils, and tongue), and 7,550 Americans will die from it. Surgical treatment for these cancers may result in a loss of the ability to speak and swallow. In the largest long-term study of its kind, NIH-supported scientists determined that patients who showed a decline in specific cancer-related proteins after chemotherapy and radiation are more likely to remain in remission. These patients may not need to undergo surgery that may rob them of their speech and swallowing abilities. These findings could help lead to the development of a blood test that enables doctors to detect the recurrence of throat cancer at an early stage. A blood test that enables doctors to closely monitor a patient’s rehabilitation while sparing the patient’s voice, speech, and swallowing ability is an excellent example of NIH’s predictive, preemptive, and personalized approach to medicine.

- [Allen C, et al. \*Clin Cancer Res\* 2007;13:3182-90](#), PMID: 17545521
- (I) (NIDCD, NCI)

**The Dog Genome and Human Cancer:** Cancer is the number-one killer of dogs, and studying the major cancers in dogs provides a remarkably valuable approach for developing a better understanding of the development of cancer in humans. The clinical presentation, histology, and biology of many canine cancers very closely parallel those of human malignancies, so comparative studies of canine and human cancer genetics should be of significant clinical benefit to both species. Furthermore, information gained from studying the genetic variant involved in dog size can provide important information for studying cell growth in humans and has the

potential to be a useful tool in cancer research. A 2007 article by NIH's Dr. Elaine Ostrander and colleagues reported a genetic variant that is a major contributor to small size in dogs. In the following month, Dr. Ostrander and colleagues published a study reporting that a mutation in a gene that codes for a muscle protein can increase muscle mass and enhance racing performance in dogs.

- [Sutter NB, et al. \*Science\* 2007;316:112-5](#), PMID: 17412960
- [Mosher DS, et al. \*PLoS Genet\* 2007;3:e79](#), PMID: 17530926
- For more information, see <http://www.genome.gov/25520294>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (I) (NHGRI)

**Salivary Gene Transfer and Therapeutics:** Gene transfer may be an ideal strategy to boost salivary production for cancer patients whose salivary glands were damaged during radiation therapy. Although radiation therapy kills cancerous cells, it frequently also destroys the acinar (fluid-producing) salivary gland cells that lie within the salivary gland in grapelike clusters. Patients are unable to produce adequate saliva and suffer a host of long-term problems such as recurrent oral infections and difficulties with swallowing, speech, and taste. Unlike acinar cells, ductal cells in the salivary gland (which can be thought of as the “stems” on the grapes) often survive irradiation. However, they cannot make or secrete saliva. NIH scientists used gene transfer techniques to insert an aquaporin protein gene into the ductal cells; aquaporins are a family of proteins that form pores in cell membranes, through which fluid can pass. Their insertion “plumps up” the stems and allows the flow of fluid into the mouth again. The scientific team has collaboratively and methodically moved this promising idea through the research process, benefiting greatly from the wealth of scientific expertise on the NIH campus. This year, FDA approved the first clinical trial of gene transfer into the salivary glands for cancer patients with dry mouth. Although the outcome of clinical trials is always hard to predict, the preclinical data have been extremely promising.

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I) (NIDCR)

**Cancer.gov in Español:** This Spanish-language version of the NCI Web site is designed to reach the Hispanic-Latino population—the fastest growing online audience in the country—to communicate the message that cancer can be prevented and treated and to offer information on all aspects of the disease. The site is specifically tailored for Hispanics and Latinos, and pages are organized around issues of greatest concern. The site will be updated with evidence-based approaches and emerging technologies to ensure that accurate, relevant, and audience-appropriate information is provided. The site demonstrates the commitment to reducing cancer health disparities by making information readily available to underserved populations.

- For more information, see <http://www.cancer.gov/espanol>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NCI)

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## Accomplishments

**A Multidisciplinary Approach to Nicotine Addiction:** Nicotine addiction is the number-one preventable public health threat and has enormous associated morbidity, mortality, and economic costs. NIH-supported research has generated new knowledge to support the development of more effective prevention messages and treatment approaches. Several notable examples characterize NIH's multidisciplinary approach to targeting the best treatment (or combination of treatments) for nicotine addiction. Genomic studies have recently uncovered a series of genes that are associated with nicotine addiction and that could provide new targets for medication development and for the optimization of treatment selection. Pharmacologic studies, critical to understanding the basis of nicotine's mode of action, have recently revealed that its addictiveness may hinge upon its ability to slowly shut down or desensitize the brain's response to nicotine. A recent imaging study indicated that a part of the brain called the insula may play an important role in regulating conscious craving. This exciting finding provides a new target for research into the neurobiology of drug craving and for the development of potentially more effective smoking cessation and other addiction treatments. Results of a Phase II clinical trial strongly suggest that a nicotine vaccine, which works by preventing nicotine from reaching the brain, may be a particularly useful tool for cessation programs in the not-too-distant future.

- For more information, see <http://www.drugabuse.gov/researchreports/nicotine/nicotine.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Clinical and Translational Research*, and Chapter 3: *Genomics*.
- (E) (NIDA, NCI) (GPRA Goal)

**Developmental Windows of Vulnerability to Environmental Exposures:** The Breast Cancer and Environment Research Centers (BCERCs) supported by NIH function as a consortium to study the impact of prenatal to adult environmental exposures that may predispose a woman to breast cancer. The centers bring together basic scientists, epidemiologists, research translational units, and community advocates within and across the centers to investigate mammary gland development in animals and young girls to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. The overall goals of the BCERC are to develop public health messages to educate young girls and women who are at high risk of breast cancer about the role of specific environmental stressors in breast cancer and how to reduce exposures to those stressors. These public health messages will be based on the integration of basic biological, toxicological, and epidemiological data.

- For more information, see <http://www.bcerc.org>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIEHS, NCI) (GPRA Goal)

**Clinical Trials Education:** The materials in the Clinical Trials Education series represent a collection of over 20 resources developed to increase awareness and participation in cancer prevention and treatment clinical trials. These materials include workbooks, a guide for



community outreach, a trainer's guide, online courses for health professionals, DVDs, and slide sets to assist in education programs.

- For more information, see <http://www.cancer.gov/clinicaltrials/learning/clinical-trials-education-series>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (NCI)

### **Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer**

**Care:** NIH supports several research consortia that are designed to enhance understanding of cancer control across the continuum of prevention, screening, and treatment within the context of health care delivery.

- ▷ The most comprehensive of these initiatives, the *Cancer Research Network (CRN)*, seeks to improve the effectiveness of preventive, curative, and supportive interventions for major and rare tumors. The CRN consists of the research programs, enrolled populations, and data systems of 13 health maintenance organizations covering care for more than 9 million enrollees, or 3 percent of the U.S. population. This initiative uses a consortium of delivery systems to conduct research on cancer prevention, early detection, treatment, long-term care, and surveillance. Given its large and diverse populations, the CRN is uniquely positioned to study the quality of cancer care in community-based settings and to explore rare conditions. Seminal research includes CRN research documenting specific gaps in implementing effective tobacco cessation services among clinicians, reasons for late diagnosis of breast and cervical cancers, more rapid uptake in the use of aromatase inhibitors in comparison with tamoxifen in treatment for breast cancer, and examination of the role of a number of common drugs and cancer outcomes using its large and automated pharmaceutical databases.
- ▷ In the area of the evaluation of cancer screening in clinical care, the *Breast Cancer Surveillance Consortium (BCSC)* is a collaborative network of mammography registries linked to tumor and/or pathology registries. The network is designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. Because of the vast size and continually updated clinical information in this research initiative, the BCSC is responsible for research that, for the first time, documented the falling incidence of hormone replacement therapy among screened women; quantified the extent of difference in the association of breast density with breast cancer risk among pre- and postmenopausal women; and determined that, although biopsy rates are twice as high in the United States than in the United Kingdom, cancer detection rates are very similar in the two countries.
- ▷ The *Cancer Care and Outcomes Research Surveillance Consortium (CanCORS)* was established to identify how characteristics of patients, providers, and care delivery systems affect the cancer management and treatment services that patients receive, as well as the relationship between cancer-related clinical practices and outcomes, including patient-centered outcomes such as symptom control and quality of life. CanCORS supports prospective cohort studies on 10,000 patients with newly diagnosed lung or colorectal cancers across geographically diverse populations and health care systems and examines

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issues related to health outcomes, costs, and patient-centered issues such as symptom control and quality of life.

- For more information, see <http://crn.cancer.gov>
- For more information, see <http://breastscreening.cancer.gov>
- For more information, see <http://healthservices.cancer.gov/cancers>
- This example also appears in Chapter 3: *Clinical and Translational Research*, Chapter 3: *Epidemiological and Longitudinal Studies*, and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (I) (NCI)

**Childhood Cancer Survivors Study (CCSS):** Although survival rates from childhood cancers are encouraging, researchers have found that these young survivors may particularly suffer from late effects of treatment. In 2006, CCSS researchers documented serious long-term health issues in adults after radiation for childhood cancers. These findings will change treatment regimen guidelines for current childhood cancers and have implications for individuals from the study who are now adults. The Children's Oncology Group (COG) has prepared a resource for physicians, *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*.

- For more information, see <http://www.cancer.gov/cancertopics/coping/childhood-cancer-survivor-study>
- For more information, see <http://www.survivorshipguidelines.org>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NCI)

**The Centers for Transdisciplinary Research on Energetics and Cancer (TREC):** These Centers foster collaboration among transdisciplinary teams of scientists to accelerate progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet. The biology and genetics of the many factors that influence diet, physical activity, and obesity across the stages of life are applied to behavioral, sociocultural, and environmental factors, and transdisciplinary training opportunities are provided for scientists. The TREC initiative is interfacing with a number of established NCI initiatives in the area of diet, physical activity, and weight and is integrated with the NIH Obesity Research Task Force Strategic Plan.

- For more information, see <http://cancercontrol.cancer.gov/trec>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NCI)

**Transdisciplinary Tobacco Use Research Centers:** Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships.

- For more information, see <http://dceps.nci.nih.gov/tcrb/tture>



- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NCI, NIAAA, NIDA)

**Reports of the Clinical Trials Working Group (CTWG) and the Translational Research Working Group (TRWG):** Recognizing the importance of translational and clinical research, two recently released, major reports of comprehensive evaluations will lead to more rapid progress in translating important research findings into new, effective interventions. The CTWG and TRWG were constituted as broad and inclusive panels (memberships comprise experts from academia, the pharmaceutical industry, advocacy groups, NIH, and other governmental agencies) to review and evaluate the current portfolio of research in this area and to identify ways to synergize, integrate, and coordinate efforts.

- For more information, see <http://www.cancer.gov/trwg>
- For more information, see <http://integratedtrials.nci.nih.gov>.
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E/I) (NCI)

**Patient and Health Professional Education and Outreach:** NIH provides comprehensive cancer information to those at risk and to patients, caregivers, and health care providers. This information ranges from prevention, through treatment, to end-of-life topics. For example, clinical sites across the country extensively utilize NIH print and Web-based materials to support their educational programs. The Cancer Information Service (CIS) effectively communicates information through a Partnership Program to help reach those with limited access to health information; an Information Service that provides cancer information by telephone, TTY, instant messaging, and e-mail; and a Research Program that helps advance health communication practices.

- For more information, see <http://www.cancer.gov> (click on “NCI Publications”)
- For more information, see <http://www.cancer.gov/cancertopics>
- For more information, see <http://www.cancer.gov/aboutnci/epeco>
- For more information, see <http://cis.nci.nih.gov>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (NCI)

**Surveillance, Epidemiology, and End Results (SEER) Program and Software Analysis Tools:** SEER is an authoritative source of information on cancer incidence and survival in the United States. Publications such as the *Annual Report to the Nation on the Status of Cancer*, as well as interpretation of recent trends in cancer, inform the public, researchers, Federal and private agencies, and Congress on national cancer rates and trends. SEER is the only comprehensive source of U.S. population-based information that includes stage of cancer at the time of diagnosis, patient survival, and treatment. Linkage with Medicare and other Federal databases yields information sources that are used routinely to answer major questions on quality, cost, and variability of cancer care, as well as differences by racial and ethnic populations. SEER currently collects and publishes data from approximately 26 percent of the U.S. population. The team is developing computer applications to unify cancer registration

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systems, analyze and disseminate data, and provide limited access to the public file. SEER is considered the standard for quality among cancer registries around the world.

- For more information, see <http://seer.cancer.gov/>
- For more information, see <http://surveillance.cancer.gov/>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NCI)

**Cancer Control P.L.A.N.E.T.:** The Cancer Control P.L.A.N.E.T. (Plan, Link, Act, Network with Evidence-Based Tools) Web portal is a collaboration aimed at providing access to data and resources that can help cancer control planners, health educators, program staff, and researchers design, implement, and evaluate evidence-based cancer control programs. It assists local programs with resources that help them determine cancer risk and cancer burden within their State. It also helps States identify potential partners and provides online resources for interpreting research findings and recommendations and accessing products and guidelines for planning and evaluation.

- For more information, see <http://cancercontrolplanet.cancer.gov>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NCI)

**The Minority Institution/Cancer Center Partnership (MI/CCP):** The MI/CCP provides support for Minority-Serving Institutions (MSI) to partner with Cancer Centers. MI/CCP goals include: (1) increasing the participation of MSIs in the Nation's cancer research and training enterprise, (2) enhancing the number of competitive grant funding from minority investigators, (3) augmenting the research capacity at MSIs, (4) increasing the involvement and effectiveness of the Cancer Centers in research and training relating to ethnic minorities, and (5) developing more effective research, outreach, and education programs that will have an impact on ethnic minority and underserved populations.

- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCI)

**Transdisciplinary Tobacco Use Research Centers:** Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships.

- For more information, see <http://dceps.nci.nih.gov/tcrb/tture>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NCI, NIAAA, NIDA)

**Databases for Cervical Cancer Research:** NIH has developed data analysis and image recognition tools for studying biomedical images of HPV infection and cervical neoplasia. Image data include 100,000 cervicographs (high-definition cervical photographs), Pap test, and histology images. Tools allow the exploration of visual aspects of HPV and cervical cancer for research, training, and teaching.

- [Castle PE, et al. \*Cancer Res\* 2006;66:1218-24](#), PMID: 16424061
- [Jeronimo J, et al. \*J Low Genit Tract Dis.\* 2006;10:39-44](#), PMID: 16378030
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (I) (NLM, NCI)

**Understanding the Interface Between Aging and Cancer:** Through a collaborative effort between NIA and NCI, eight NCI-designated Cancer Centers are developing studies on the biology of aging and cancer; patterns of care, treatment efficacy, and tolerance; the effects of comorbidity, prevention, and screening in older persons; and symptom management and palliative care in older patients. This research will help gain insights into why cancer occurs more frequently in older people, whether cancer behaves differently in older adults than in younger people, and how we need to adapt prevention and screening services to reach a greater number of older people as well as to aid in the development of predictive models for tolerance to therapy.

- For more information, see <http://www.nci.nih.gov/newscenter/pressreleases/AgingGrants>
- (E) (NCI, NIA)

## NIH Strategic Plans Pertaining to Cancer

### National Cancer Institute (NCI)

- *NCI Strategic Plan for Leading the Nation*
- [The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2007](#)
- [The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2008](#)

### National Institute of Dental and Craniofacial Research (NIDCR)

- [NIDCR Strategic Plan](#)
- [NIDCR Implementation Plan](#)

### National Center for Complementary and Alternative Medicine (NCCAM)

- [Expanding Horizons of Health Care: Strategic Plan 2005-2009](#)

### John E. Fogarty International Center (FIC)

- [Pathways to Global Health Research](#) (Draft)

### Office of AIDS Research (OAR)

- [FY 2008 Trans-NIH Plan for HIV-Related Research](#)

**Other Trans-NIH Plans**

- [Report of the Brain Tumor Progress Review Group](#)  
(NCI, NINDS)



## NEUROSCIENCE AND DISORDERS OF THE NERVOUS SYSTEM

*In 1953, when 27-year-old Henry M. (H.M.) turned to brain surgery to end his struggles with intractable epilepsy, he unwittingly ushered in a new era in research and understanding of memory and the brain. After determining the origin of H.M.'s seizures, neurosurgeon William Scoville removed portions of his brain containing and surrounding a structure called the hippocampus. The operation successfully quieted H.M.'s seizures but left him with profound amnesia—an unintended consequence that fascinates neuroscientists to this day. H.M. retained his former intelligence, his perceptual and motor abilities, and, most notably, his memory of early life events. Yet his recall of new events since the time of the surgery is only fleeting: he still believes he is about 30 years old and, even after many introductions, greets people in his life as though they have never met. Over the last 50 years, some 100 investigators have examined H.M.'s case. Their observations, as well as studies of patients with damage in similar brain regions, including those with Alzheimer's disease, have revolutionized understanding of how memories are formed and where in the brain they are stored. Today, these insights both guide and are extended by human brain imaging studies during learning and memory tasks and by investigations in animals at the level of single neurons and even molecules, leading to the development of drugs to treat memory deficits in people.*

### Introduction

Composed of the brain, spinal cord, and nerves of the body, the nervous system underlies perception, movement, emotions, learning and memory, and other functions essential to individual and societal well-being. The nervous system interacts with all other organ systems and is affected by countless diseases, conditions, and environmental factors. Moreover, with limited capacity for self-repair, the nervous system is particularly vulnerable to damage due to injury or infection, and its repair mechanisms are poorly understood. Neuroscience research seeks to understand the nervous system and its functions in health and disease. Given its intrinsic complexity and central role in physiology and behavior, this understanding must necessarily come from multiple perspectives. Accordingly, neuroscience research spans many disciplines, from genetics to physiology to psychology, and applies tools from areas such as molecular biology, anatomy, computer science, and imaging technologies.

Neuroscience is a unifying theme in NIH research. The intramural and extramural programs of several ICs have a major focus on the nervous system, but the full scope of neuroscience activities extends to components of research portfolios across most of NIH, reflecting the multidisciplinary nature of the field and the importance of the nervous system to many aspects of human health, development, and disease. These activities often involve collaborative efforts combining the unique strengths and expertise of individual ICs. NIH established the [Blueprint for Neuroscience Research](#)<sup>11</sup> to reinforce such collaboration and to accelerate neuroscience research through training initiatives and the development of shared tools and resources.

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<sup>11</sup> Institutes and Centers participating in the NIH Blueprint for Neuroscience Research: NEI, NIA, NIAAA, NIBIB, NCCAM, NICHD, NCR, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, and OBSSR.

The principal aim of NIH research in neuroscience is to reduce the burden of diseases that affect the nervous system, including a broad range of neurological disorders; disorders affecting cognitive, emotional, and behavioral function; diseases and conditions that impair the primary senses; and developmental and age-related disorders. Whether led by single investigators or conducted through centers and consortia, NIH neuroscience research includes basic science studies of normal function and development in both humans and animal models, translational research that develops medications or other therapies, and clinical trials that test interventions in patients.

Nervous system disorders include common killers and major causes of disability like stroke, multiple sclerosis, and epilepsy, as well as hundreds of less common diseases, such as lysosomal storage disorders, spinal muscular atrophy, muscular dystrophies, neurofibromatosis, tuberous sclerosis, and Rett and Tourette syndromes. Many neurological disorders have genetic or developmental origins. Others result from trauma to the nerves, spinal cord, or brain; from autoimmune, infectious, or systemic disease; from tumor growth in nervous system tissues (see the section “Cancer”); or from neurodegenerative processes as in Parkinson’s disease, frontotemporal dementia, and amyotrophic lateral sclerosis (ALS). NIH research on neurological diseases, largely supported by NINDS, seeks to uncover their causes and mechanisms and to develop drugs and other treatments or preventive strategies. This research also aims to understand the multiple aspects of the nervous system that disease can affect and has shared support across NIH for basic science studies of the cerebral vasculature, electrochemical signaling in neurons and other cells, mechanisms of development and cell death, neuromuscular function and motor control, and behavior and cognition. In addition, NIH works to enhance the lives of those disabled by stroke, traumatic brain injury, spinal cord injury, and other neurological conditions through research, supported by NICHD’s [National Center for Medical Rehabilitation Research](#) and other ICs, on neuroplasticity, recovery and repair of motor and cognitive function, and rehabilitative and assistive strategies and devices (see the section “Life Stages, Human Development, and Rehabilitation”).

Brain disorders affecting cognitive, emotional, and behavioral function include schizophrenia and psychoses; autism and other developmental disorders; mood and anxiety disorders; and addiction to nicotine, alcohol, and other substances; as well as posttraumatic stress disorder, eating disorders, attention deficit hyperactivity disorder, and other behavioral disorders. These disorders have complex causes involving genetic and environmental influences and their interactions throughout life. Through research efforts led by NIAAA, NIDA, and the National Institute of Mental Health (NIMH), NIH focuses on uncovering these causes, understanding their neural and behavioral bases, and developing therapies and interventions for treatment and prevention. NIH research also seeks to understand the acute and long-term effects of abused substances on the nervous system.

Sight, smell, balance and our other primary senses, as well as the ability to communicate allow interactions with a changing external environment. The National Eye Institute (NEI) and the National Institute on Deafness and Other Communication Disorders (NIDCD) sponsor most of NIH’s research on basic mechanisms of sensory perception and communication and on diseases and conditions affecting the eyes and vision, hearing and balance, speech and language, taste and smell, and somatosensory function, including the senses of temperature and touch. Although

vital to survival, the sensation of pain is also symptomatic of many diseases with origins in and outside the nervous system, from migraine and other headaches to chronic pain in cancer. NIH pain research is led by NIDCR and the [NIH Pain Consortium](#), which coordinates research across NIH on pain and its treatment (see the section “Chronic Diseases and Organ Systems”). NIH-supported research also studies the many ways the nervous system interacts with and regulates changes in the body’s internal environment. This research, including efforts supported by NHLBI and NIDDK, focuses on areas such as circadian rhythms and sleep disorders; neuroendocrine processes that regulate stress responses, hormone levels, and motivational states; and the neural basis of appetite and feeding, which is of key relevance to slowing the increasing rates of obesity worldwide.

Nervous system disorders may arise in development, strike young adults, or emerge late in life. NICHD and other ICs sponsor research on the development of the nervous system and its functions. This research encompasses studies of structural birth defects, including spina bifida and other neural tube defects and associated conditions such as hydrocephalus. NIH also invests in research on developmental disorders like cerebral palsy, Down’s syndrome, autism, and other causes of intellectual and learning disabilities. Nervous system development continues into early adulthood in humans, and developmental processes and their external influences contribute to mental fitness and disease risk later in life, including the risk for addiction, which often begins in childhood or adolescence. At the other end of the lifespan, with key support by NIA, NIH research on the aging nervous system includes studies of age-related disorders such as Alzheimer’s disease and other dementias, as well as environmental and lifestyle factors affecting neurological, cognitive, and emotional health in aging populations.

Across all ages, the nervous system is a common target of exposure to toxins, pollutants, and other agents, whose effects range from acute reactions to developmental disorders and neurodegeneration. NIH-sponsored research on the consequences of such environmental exposures for nervous system function and disease includes a particular focus by NIEHS. NIH also considers diseases of the nervous system from a global point of view. Coordinated primarily by FIC, neuroscience-related research is supported by NIH in unique populations and environments and on factors contributing to disparities in disease vulnerability and treatment quality and access around the world, such as socioeconomic conditions and infectious disease.

## **The Burden of Nervous System Disorders**

Nervous system disorders take an enormous toll on human health and the economy. Even rare disorders carry a substantial collective burden, as they often have an early onset and long duration, and the stigma commonly attached to neurological and mental illnesses further compounds individual and societal impact. According to 2005 estimates, neurological disorders strike more than 1 billion people worldwide, account for 12 percent of total deaths, and result in more disability than HIV/AIDS, ischemic heart disease, or malignant tumors.<sup>12</sup> In the United States, stroke is the third leading killer of adults and results in annual medical and disability costs totaling over \$60 billion.<sup>13</sup> Another 1.4 million Americans sustain a traumatic brain injury each

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<sup>12</sup> World Health Organization. *Neurological Disorders: Public Health Challenges*. Geneva: WHO Press, 2006.

<sup>13</sup> [Rosamond W, et al. \*Circulation\* 2007;115:e69-171](#), PMID: 17194875



year; it is the leading cause of death and long-term disability in young adults.<sup>14</sup> Traumatic brain injury accounted for an estimated \$60 billion in direct medical costs and indirect costs in 2000.<sup>15</sup>

Although less often cited as direct causes of mortality, mental disorders result in more disability for U.S. adults than any other class of medical illness,<sup>16</sup> and mental illnesses other than drug abuse and addiction account for more than \$150 billion in costs annually.<sup>17</sup> In a given year, approximately 12.5 million American adults (or 1 in every 17) suffer mental illness symptoms so severe as to cause significant disability.<sup>18,19</sup> In 2005, 23.2 million Americans needed treatment for an alcohol or illicit drug use problem, and costs related to illicit drug use alone totaled about \$180 billion.<sup>20</sup> Nervous system disorders also severely affect the lives of children; an estimated 17 percent of U.S. children have a developmental or behavioral disorder such as autism, intellectual disability, or attention deficit hyperactivity disorder.<sup>21</sup>

Demographic trends project an increasing burden from nervous system disorders. In particular, the prevalence of age-related diseases of the nervous system is expected to increase in aging populations benefiting from increased longevity. Current estimates of the number of U.S. adults with Alzheimer's disease range from 2.4 million to 4.5 million, and unless effective interventions are developed, this number is expected to rise almost threefold by 2050.<sup>22, 23</sup>

## NIH Funding for Neuroscience and Disorders of the Nervous System

In FYs 2006 and 2007, NIH funding for research in neuroscience and disorders of the nervous system was \$4.830 billion and \$4.809 billion respectively. The table at the end of this chapter indicates some of the research areas involved in this investment (see “Estimates of Funding for Various Diseases, Conditions, and Research Areas”).

### Summary of NIH Activities

Many common themes reflect shared biological processes found in many aspects of nervous system function and disease. Three such themes—neurodevelopment, neuroplasticity, and neurodegeneration—provide a useful perspective on the broad, multidisciplinary field of

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<sup>14</sup> Langlois JA, Rutland-Brown W, Thomas KE. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2006.

<sup>15</sup> Finkelstein E, Corso P, Miller T, et al. *The Incidence and Economic Burden of Injuries in the United States*. New York: Oxford University Press, 2006.

<sup>16</sup> World Health Organization, 2006.

<sup>17</sup> For more information, see <http://www.mentalhealthcommission.gov/reports/FinalReport/toc.html>

<sup>18</sup> Kessler RC, et al. *Arch Gen Psychiatry* 2005;62:617-27, PMID: 15939839

<sup>19</sup> For more information, see <http://www.census.gov/popest/national/asrh>

<sup>20</sup> Substance Abuse and Mental Health Services Administration. Results from the 2005 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-30, DHHS Publication No. SMA 06-4194). Rockville, MD; 2006; For more information, see <http://oas.samhsa.gov/NSDUH/2k5NSDUH/2k5results.htm>

<sup>21</sup> U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. The National Survey of Children with Special Health Care Needs Chartbook 2001. Rockville, MD: U.S. Department of Health and Human Services, 2004; For more information, see <http://www.cdc.gov/ncbddd/child/improve.htm>

<sup>22</sup> Plassman BL, et al. *Neuroepidemiology* 2007;29:125-32, PMID: 17975326

<sup>23</sup> Hebert LE, et al. *Arch Neurol* 2003;60:1119-22, PMID: 12925369

neuroscience research and illustrate the dynamic nature of the nervous system across the lifespan. In this section, these themes will serve to highlight selected examples of activities and progress in neuroscience research enabled by NIH, as well as challenges and future opportunities. Additional activities and initiatives exemplify how collaborative approaches are facilitating advances in basic, translational, and clinical neuroscience. More information, as well as more examples, may be found in the bulleted list at the end of this chapter.

## **Neurodevelopment: Periods of Growth, Maturation, and Vulnerability**

Complex interactions between gene expression and function, endocrine and other physiological processes, neuronal activity, and external influences guide the development of the nervous system. From the early differentiation of its many neuronal and other cell types to the establishment of billions of connections, or synapses, between neurons, each step in nervous system development is vulnerable to disruption by disease, injury, or environmental exposures. Each also has implications for normal neurological, mental, and behavioral function and for health and disease risk across the lifespan.

Human brain development continues into early adulthood and proceeds at different rates in different brain areas and pathways. Understanding normal nervous system development is essential to identifying when, where, and how developmental processes can go wrong. To this end, NIH-supported investigators are applying advanced brain imaging technologies to large-scale studies of human brain development in healthy children and adolescents. For example, in the [NIH Magnetic Resonance Imaging \(MRI\) Study of Normal Brain Development](#), extramural researchers at seven collaborating institutions are collecting brain scans and clinical and behavioral data from more than 500 infants, children, and adolescents over the course of 7 years. Data gathered and analytical tools developed for this longitudinal study will be available to the broader research community in a Web-based, searchable database.

As another example, in the largest longitudinal pediatric neuroimaging study to date (829 MRI scans from 387 subjects, ages 3 to 27 years), intramural NIH scientists have reported different trajectories of brain development in males and females, finding that brain volume peaks earlier in girls than in boys. Such studies of normal brain development and maturation are providing scientists with important baseline data that will help them identify signs of atypical development as well as factors that may be associated with disease risk later in life. Moreover, understanding the developmental course of different brain areas can help to explain behavioral and cognitive development and its consequences for mental health and disease risk. For instance, previous brain imaging studies have suggested that brain pathways that are important for decision-making and impulse control are among the last to fully mature. This aspect of brain development may contribute to impulsive behavior in teenagers and help explain their increased susceptibility to drug abuse and addiction.

In a remarkable feat of nervous system development, the estimated 100 billion neurons in the human brain are wired together into functional networks that underlie brain functions, from sensory perception, to learning and memory, to motor control. Insight into the wiring diagrams of these networks and the developmental processes that lead to their establishment promises to unlock some of the most fundamental questions in neuroscience research. Indeed, certain brain

diseases, including schizophrenia and autism, are hypothesized to involve aberrant development of brain connectivity. Research in this area benefits from new technologies for manipulating and visualizing neurons in experimental animal models, in which neuronal connections are established and organized according to rules similar to those found in the human nervous system. In one recent example, NIH-supported scientists developed a technique that can label thousands of direct synaptic connections received by individual neurons in the rat brain. By enabling neuroscientists to map neuronal networks, such experimental techniques will help show how changes in brain function and behavior can result from changes in these networks, whether they occur during normal development and learning or as a consequence of injury or disease.

One salient feature of the developing nervous system is its heightened sensitivity to external influences. Although crucial for shaping the proper development of many brain pathways and their corresponding sensory, motor, cognitive, and emotional functions, this heightened sensitivity also makes the developing nervous system especially vulnerable to potentially damaging environmental factors. These factors include exposures to toxins, viral infections, nutritional deficits, traumatic events, and social experiences throughout life. For instance, prenatal exposure to alcohol can lead to fetal alcohol syndrome (FAS), a devastating developmental disorder characterized by lifelong nervous system impairments that may include intellectual and learning disabilities, and behavioral and social deficits. NIH supports a broad research portfolio on FAS and its diagnosis, treatment, and prevention. A growing area of neuroscience research focuses on how genetic and environmental factors interact in nervous system development, function, and disease. The interplay between external influences and genetic predispositions appears likely to contribute to a range of disorders, such as depression and other mood and anxiety disorders, addiction, multiple sclerosis, Parkinson's disease, and autism. As one example of research in this area, NIH supports several efforts to understand how autism spectrum disorders may arise from the combined effects of genetic vulnerabilities and exposure to harmful environmental agents during key periods of development. Ongoing projects co-funded by NIH and the Environmental Protection Agency (EPA) are looking for biomarkers of these disorders and for differences in immune system function that may increase susceptibility to potential environmental triggers.

## **Neuroplasticity: Substrates for Change and Repair**

Throughout development, and even once its basic structure and circuitry have been established, the nervous system retains a remarkable capacity to adapt to or be affected by changes in the body's internal environment and external conditions and events. This capacity, known as *plasticity*, results in changes in the electrical activity and composition of neuronal networks. Plasticity occurs at many levels of the nervous system, from altered signaling at synapses thought to underlie learning and memory, to large-scale functional and neuroanatomical reorganization accompanying the loss of a limb or sensory organ.

Neuroplasticity enables beneficial adaptations, including acquiring new knowledge, improving performance on practiced tasks, and adjusting behavior based on positive or rewarding consequences. A recent NIH-funded study demonstrated how such adaptive plasticity might be exploited for therapeutic intervention. In this study, using real-time brain imaging, patients with chronic pain learned to exert voluntary control over activation of a particular brain region

involved in pain perception and its regulation, effectively reducing the impact of their painful sensations. Unfortunately, plasticity can also be maladaptive. Accumulating evidence from NIH-supported research indicates that the same brain mechanisms that mediate reward-related learning are involved in the development of addiction and compulsive overeating. Continued research into how plasticity contributes to addiction and other mental disorders may lead to intervention strategies that reverse or prevent these mechanisms.

Neuroplasticity also plays a role in many aspects of epilepsy, a class of disorders characterized by abnormal bursts of electrical activity (seizures) in networks of neurons that can lead to odd sensations, emotions, behaviors, convulsions, muscle spasms, and loss of consciousness. Basic neuroscience studies on the plasticity of synaptic connections and brain circuits are showing how epileptic activity emerges and how seizures themselves can in turn cause plasticity in affected circuits, often increasing the probability of seizure recurrence. In addition to these basic science studies, NIH supports translational research and clinical trials of potential anticonvulsant therapies, including extensive efforts through the NIH [Anticonvulsant Screening Program](#), a drug discovery program that conducts state-of-the-art evaluations to determine both potential efficacy and toxicity of preclinical candidate compounds in validated epilepsy model systems. NIH also works with the epilepsy community to develop and pursue benchmarks for research to prevent and treat epilepsy and co-occurring disorders.

Harnessing the capacity of the nervous system to adapt by activating its intrinsic mechanisms for repair and plasticity offers great hope for restoring function in the injured or diseased brain and spinal cord. For example, after spinal cord injury, neurons near the site of damage sprout new nerve fibers. Although this sprouting is limited in the absence of intervention, an understanding of the mechanisms that guide and restrict such spinal plasticity may allow neuroscientists to design strategies that integrate the new nerve fibers into spinal circuitry, replacing damaged connections and promoting functional recovery. In addition, NIH has long supported a program to develop neural prostheses, devices that restore functions that have been lost due to injury or disease, as in deafness or paralysis from spinal cord injury. The success of neural prostheses depends not only on their ability to bypass or replace injured components of the nervous system, but also on their integration into remaining functional circuits, which relies on plasticity mechanisms.

Stem cells are another promising source of plasticity and repair in the nervous system, and although many challenges and questions remain in this young area of research, basic and translational neuroscience studies are making progress in advancing stem cell-based therapies toward the clinic. During early embryonic development, stem cells have the potential to become any cell type in the body; as development proceeds, the range of potential fates narrows, depending on the tissue generating the cells. Beyond early development, stem cell production and neurogenesis—the generation of new neurons—occurs only in restricted regions of the brain. One active area of basic neuroscience research examines the role of neural stem cells in normal function and the brain's response to injury and disease, and the potential for treatments that tap into this intrinsic renewal mechanism. Other stem cell research in neuroscience focuses on the development of therapies in animal models that transplant stem cells into the damaged or diseased nervous system. Transplanted cells may be embryonic stem cells or other non-neuronal stem cells, they may be engineered to become certain desired cell types, or they may be designed

to express specific genes that could act to promote recovery or repair or restore genetic deficits. As part of the [Quantum Grants Program](#) designed to make profound advances in health care, NIH has recently funded research to engineer implants from neural and vascular stem cells and innovative biomaterials to provide a source of cells for tissue repair in an animal model of stroke.

## **Neurodegeneration: Fighting the Effects of Age, Exposure, and Disease**

The progressive loss of neurons is a common endpoint of many diseases and insults to the nervous system. Such degeneration presents challenges to developing strategies to slow and prevent cell death, protect remaining neurons, and possibly replenish those that are lost. Although recent and ongoing research continues to yield exciting insights into the biological and environmental causes of neurodegenerative disorders, much remains unexplained, and while some interventions alleviate disease symptoms, none currently exists that can halt progressive degeneration.

Aging is the most consistent risk factor for developing a neurodegenerative disorder, and many of the 50 million adults in the United States who are older than age 60 are at substantial risk for cognitive impairment and emotional disorders from many causes as they age. The trans-NIH [Healthy Brain Project](#) focuses on demographic, social, and biologic determinants of cognitive and emotional health in aging adults. The risk for degenerative disorders affecting sensory systems also increases with age, leading to hearing and visual impairments. Building on a previous demonstration that antioxidant supplements could slow age-related macular degeneration (AMD), the leading cause of blindness in the elderly, a large-scale NIH study is assessing the benefits of other supplements and dietary changes on AMD and cataracts.

Alzheimer's disease is the most common cause of dementia in the elderly, though some inherited forms of the disease become symptomatic in middle age, and scientists now believe that damage to the brain begins well before symptoms appear. Basic science studies have identified genetic factors and protein abnormalities that contribute to neuronal dysfunction and death in Alzheimer's disease. NIH also funds 29 [Alzheimer's Disease Centers](#), which carry out clinical studies and other research on Alzheimer's and related degenerative diseases (see Chapter 4). In addition, NIH supports clinical trials for treating and slowing Alzheimer's disease, many of which are coordinated through the [Alzheimer's Disease Cooperative Study](#), which involves nearly 70 sites in the United States and Canada. Ongoing trials include the Docosahexaenoic Acid trial, which is examining whether treatment with DHA, an omega-3 fatty acid, will slow decline in patients with Alzheimer's disease. Observational studies have shown a reduced risk of Alzheimer's disease associated with DHA consumption, and animal studies have shown that DHA reduces brain levels of beta-amyloid, oxidative damage associated with beta-amyloid, and neurotoxicity. Recent research has also shown that an extract from the leaf of the *Ginkgo biloba* tree reduces neuronal pathology and symptoms in an animal model of the disease, and NIH is supporting the largest clinical trial to date to test the effectiveness of *Ginkgo biloba* in preventing dementia in humans. Additional research supported through the [Alzheimer's Disease Neuroimaging Initiative](#) aims to identify biomarkers and develop imaging technologies to aid early diagnosis, which may enable more targeted and timely interventions.

Neurodegenerative disorders are often associated with degeneration in specific populations of neurons or regions of the nervous system. For example, Parkinson's disease results in the loss of a class of dopamine-producing neurons in the substantia nigra, a part of the brain important for motor control. NIH-funded scientists recently described a mechanism in substantia nigra neurons that contributes to their selective vulnerability and that, like the disease itself, becomes more prevalent with age. Manipulations to "rejuvenate" the neurons by blocking this mechanism promoted their survival, suggesting a new potential target for drug development. NIH also supports 14 [Morris K. Udall Centers for Excellence in Parkinson's Disease Research](#) and engages with the Parkinson's disease research community to identify and pursue research opportunities.

Neurons are not unique in their vulnerability to degenerative disorders. Muscular dystrophies are a class of neuromuscular disorders that lead to progressive muscle weakness and degeneration. NIH support for research on muscular dystrophies includes funding for six [Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers](#) (see Chapter 4), as well as other efforts to translate basic science findings to the clinic. Multiple sclerosis is the most common of a number of diseases that lead to the degeneration of myelin, a fatty substance that ensheathes many nerve fibers in the brain. NIH-supported scientists recently reported the first genetic risk factors for multiple sclerosis to be identified in more than 20 years (see also the section "Autoimmune Diseases" in this chapter). These studies benefited from new technologies in genetic research that allow simultaneous analysis of many thousands of genetic variations, or polymorphisms, across the entire genome. Such genome-wide studies are giving scientists unprecedented insight into disorders that result from the combined effects of many genetic variations and their interactions with environmental influences.

### **Advancing Neuroscience Research Through Collaboration**

The melding of disciplines involved in the study of the nervous system and the overarching themes linking its many functions and disorders make neuroscience a naturally collaborative field of research. Today's fast global communication and the power and storage capacity of modern computer systems are enabling collaborative research on increasingly large scales. A major priority of the [NIH Blueprint for Neuroscience Research](#) is to facilitate research by funding the creation of shared resources and tools for scientists. Examples include a publicly available atlas of gene expression in the mouse brain and spinal cord across the lifespan, a clearinghouse for informatics tools and resources for brain imaging applications, and an effort to develop common measures of neurological and behavioral function for use in clinical trials and epidemiological and longitudinal studies. NIH also supports several data registries, databases, and tissue consortia for neurological diseases and mental disorders that offer shared access to genetic and clinical data and biological samples. Genome-wide and other genetic studies using such materials are identifying genes that contribute to bipolar disorder, that influence the effectiveness of antidepressant therapies, and that predispose individuals to drug abuse and addiction (see also the section "Genomics" in Chapter 3).

Collaborative approaches are also transforming clinical and translational research in neuroscience, which build on advances and knowledge gained through basic science studies to develop treatments and interventions for disease in people. NIH supports seven centers as part of



the [Specialized Program of Translational Research in Acute Stroke](#), a national network of research centers established to develop acute stroke therapies from preclinical research through early-phase clinical trials. These centers also work to improve prehospital stroke care, participate in community education, and develop telemedicine to expand rapid access to acute stroke care. NIH also supports the Silvio O. Conte Centers for the Neuroscience of Mental Disorders, which integrate and translate basic and clinical neuroscience research on severe mental illnesses, such as schizophrenia and mood disorders. As another example, the [Spinal Muscular Atrophy \(SMA\) Project](#) is a new translational approach to preclinical drug development, motivated by the recent discovery of the gene defect that causes this degenerative disease that affects motor neurons of the spinal cord. With expertise from NIH as well as FDA, academia, and industry, the SMA Project has created a multisite enterprise for accelerated drug development.

Scientific research is an increasingly global endeavor, and because brain disorders are the leading contributors to disability in almost all parts of the world, global capacity for neuroscience research is essential. Through a program entitled [Brain Disorders in the Developing World](#), NIH supports innovative, collaborative programs to build sustainable neuroscience research capacity in low- and middle-income nations. Projects focus on some of the unique challenges facing neuroscience research in the developing world and on topics that are relevant worldwide, including the neurological consequences of infectious diseases and nutritional deficits. For example, one study suggests that a form of the *APOE4* gene, which is associated with an increased risk for developing Alzheimer's disease, may have a protective effect early in life against the negative consequences of malnutrition. This finding may help elucidate mechanisms to protect the brain and body during times of nutritional deficit.

## **Looking to the Future**

NIH-supported neuroscience research is steadfastly advancing its mission to reduce the burden of nervous system disorders. New technologies that allow neuroscientists to observe and manipulate neuronal networks could provide insights into how neural activity leads to complex brain functions. Continued innovation in neuroimaging techniques may identify disease risk or presence early, enabling more rapid diagnosis and intervention. With knowledge gained through large-scale genetic and epidemiological studies, clinicians of the future may personalize preventive and therapeutic strategies according to the genetic profile and lifestyle of individual patients. Future medications for treating nervous system disorders may reach specific brain targets with ease, and advances in neuroprostheses may more successfully restore motor, sensory, and cognitive function after disease or injury. These are just a few of the possibilities to come as NIH-supported neuroscience research continues to build on past progress and identify and pursue new opportunities. A glimpse into the future might reveal the ability to replenish damaged nerve cells, reprogram neuronal connections that support addiction, and stop degenerative processes that rob millions of their thoughts and memories.

## Notable Examples of NIH Activity

### Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

### Neurodevelopment: Periods of Growth, Maturation, and Vulnerability

**Research on Environment and Autism:** NIH has several innovative research studies aimed at understanding how autism and autism-spectrum disorders may arise from a combination of genetic vulnerability and exposure to harmful environmental agents during key periods of early development. The NIEHS/EPA Children's Center for Environmental Health at the University of California, Davis supports a highly integrated research program spanning human-to-animal cellular models to explore the interplay of immune, genetic, and environmental factors in autism susceptibility. In 2001, this center launched the first and most comprehensive large-scale epidemiological investigation of environmental exposures and susceptibility factors for autism, the Childhood Autism Risk from Genes and Environment (CHARGE) study. Scientists are exploring how persistent organic pollutants such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) may contribute to neurological development disorders such as autism by interacting with cellular epigenetic mechanisms that control timing and patterns of gene expression. NIH also supports an exploratory study at Johns Hopkins University to develop new methods to measure individual differences in the immunotoxicity of mercury.

- For more information, see <http://www.vetmed.ucdavis.edu/cceh>
- (E/COE) (NIEHS)

**Autism Centers of Excellence (ACE):** In 2007 and 2008, NIH created the unified ACE program in order to maximize coordination and cohesion of NIH-sponsored autism research efforts. The ACE programs will focus on a broad range of autism-related research, including but not limited to neuroimaging, biomarkers and susceptibility genes, pharmacotherapy, early intervention, and risk and protective factors.

- For more information, see Chapter 4: *NIH Centers of Excellence*.
- (E) (NIMH, NICHD, NIDCD, NIEHS, NINDS)
- (COE)

**National Database for Autism Research (NDAR):** NDAR is a collaborative biomedical informatics system being created by NIH to provide a national resource to support and accelerate research in autism.

- For more information, see <http://ndar.nih.gov>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E/I) (NIMH, CIT, NICHD, NIDCD, NIEHS, NINDS)



**Genomic Studies of Autism:** NIH has supported a number of studies that are pointing to potential genetic causes of autism.

- For more information, see <http://www.nimh.nih.gov/press/gene-mutations-autism.cfm>
- For more information, see <http://www.nimh.nih.gov/press/largest-ever-search-for-autism-genes-reveals-new-clues.cfm>
- For more information, see <http://www.nimh.nih.gov/press/autismmetgene.cfm>
- For more information, see <http://www.nimh.nih.gov/press/moy-crawley-autism.cfm>
- This example also appears in Chapter 3: *Genomics*.
- (E) (NIMH, NCCR, NICHD, NINDS)

**New Genetics Tools Shed Light on Addiction:** NIH-supported research is taking full advantage of the massive databases and rapid technologies now available to study how genetic variations influence disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms and genetic predispositions underlying diseases like addiction. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases by using custom screening tools known as “gene chips” (e.g., the *neurexin* gene has been found to play a role in drug addiction). A next-generation “neurochip” is being developed with 24,000 gene variants related to substance use and other psychiatric disorders. Applying this tool to addiction and other brain disorders will advance our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient’s genetic profile (i.e., a “pharmacogenetic” approach). To complement these efforts, NIH is investing heavily in the emerging field of *epigenetics*, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. A focus on gene-by-environment interactions has recently been expanded to incorporate developmental processes, which are now known to also affect the outcome of these interactions. The resulting Genes, Environment, and Development Initiative (GEDI) seeks to investigate how interactions among these factors contribute to the etiology of substance abuse and related phenotypes in humans.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/rfa-da-07-012.html>
- For more information, see <http://nihroadmap.nih.gov/roadmap15update.asp>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E/I) (NIDA, NCI, NIAAA, NIMH)
- (GPRA Goal)

**Underage Drinking Research Initiative:** In 2004, NIH launched the Underage Drinking Research Initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence, all framed within the context of overall development. Activities and accomplishments in 2007 include:

- ▷ Provided the scientific foundation for *The Surgeon General’s Call to Action to Prevent and Reduce Underage Drinking* (released March 6, 2007) and for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking

- ▷ Convened scientific meetings of experts, including the Underage Steering Committee that met four times over a 2-year period, a Meeting on Diagnosis of Alcohol Use Disorders Among Youth (April 2006), and a Meeting on Screening for Child and Adolescent Drinking and AUDs Among Youth (June 2007)
- ▷ Issued three Requests for Applications (RFAs), including “Underage Drinking: Building Health Care System Responses” (four projects awarded in FY 2006), “Impact of Adolescent Drinking on the Developing Brain” (five projects awarded in FY 2007), and “Alcohol, Puberty, and Adolescent Brain Development” (three projects awarded in FY 2007).
- ▷ Published *Alcohol Research & Health, Vol. 28, Number 3: Alcohol and Development in Youth: A Multidisciplinary Overview*
- ▷ Published a supplement of seven developmentally focused papers covering a broad range of underage drinking topics (accepted for the journal *Pediatrics*).
  - For more information, see <http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm>
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
  - (E) (NIAAA)

### **Prenatal Alcohol, Sudden Infant Death Syndrome, and Stillbirth (PASS) Research Network:**

Following a 3-year feasibility study, the NIH established this multidisciplinary consortium to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of sudden infant death syndrome (SIDS), stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study will prospectively follow 12,000 pregnant, high-risk, American Indian and South African women and their infants until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

- For more information, see <http://www.nichd.nih.gov/research/supported/pass.cfm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NICHD, NIAAA)

**The Role of Development in Drug Abuse Vulnerability:** NIH supports a number of longitudinal studies at various stages of development, following cohorts over extended timeframes. Information is gathered on children’s cognitive and emotional development, as well as their vulnerability to addiction later in life. These studies have been critical to estimate, for example, the contribution of in utero drug exposure to emotional and cognitive development, vulnerability to substance abuse, and other mental disorders. This knowledge, together with animal studies that provide complementary and validating information while minimizing the confounding factors that are likely to play a role in prenatal effects of drug exposure in humans, will help us to mitigate the deleterious impact of substance abuse on the developing fetus. With regard to later developmental stages, the application of modern brain imaging technologies has generated unprecedented structural and functional views of the dynamic changes occurring in the developing brain (from childhood to early adulthood). The discovery of these changes has been critical to understanding the role of brain development in decision-making processes and responses to stimuli, including early exposure to drugs. Such studies have suggested, for

example, that an unbalanced communication between volitional control and emotional circuits may explain some of the impulsive reactions typical of adolescents, who tend to engage in risky behaviors and are at heightened risk for developing addictions. Collectively, these longitudinal studies, using new imaging and genetics tools, promise a greatly enhanced ability to interpret the effects of myriad environmental variables (e.g., quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics) on brain development and behavior.

- For more information, see [http://www.drugabuse.gov/NIDA\\_notes/NNvol19N3/Conference.html](http://www.drugabuse.gov/NIDA_notes/NNvol19N3/Conference.html)
- For more information, see [http://www.nida.nih.gov/NIDA\\_notes/NNvol19N3/DirRepVol19N3.html](http://www.nida.nih.gov/NIDA_notes/NNvol19N3/DirRepVol19N3.html)
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDA, NICHD) (GPRA Goal)

**MRI Study of Normal Brain Development:** Understanding healthy brain development is essential to finding the causes of many childhood disorders, including those related to intellectual and developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases. NIH is creating the Nation's first database of MRI measurements and analytical tools, as well as clinical and behavioral data to understand normal brain development in approximately 500 children across the Nation. This large-scale, longitudinal study uses several state-of-the-art brain-imaging technologies. The data will be disseminated as a Web-based, user-friendly resource to the scientific community.

- [Evans AC, et al. \*Neuroimage\*. 2006;30:184-202](#), PMID: 16376577
- For more information, see <http://www.bic.mni.mcgill.ca/nihpd/info/index.html>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E/I) (NICHD, NIDA, NIMH, NINDS)

**Studies of Normal Brain Development:** The NIH Intramural Research Program is conducting studies to explore brain development in healthy children and adolescents with MRI. Recent studies have addressed brain structure differences related to risk for Alzheimer's disease and sex differences in brain development trajectories.

- [Shaw P, et al. \*Lancet Neurol\* 2007;6:494-500](#), PMID: 17509484
- [Lenroot RK, et al. \*Neuroimage\* 2007;36:1065-73](#), PMID: 17513132
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIMH) (GPRA Goal)

**Powerful New Technique Reveals How Brain Cells Wire Together:** In order to understand how the brain processes visual information and performs other tasks, researchers have wanted to construct a "wiring diagram" of the billions of neurons connected in precise, identifiable circuits. A breakthrough technology has helped clear this major hurdle by revealing all the connections made by a single nerve cell. The new tool uses a modified rabies virus, which can spread indefinitely through the nervous system by jumping between communicating nerve cells. However, scientists modified the virus so that it jumps once and then leaves a fluorescent tag in the neurons connected to a single cell. This permits visualization of functional processing circuits

in living brains. It can also be used in transgenic mice to deactivate targeted classes of neurons expressing specific genes, revealing changes in brain function, including behavior.

- [Wickersham JR, et al. \*Neuron\* 2007;53:639-47](#), PMID: 17329205
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*
- (E) (NEI)

## Neuroplasticity: Substrates for Change and Repair

**Promising Approaches to Treating Chronic Pain:** Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can produce drug dependence. Thus, an area of enormous need is the development of potent non-opioid analgesics. In recognition of this, NIH has implemented an aggressive and multidisciplinary research program. Many of these initiatives are yielding tangible results that stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to selectively activate the CB system to provide analgesia with minimal or no psychotropic side effects or abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different receptors, the targeting of which could provide a vastly expanded range of pharmacotherapeutic effects. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on a non-neuronal brain cell type, glia, has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their pro-inflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of analgesic drugs. At the brain circuit level, a new approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects "learn" how to regulate pain by viewing and then controlling images of their own brains in real time.

- For more information, see: <http://www.nida.nih.gov/whatsnew/meetings/default.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDA, NINDS)

**Tools to Reveal the Mechanisms Governing Behavior:** Newly acquired but rapidly evolving tools and techniques that monitor or probe discrete brain systems have allowed NIH-supported researchers to begin filling in the information gap between molecular or cellular events and behavioral outcomes. A notable preclinical example of this trend is the development of a genetically engineered method to turn the electrical impulses of brain cells on and off with pulses of light—in sync with the split-second pace of real-time neuronal activity. The novel technique borrows genes from light-responsive algae and bacteria to unravel the intricate workings of brain circuits with extreme precision. This powerful new tool could be used to assess the role of neuronal activity in regulating normal behavior and disease processes. On the clinical side, an array of brain imaging devices has produced much information on how neural circuits develop and process information under normal conditions and how they become impaired by a disease like addiction. These advances have led to the fertile concept that the transition from abuse to addiction is not a switch but a gradual degradation of the ability of different circuits to "talk" to each other as they attempt to compensate for their deficiencies. Interestingly, these studies are

also showing significant overlap in the circuits involved in drug abuse and the circuits underlying compulsive overeating and obesity. Moreover, in preclinical studies, compounds that interfere with food consumption in animal models of compulsive eating also interfere with drug administration.

- For more information, see <http://www.nimh.nih.gov/press/lightswitchneurons.cfm>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NIDA, NIMH)

**The Scientific Basis of Acupuncture:** Ongoing research on acupuncture includes a substantial portfolio of basic and translational studies employing state-of-the-art neuroimaging technology. This work is beginning to provide powerful scientific insight into the potential neurobiological mechanisms of action by which acupuncture might work. Clinical trials of acupuncture for a number of medical conditions are also under way, including studies examining (1) the potential role of traditional acupuncture as an additive/alternative treatment for the prevention of acute cardiac events in patients with coronary artery disease, (2) whether manual or electro-acupuncture contributes to neurological recovery after spinal cord injury, and (3) the efficacy of acupuncture in relieving post-thoracotomy pain syndrome (severe and persistent aching or burning pain along surgical scars in the chest).

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**Cochlear Implants:** One of the more groundbreaking biomedical achievements in the last 30 years has been the cochlear implant, an electronic device that provides a sense of sound to individuals who are profoundly deaf or severely hard-of-hearing. Cochlear implants process sounds from the environment and directly stimulate the auditory nerve, bypassing damaged portions of the inner ear. Nearly 100,000 individuals worldwide have been fitted with cochlear implants. In the United States, approximately 22,000 adults and nearly 15,000 children have received them. Derived in part from NIH-funded research that dates back to the early 1970s and continues today, this remarkable technology has enabled deaf and severely hard-of-hearing individuals to enjoy an enhanced quality of life. NIH-supported scientists showed that profoundly deaf children who receive cochlear implants at an early age develop language skills at a rate comparable to that of children with normal hearing. They also found that the benefits of the cochlear implant in children far outweigh its costs. Scientists can now study the large groups of children who were identified early for hearing loss and use this knowledge to document how treatments such as cochlear implants can lead to improved speech and language acquisition, academic performance, and economic outcomes for these children.

- [Nicholas JG, Geers AE. \*Ear Hear\* 2006;27:286-98](#), PMID: 16672797
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*.
- (E) (NIDCD)

**Neurobiology of Appetite Control:** NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. Examples include research on how



serotonin reduces appetite; the actions of the protein mTOR in sensing nutrients in the body so as to modulate food intake; and a strategy to block ghrelin, a stomach-secreted hormone that signals the brain to increase food intake. This research has implications for new therapies for obesity.

- [Cota D, et al. \*Science\* 2006;312:927-30](#). PMID: 16690869
- [Heisler LK, et al. \*Neuron\*. 2006;51:239-49](#), PMID: 16846858
- [Zorrilla EP, et al. \*Proc Natl Acad Sci U S A\* 2006;103:13226-31](#), PMID: 16891413
- For more information, see <http://tinyurl.com/22o9my> (“Obesity” chapter)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK)

**A Multidisciplinary Approach to Nicotine Addiction:** Nicotine addiction is the number-one preventable public health threat and has enormous associated morbidity, mortality, and economic costs. NIH-supported research has generated new knowledge to support the development of more effective prevention messages and treatment approaches. Several notable examples characterize NIH’s multidisciplinary approach to targeting the best treatment (or combination of treatments) for nicotine addiction. *Genomic studies* have recently uncovered a series of genes that are associated with nicotine addiction and that could provide new targets for medications development and for the optimization of treatment selection. *Pharmacologic studies*, so critical to understanding the basis of nicotine’s mode of action, have recently revealed that its addictiveness may hinge upon its ability to slowly shut down or desensitize the brain’s response to nicotine. A recent *imaging study* indicated that a part of the brain called the insula may play an important role in regulating conscious craving. This exciting finding provides a new target for research into the neurobiology of drug craving and for the development of potentially more effective smoking cessation and other addiction treatments. Results of a Phase II *clinical trial* strongly suggest that a nicotine vaccine, which works by preventing nicotine from reaching the brain, may be a particularly useful tool for cessation programs in the not-too-distant future.

- For more information, see <http://www.drugabuse.gov/researchreports/nicotine/nicotine.html>
- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Genomics*, and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDA, NCI) (GPRA Goal)

**Treatments to Fight Methamphetamine Addiction:** The abuse of methamphetamine—a potent and highly addictive psychostimulant—is a serious problem in the United States. Methamphetamine abuse can have devastating medical, psychological, and social consequences. Adverse health effects include memory loss, aggression, psychotic behavior, heart damage, and abnormal brain function. Methamphetamine abuse also contributes to increased transmission of hepatitis and HIV/AIDS and can spawn increased crime, unemployment, and other social ills. The good news is that methamphetamine abuse and addiction are treatable, and people do recover. As methamphetamine abuse has increased, so has NIH’s support of research to combat it, including research on genetics, brain development, and translation of findings. This research has led to the development of two effective behavioral therapies for methamphetamine addiction: (1) the Matrix Model, consisting of a 16-week program that includes group and individual therapy and addresses relapse prevention, behavioral changes, establishment of new drug-free environments, and other areas, and (2) Motivational Incentives for Enhanced Drug Abuse Recovery, a cost-effective incentive method for cocaine and methamphetamine addiction that has been shown to sustain abstinence in twice the number of participants engaged in treatment as

usual. Increasingly, community treatment providers nationwide are implementing motivational incentives as part of drug addiction treatment.

- For more information, see <http://www.drugabuse.gov/ResearchReports/Methamph/Methamph.html>
- For more information, see <http://www.drugabuse.gov/Testimony/6-28-06Testimony.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDA)

**Quantum Program:** The NIH Quantum Grants Program has been developed to make a profound (quantum-level) advance in health care by funding research, over two phases, on targeted projects that will develop new technologies for the diagnosis, treatment, or prevention of a major disease or national public health problem. The first of the Quantum Grants was to engineer stem cell-based neurovascular regenerative units in a laboratory environment, which can then be implanted into the damaged cortex of stroke patients to provide a source of neural and vascular cells that will continue to develop and differentiate. This approach may lead to the first true treatment for stroke, which is one of the most common causes of disability and severely affects the quality of life of patients throughout the world. Another Phase I Quantum competition was completed in September 2007, with four additional grants awarded. The Phase II Quantum competition will begin in FY 2009.

- For more information, see <http://www.nibib.nih.gov/Research/QuantumGrants>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIBIB)

**Prevention of Trauma-Related Mental Disorders in High-Risk Occupations:** NIH is supporting a research initiative to develop and test preemptive interventions to prevent trauma-related disorders, such as posttraumatic stress disorder, among occupational groups at high risk for trauma exposure, such as the military, firefighters, police, and rescue workers.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-010.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIMH)

**Traumatic Brain Injury Program:** Traumatic brain injury (TBI) presents enormous challenges to neuroscience because of the numbers of people affected and the range of problems TBI can cause. The consequences of TBI may be subtle or severe, immediate or delayed, perhaps even predisposing to problems many years later in life. TBI can compromise virtually any human ability, depending on which parts of the brain are damaged. NIH supports a broad program of research, from studies of how TBI causes immediate and delayed damage to brain cells, to development of measurable diagnostic markers of damage, through large clinical trials to test interventions. NIH clinical studies are developing both emergency interventions to minimize damage and rehabilitation strategies to compensate for damage or encourage the brain to adapt. The high rate of TBI among military personnel in Afghanistan and Iraq presents a special concern. NIH intramural scientists are working with the Departments of Defense and Veterans Affairs to study the psychobiological consequences of TBI among military personnel, and NIH is working with all relevant Federal agencies to coordinate research activities on high-priority



issues, including a 2006 interagency conference on TBI and follow-up meetings in 2007 and 2008 focusing on issues such as injury classification and potential combination therapies.

- (E/I) (NINDS, NICHD)

**Epilepsy Research Benchmarks:** In March 2000, NINDS convened a broad group of scientists, clinicians, people impacted by epilepsy, and public policymakers for a White House-initiated conference on the disorder. After this conference, NINDS developed a series of epilepsy research goals in three major topic areas: (1) interrupting and monitoring the development of epilepsy, (2) preventing epilepsy, and (3) developing more effective therapies. The Institute worked with the epilepsy research and patient communities to develop a series of benchmarks for tracking progress toward these goals. Researchers have made substantial progress since this meeting, and science has also evolved over this time. As a result, NINDS organized a session at the most recent Curing Epilepsy 2007 conference for the participants to discuss revisions to the first set of benchmarks. NINDS is currently collecting public feedback on these revised goals and will work with a group of representatives from the scientific community to refine the benchmarks for release at the 2007 American Epilepsy Society meeting.

- For more information, see <http://www.ninds.nih.gov/funding/research/epilepsyweb/index.htm>
- (E) (NINDS)

**Neural Prosthesis Program:** Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. The NINDS Neural Prosthesis program pioneered the development of this technology beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants for the hearing impaired, respiratory and hand grasp devices for people with spinal cord injuries, and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore standing and voluntary bowel and bladder control after spinal cord injury, to allow paralyzed persons to control devices directly from their brains, and to control seizures. Ongoing research also seeks to improve cochlear implants and to advance deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community that now includes private-sector companies and represents a cooperative effort among several NIH Institutes, which coordinate their efforts with programs now under way in the Department of Veterans Affairs and the Department of Defense.

- For more information, see <http://www.ninds.nih.gov/funding/research/npp/index.htm>
- For more information, see <http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*.
- (E) (NINDS, NCRR, NEI, NIBIB, NICHD, NIDCD)

**Link Between Eye Movement and Reward:** Dopamine is vital to motor behaviors, but neurons that release dopamine carry signals related to rewards, not body movements. As a solution to this puzzle, recent theories propose that the reward-related dopamine signals are used for learning of motor behaviors. However, it is unknown how dopamine neurons acquire the reward-related signals. NIH scientists have shown that a small brain area called the lateral habenula controls

dopamine neurons by inhibiting them and thereby suppressing less rewarding eye movements. This discovery opens up new research connecting emotion and motivation to motor behaviors.

- [Matsumoto M, Hikosaka O. \*Nature\* 2007;447:1111-5](#), PMID: 17522629
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (NEI)

**Genes Involved in the Regulation of Sensitivity to Alcohol:** Low doses of alcohol are stimulating in both humans and animals while higher doses have sedating effects. Sensitivity to alcohol, however, varies across individuals and low sensitivity to alcohol is a risk factor for the development of alcohol dependence in humans. Recent animal studies have identified several genes that alter sensitivity to alcohol and may provide targets for medications development.

▷ Researchers have discovered a genetic mutation that disrupts the function of the fruit fly gene RhoCAP18B, causing the flies to be much more resistant to alcohol sedation. Other variants of the same gene, each of which has a distinctly different effect on the response to alcohol, were subsequently identified.

- [Rothenfluh A, et al. \*Cell\* 2006;127:199-211](#), PMID: 17018286

▷ Another fruit fly gene, *homer*, has been shown to be required for normal sensitivity and tolerance to alcohol. This study shows that ethanol sensitivity and tolerance co-map to the same population of neurons, suggesting that the neuronal circuits controlling these two behaviors, known to contribute to alcohol dependence, are shared.

- [Urizar NL, et al. \*J Neuroscience\* 2007;27:4541-51](#), PMID: 17460067
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAAA)

**Increased Endocannabinoid Signaling Increases Ethanol Consumption and Decreases Acute Ethanol Intoxication:** Endocannabinoids, the naturally occurring substances in the brain that act on the same receptors as the active ingredients of marijuana, have been discovered to play a role in regulating appetite for alcohol. NIH-supported scientists discovered that mice lacking expression of fatty acid amidohydrolase (FAAH), the main endocannabinoid-degrading enzyme, showed an increased appetite for ethanol, decreased sensitivity to ethanol-induced sedation, and faster recovery from ethanol-induced motor incoordination. These results show that impaired FAAH function leads to increased voluntary alcohol intake and point to FAAH both as a potential susceptibility factor and a therapeutic target for excessive alcohol consumption.

- [Hansson AC, et al. \*Neuropsychopharmacol\* 2007;32:117-26](#), PMID: 16482090
- [Blednov YA, et al. \*Neuropsychopharmacol\* 2007;32:1570-82](#), PMID: 17164820
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E/I) (NIAAA)

**Re-innervation of Regenerated Hair Cells:** Hair cells detect sound and are named for the hairlike projection from their top surface. Researchers hope one day to regenerate hair cells in the inner ears of people who have experienced damage due to noise, drugs, or disease. However, the ability to regrow hair cells will not restore hearing or balance without properly reconnected nerve endings. NIH-supported scientists used drugs to destroy hair cells and corresponding nerve

endings in adult pigeons. (Unlike mammals, birds and other vertebrates are able to regenerate hair cells naturally.) Using a high-powered microscope, the scientists examined tissue sections and determined that the re-innervation process was similar to the pattern observed during normal nerve cell development. Although the regenerated nerve endings were less complex than those generated in normal development, many balance-related behaviors nevertheless fully recovered. This finding suggests that scientists may need only to regenerate simple nerve endings to restore the sense of balance. Further clarification of the mechanisms involved in nerve cell regeneration is essential for the potential recovery of balance and hearing in people with inner-ear damage.

- [Zakir M, Dickman JD. \*J Neurosci\* 2006;26:2881-93](#), PMID: 16540565
- (E) (NIDCD)

## Neurodegeneration: Fighting the Effects of Age, Exposure, and Disease

**Alzheimer’s Disease Neuroimaging Initiative (ADNI):** ADNI is an innovative public-private partnership for examining the potential for serial MRI, positron emission tomography (PET), or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer’s disease. Early results suggest that researchers may be able to reduce the costs associated with clinical trials by improving imaging and biomarker analysis. One ADNI study found that a standard model can be used to monitor the performance of MRI scanners at multiple clinical sites, ensuring the accuracy of the MRI images. In another study, investigators compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and Alzheimer’s disease and found that scans correlated with symptoms of each condition and that images were consistent across sites. This finding suggests that PET scans may be a valid method for monitoring the effectiveness of therapies in future clinical trials. More than 200 researchers have already accessed a public database containing thousands of brain images and related clinical data obtained through blood and cerebrospinal fluid analyses.

- For more information, see <http://www.loni.ucla.edu/ADNI>
- For more information, see <http://www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials/ADNI.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIA, NIBIB)

**Genome-Wide Genotyping in Parkinson’s Disease:** NIH researchers recently conducted genome-wide genotyping of publicly available samples from a cohort of 267 patients with Parkinson’s disease and 270 neurologically normal control subjects to identify any common genetic variability with significant effect on the risk for Parkinson’s disease. The project has produced approximately 220 million data points in the 537 subjects, the largest collection of publicly available genotypes in a case-control cohort. The release of these data facilitates research on Parkinson’s disease and other neurodegenerative disorders, and the genotypes from neurologically normal control subjects can be used as a comparison cohort for other studies, dramatically reducing the cost of future research.

- [Fung HC, et al. \*Lancet Neurol\* 2006;5:911-6](#), PMID: 17052657
- For more information, see <http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20060927parkinsons.htm>

- This example also appears in Chapter 3: *Genomics*.
- (E/I) (NIA, NINDS)

### **Ongoing Research on Complementary and Alternative Medical Approaches for Patients with Alzheimer's Disease or Dementia and Their Caregivers:**

- ▷ A study in an animal model of Alzheimer's disease, evaluating whether fish oil, a safe and relatively inexpensive dietary supplement source of omega-3 fatty acids, shows similar or better effects than docosahexaenoic acid (DHA) in slowing the progression of changes associated with cognitive and functional decline in humans with Alzheimer's disease
  - ▷ A feasibility study of polarity therapy as an intervention for family caregivers of people with dementia who experience high levels of stress and are at risk for physical and mental health illness
  - ▷ Preclinical investigations of the potential activity and mechanisms of effect of (1) D-pinitol, a natural compound found in high concentrations in pine tree components and in smaller but significant concentrations in soy, and (2) substances derived from heat-processed ginseng and other related natural products.
- (E) (NCCAM)

**Alzheimer's Disease Cooperative Study (ADCS):** Much of the NIH-supported clinical research on Alzheimer's disease takes place through the ADCS. The study involves a consortium of centers in the United States and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of Alzheimer's disease or predict the disease's development in vulnerable people. To date, approximately 4,600 people have participated in the trials. In FY 2007, new studies included a trial to demonstrate whether intravenous immunoglobulin is clinically useful for treating Alzheimer's disease and a trial to examine whether treatment with docosahexaenoic acid, an omega-3 fatty acid, will slow cognitive decline in patients with Alzheimer's disease.

- For more information, see <http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20061017ADCS.htm>
- For more information, see <http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/NeuroscienceOfAging/ProgramInitiatives/ADCS.htm>.
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIA)

**Parkinson's Disease Registry:** NIEHS has begun to address the need for more precise data on the incidence and prevalence of Parkinson's disease through support of a Parkinson's disease registry in the State of California, where the large and diverse population, coupled with the wide range of exposures that exist through agriculture and other activities, provides a unique opportunity to investigate disease-environment links. The United States does not have a national health registry to supply data on Parkinson's disease, so estimates are based on sampling by individual studies in specific locales. The Parkinson's registry in California will allow us to base national estimates on a registry drawing upon a cross-section of the population in our most populous state.

- For more information, see <http://www.thepi.org/site/parkinson/section.php?id=101>

- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NIEHS)

**Multiple Sclerosis:** Although the exact cause of multiple sclerosis is unknown, research suggests a strong genetic component. NIH funds a number of studies to determine the underlying genetic causes of multiple sclerosis, including a project to identify regions of the genome containing multiple sclerosis susceptibility genes using a large familial dataset and genomic analysis tools. NIH also funds clinical trials to test therapies for multiple sclerosis, including the CombiRx trial, a randomized, controlled clinical trial comparing the efficacy of treatment combining beta-interferon and glatiramer acetate versus treatment with a single agent for relapsing forms of MS. A study conducted in conjunction with CombiRx by NIH intramural researchers (BioMS) is assessing multiple sclerosis biomarkers by using genomic and proteomic technology and relating the information obtained back to clinical and MRI data generated by the CombiRx clinical trial.

- [Gregory SG, et al. \*Nat Genet.\* 2007;39:1083-91](#), PMID: 17660817
- [International Multiple Sclerosis Genetics Consortium, et al. \*N Engl J Med.\* 2007;357:851-62](#), PMID: 17660530
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NINDS)

**Age-Related Eye Disease Study, Part 2 (AREDS2):** Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly in the United States and will be an increasing burden in future years, based on demographics. The original AREDS, which was completed in 2005, demonstrated that antioxidant vitamin and mineral supplements reduced the progression to advanced AMD by 25 percent. Building on these landmark findings, AREDS Part 2 (AREDS2) is assessing additional supplements (lutein, zeaxanthin, and long-chain omega-3 fatty acids) as a treatment for AMD and cataracts. AREDS2 is also evaluating effects of eliminating beta-carotene and/or reducing zinc in the original AREDS formulation on AMD progression. AREDS2 investigators will also explore gene-environment interactions in the development of these conditions, cognitive function, and cardiovascular health.

- For more information, see <http://www.areds2.org>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NEI, NIA)

**Retinal Neurodegeneration Program:** The Retinal Neurodegeneration Program is a new multidisciplinary intramural research program that combines basic, preclinical, and translational research to develop and test therapeutic interventions in several retinal degenerative diseases. These interventions include gene therapy, small molecules, neurotrophic factors, and cell-based systems, in combination with a variety of treatment delivery technologies.

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (NEI)

**Alzheimer's Disease Genetics Initiative and Data Storage:** Only one of the four validated Alzheimer's disease genes, *APOE*, has been definitively linked with the more common late-onset form of the disease. A fifth gene, *SORL1*, has recently been linked with late-onset Alzheimer's disease in some studies. The goal of the Alzheimer's Disease Genetics Initiative is to develop the resources necessary for identifying the late-onset Alzheimer's disease risk factor genes and the interactions of genes with the environment. In FY 2006, NIH achieved its goal to recruit 1,000 families with two or more siblings living with Alzheimer's disease through an unprecedented alliance of Alzheimer's disease centers, researchers, and outreach with the Alzheimer's Association. To facilitate access by qualified investigators, all genetic data derived from NIH-funded studies on late-onset Alzheimer's disease genetics are deposited at a central data storage site at Washington University in St. Louis, another NIH-approved site, or both. Discovery of risk factor genes will help illuminate the underlying disease processes of Alzheimer's disease, open up novel areas of research, and identify new targets for drug therapy.

- For more information, see <http://www.niageneticsdata.org>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E/I) (NIA)

**Understanding the Mechanisms of Alcohol-Induced Tissue Injury:** Heavy alcohol use has an impact on nearly every organ system of the body (the most vulnerable being the brain and liver), and the resulting pathological conditions contribute to increased mortality and morbidity among all age and racial/ethnic groups and both sexes. NIH is especially interested in elucidating mechanisms of injury common to multiple body and organ systems. A number of Program Announcements and RFAs have been issued to support research to increase our understanding of the underlying cellular and molecular mechanisms of tissue injury caused by alcohol consumption, including alcohol's genetic, epigenetic, and metabolic effects. The long-term goals of these initiatives are to identify biomarkers for alcohol exposure and for the early detection of alcohol-induced tissue injury, as well as to develop new therapeutics that control or modify outcomes of chronic alcohol use.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-065.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-360.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-361.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-004.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-005.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E/I) (NIAAA)

**Cognitive and Emotional Health Project: The Healthy Brain:** The purpose of this initiative is to assess the state of longitudinal and epidemiological research on determinants of cognitive and emotional health in aging adults. The project has completed a comprehensive review of measures that have been (or could be) used in epidemiological research. To help NIH learn what epidemiological data exist on the cognitive and emotional health of adults in the United States, the project polled investigators who are conducting these types of studies and created an online database. In addition, a Critical Evaluation Study Committee conducted an analysis and published a summary of the existing scientific literature pertaining to factors involved in the



maintenance of cognitive and emotional health in adults. NIH is discussing new initiatives to expand this project, including promoting the use of existing datasets and developing ancillary studies to examine how cognitive and emotional health influence each other.

- For more information, see [http://www.alzheimersanddementia.com/article/S1552-5260\(05\)00503-0/abstract?articleId=&articleTitle=&citedBy=false&medlinePmidWithoutMDLNPrefix=&overridingDateRestriction=&related=false&restrictdesc\\_author=&restrictDescription=&restrictName.jalz=jalz&restrict](http://www.alzheimersanddementia.com/article/S1552-5260(05)00503-0/abstract?articleId=&articleTitle=&citedBy=false&medlinePmidWithoutMDLNPrefix=&overridingDateRestriction=&related=false&restrictdesc_author=&restrictDescription=&restrictName.jalz=jalz&restrict)
- For more information, see <http://trans.nih.gov/cehp>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NINDS, NIA, NIMH)

**Progress in Parkinson’s Disease Research:** For the past 7 years, NIH has been actively engaged in identifying gaps in Parkinson’s disease research and developing programs to address them. Examples of progress include initiation of Phase III clinical trials of creatine and coenzyme Q10 to treat early Parkinson’s disease; development of diagnostic criteria for depression and psychosis in people with Parkinson’s disease; and support for a Parkinson’s disease Gene Therapy Study Group. NIH has also begun to formally assess the effectiveness of its programs by completing an evaluation of its Morris K. Udall Centers of Excellence in Parkinson’s Disease Research. This evaluation included an assessment of scientific progress made by the centers and the value of using a centers mechanism, as well as an exploration of the effectiveness of program management and review in supporting the centers. The Working Group tasked with this evaluation released its findings in September 2007.

- For more information, see <http://www.ninds.nih.gov/funding/research/parkinsonsweb/index.htm>
- For more information, see <http://www.parkinsontrial.ninds.nih.gov/index.htm>
- For more information, see [http://www.ninds.nih.gov/news\\_and\\_events/press\\_releases/pressrelease\\_creatine\\_03222007.htm](http://www.ninds.nih.gov/news_and_events/press_releases/pressrelease_creatine_03222007.htm)
- For more information, see [http://www.ninds.nih.gov/udall\\_centers\\_evaluation](http://www.ninds.nih.gov/udall_centers_evaluation)
- (E) (NINDS)

**Toward Better Treatment for Muscular Dystrophy:** Activities funded by NIH are pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4). NIH also recently funded two large-scale translational research projects in muscular dystrophy: one to develop small-molecule drugs for Duchenne and potentially other forms of muscular dystrophy and another to develop the optimal vector for vascular delivery of genes. A new NIH Government Performance and Results Act (GPRA) goal aims to advance two emerging strategies for treating muscular dystrophy to clinical trial readiness by 2013. The Muscular Dystrophy Coordinating Committee’s *Action Plan for the Muscular Dystrophies* also identified therapy development goals to be pursued by NIH and the committee’s partner agencies and organizations. A recent workshop convened by NIH reviewed the status of different therapeutic approaches for muscular dystrophy and discussed ways to move this research forward.

- For more information, see [http://www.ninds.nih.gov/find\\_people/groups/mdcc/MDCC\\_Action\\_Plan.pdf](http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan.pdf)
- For more information, see [www.wellstonemdccenters.nih.gov](http://www.wellstonemdccenters.nih.gov)
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (COE) (NINDS, NIAMS, NICHD) (GPRA Goal)



**Translational Research on Alzheimer's Disease:** To move basic research on Alzheimer's disease and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. To closely monitor the progress of the translational projects, provide guidance, and foster interactions among investigators involved in translational research funded by these programs, NIH staff will hold the First Annual Investigators Meeting for Translational Research in September 2007.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-048.html>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E/I) (NIA)

**Preclinical Efficacy of *Ginkgo biloba* in Alzheimer's Disease:** NIH-supported investigators recently published results showing that *Ginkgo biloba*, studied in an animal model of Alzheimer's disease, reduces both the formation of the specific brain abnormalities seen in humans and the resulting paralysis seen in the animals. These experiments lend additional support to the hypothesis that *Ginkgo biloba* may be useful in slowing the progression of Alzheimer's disease. That hypothesis is being tested in the largest clinical trial to date of *Ginkgo biloba* for the prevention of dementia, supported by NIH.

- [Wu Y, et al. \*J Neurosci\* 2006;26:13102-13](#), PMID: 17167099
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCCAM)

**Inflammatory Factor Mediates Nerve Degeneration in Glaucoma Model:** In glaucoma, elevated eye pressure plays a role in damaging fibers in the optic nerve, which relays visual signals to the brain. However, the link between pressure and nerve damage is not well understood. Recent research in mice suggests a critical role for the protein tumor necrosis factor-alpha (TNF- $\alpha$ ) in developing glaucoma. A molecular target in the glaucoma disease pathway opens up doors for drug therapy.

- [Nakazawa T, et al. \*J Neurosci\* 2006;26:12633-41](#)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NEI)

**Gene Expression Changes in Facioscapulohumeral Muscular Dystrophy:** Results from a genome-wide scan of skeletal muscle biopsies suggest a link between eye blood vessel defects and muscle defects that characterize facioscapulohumeral muscular dystrophy. Patient participants were recruited from the National Registry for Myotonic Dystrophy and patients with facioscapulohumeral muscular dystrophy and their family members.

- [Osborne RJ, et al. \*Neurology\* 2007; 68:569-77](#). PMID: 17151338
- For more information, see [http://www.niams.nih.gov/Funding/Funded\\_Research/registries.asp#dystrophy](http://www.niams.nih.gov/Funding/Funded_Research/registries.asp#dystrophy)
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Genomics*.
- (E) (NIAMS, NCRR, NINDS)

**Hereditary Hearing Loss:** NIH recognizes that one of the most rapidly developing areas of research is functional genomics, which involves determining the identity, structure, and function of genes. Hereditary or genetic causes account for approximately 50-60 percent of the severe to profound cases of childhood hearing loss. NIH-supported scientists are working to understand the normal function of these genes and how they are altered in individuals with hereditary hearing loss. At present, more than 70 genes causing nonsyndromic hereditary hearing impairment have been mapped to intervals on particular chromosomes; many of these efforts were the result of collaborations involving NIH-supported scientists. In collaborative efforts with scientists in Colombia, India, Indonesia, Israel, Lebanon, Mexico, Newfoundland, Pakistan, Tunisia, Puerto Rico, and the United States, NIH is accelerating this gene discovery effort. These research investments to understand the genetic basis of communication disorders will help scientists develop diagnostic tests and better treatments for the millions of Americans with hereditary hearing impairment.

- [Morton CC, Nance WE. \*N Engl J Med\* 2006;354:2151-64.](#) PMID: 16707752
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E/I) (NIDCD)

## Advancing Neuroscience Research Through Collaboration

**The NIH Blueprint for Neuroscience Research:** The NIH Blueprint is a collaborative framework that brings together 16 NIH ICs and Offices that support neuroscience research. The Blueprint catalyzes research progress by developing tools, resources, and training opportunities that transcend the mission of any single NIH IC and serve the entire neuroscience community. In FY 2006, the Blueprint launched initiatives to develop new neuroimaging technologies, a clearinghouse to distribute and improve existing neuroimaging software, core resource centers, a neurological and behavioral assessment tool, and new genetically modified mouse models. The Blueprint also supported training programs in neuroimaging, computational neuroscience, and translational research. In FY 2007, the Blueprint released funding announcements to identify biomarkers for neurodegeneration, develop new ways to deliver therapeutics to the nervous system, and provide interdisciplinary training in neurodegeneration research.

- For more information, see <http://www.neuroscienceblueprint.nih.gov>
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (NINDS, NCCAM, NCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

**A Clearinghouse for Neuroimaging Informatics Tools and Resources:** NIH understands that researchers seeking neuroimaging analysis software tools need a convenient way to find and compare useful software. Indeed, the best or most suitable neuroimaging analysis technologies for research may be hidden in someone's laboratory or some obscure corner of cyberspace. NIH is creating a Neuroimaging Informatics Tools and Resources Clearinghouse. The 14 NIH ICs that participate in the Neuroscience Blueprint have supported the development of sophisticated, high-quality neuroimaging informatics tools and resources. The clearinghouse is intended to facilitate the dissemination of those tools and resources and promote their adoption within the extended neuroimaging community. A contract has been awarded to the Turner Consulting Group, which specializes in delivering tailored information management solutions, to create the

clearinghouse infrastructure. The infrastructure will include a Web site that will not only provide access to tools and resources but will also provide ongoing opportunities for public comment to guide future development and enhancement of the tools. In addition to the contract award, grant awards are being made to individual extramural scientists to enable them to render their tools more suitable for this initiative. The awards will fund the enhancement of tools to make them easier to use, more broadly applicable, or more compatible with other existing tools. The clearinghouse was released to the public in October 2007.

- For more information, see <http://www.nitrc.org>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (NIBIB, NCCAM, NCCR, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

**NIMH Genetics Repository:** Over the last 9 years, NIMH has built the infrastructure for large-scale genetics studies through the NIMH Human Genetics Initiative. Through this Initiative, NIMH established a repository of DNA, cell cultures, and clinical data that serve as a national resource for researchers studying the genetics of complex mental disorders.

- For more information, see <http://nimhgenetics.org>.
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NIMH)

**Practical Clinical Trials:** NIH has completed primary and secondary phases of several practical clinical trials that have examined treatment effectiveness for mental disorders such as schizophrenia, bipolar disorder, and depression. The infrastructure developed for each of these large multisite trials—involving more than 10,000 participants at over 200 sites—has forged efficient, effective, and collaborative relationships between scientists and clinicians throughout the country. To capitalize on the national networks established for the trials, NIH will fund infrastructure-only support for the platform of clinical sites and an administrative core. It is anticipated that the platform will serve as a critical foundation for supporting participant enrollment, facilitating communication among trial sites, maintaining up-to-date training in diagnosis and treatment, and providing needed administrative organization.

- For more information, see <http://www.nimh.nih.gov/healthinformation/catie.cfm>
- For more information, see <http://www.nimh.nih.gov/healthinformation/stard.cfm>
- For more information, see <http://www.nimh.nih.gov/healthinformation/stepbd.cfm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIMH)

**NINDS Human Genetics Repository:** In 2003, NINDS established the Human Genetics Repository to collect, store, characterize, and distribute DNA samples and cell lines and standardized clinical data for the research community. By June 2007, the repository held material from 16,683 subjects, including those with stroke (4,363), epilepsy (1,065), Parkinson's disease (3,585), and motor neuron diseases such as ALS (2,445), as well as control samples (4,767). The ethnically diverse collection represents populations from the United States and several other countries. Investigators have submitted or published more than 50 scientific articles based on

data from this resource, and technological advances allowing “whole genome screening” for disease genes have also enhanced its value.

- For more information, see <http://ccr.coriell.org/Sections/Collections/NINDS/?SsId=10>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E/I) (NINDS)

**NIH Pain Consortium:** The aims of the NIH Pain Consortium are to enhance pain research and promote collaboration among researchers across the many NIH ICs that have programs and activities addressing pain. The consortium held its second annual symposium, “Advances in Pain Research,” on May 1, 2007, to feature new and exciting advances in pain research and pain management. Topics included neuropathic pain, visceral pain, inflammatory pain, and treatment-induced pain. Participants included NIH and extramural scientific communities, health care providers, and the public. Consortium ICs also issue an NIH-wide Funding Opportunity Announcement, “Mechanisms, Models, Measurement, and Management in Pain Research,” to encourage pain research and delineate cross-cutting NIH interests in pain.

- For more information, see <http://videocast.nih.gov/PastEvents.asp>
- For more information, see <http://painconsortium.nih.gov/index.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E/I) (NIDCR, CC, FIC, NCCAM, NCI, NCCR, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIGMS, NIMH, NINDS, NINR, OBSSR, OD, ODP/ORD, ORWH, OTT)

**Gene Expression Nervous System Atlas (GENSAT):** Knowing where and when genes are active is a key to understanding how the nervous system develops, how the normal brain works, and what goes wrong in disease. More than half of all genes are active at some point in the brain, yet only a small fraction of these have been well characterized. To systematically address this issue, NIH initiated the GENSAT project. The project prescreens the activity of many genes at four developmental time points in several parts of the brain and spinal cord and, for genes of high interest, generates strains of mice in which a visible marker is turned on wherever and whenever the gene of interest is active. In addition to the value of the publicly accessible GENSAT database, the mice are useful for research on normal development and function and diseases. For example, researchers used GENSAT mice to discover that one of two previously indistinguishable types of nerve cells is selectively vulnerable in Parkinson’s disease. By revealing the molecular mechanism that kills the cells, these experiments also identified a new potential drug target. GENSAT is now a resource within the NIH Neuroscience Blueprint and will expand to include nerve cells in the eye, ear, and pain pathways.

- [Day M, et al. \*Nat Neurosci\* 2006;9:251-9](#), PMID: 16415865
- For more information, see <http://www.gensat.org/index.html>
- For more information, see <http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&db=gensat>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NINDS, NCCAM, NCCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

**Programs to Accelerate Medications Development for Alcoholism Treatment:** Alcoholism is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ from one drinker to another. Therefore a diverse repertoire of

medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure their interest in taking promising compounds through the final phase of clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- ▷ Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies have already produced several targets for human studies that are now under way, such as rimonabant, a cannabinoid CB1 receptor blocker, and antalarmin, a corticotropin-releasing factor receptor blocker.
- ▷ A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early human trials network.
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
  - (E/I) (NIAAA) (GPRA Goal)

**The Collaborative Study on the Genetics of Alcoholism (COGA):** In its 18th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) who are densely affected by alcoholism. Investigators have identified several genes, including *GABRA2*, *ADH4*, *ADH5*, and *CHRM2*, that influence the risk for alcoholism and related behaviors, such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected, and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes that influence vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

- For more information, see <http://zork.wustl.edu/niaaa>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Genomics*, and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAAA) (GPRA Goal)

**Brain Disorders in the Developing World: Research Across the Lifespan:** Brain disorders are the leading contributor to years lived with disability in all regions of the world, with the exception of sub-Saharan Africa. This program boosts research in the developing world on childhood disorders such as cerebral palsy and epilepsy, on mental illnesses such as depression and schizophrenia, and on degenerative disorders, such as stroke and Alzheimer's disease. Under this program, U.S. investigators and their foreign collaborators are studying the neurocognitive



consequences of HIV/AIDS, the relationship between zinc nutrition and brain development, and the neurological disorders stemming from treatable infectious causes, such as cerebral malaria, cisticercosis, tuberculosis (TB), and bacterial sepsis.

- For more information, see [http://www.fic.nih.gov/programs/research\\_grants/brain\\_disorder](http://www.fic.nih.gov/programs/research_grants/brain_disorder)
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (FIC, NEI, NIA, NIAAA, NICHD, NIDA, NIEHS, NIMH, NINDS, ODS)

**Trans-NIH Chronic Fatigue Syndrome Research:** NIH coordinates chronic fatigue syndrome research through a trans-NIH Working Group on Research on Chronic Fatigue. This working group developed an action plan to enhance the status of chronic fatigue syndrome research at the NIH and among the external and intramural scientific communities. The working group held a workshop on grantsmanship in FY 2007 to provide researchers with an overview of funding opportunities, an understanding of the NIH funding process, and an opportunity to meet with program officials. In addition, the Office of Research on Women's Health and a subset of the working group ICs issued an RFA in FY 2006 to explicate how the brain, as the mediator of the various body systems involved, fits into the schema for understanding chronic fatigue syndrome. This RFA solicited proposals from multidisciplinary teams of scientists to develop an interdisciplinary approach to the study of chronic fatigue syndrome in men and women across the lifespan and resulted in seven new research projects on chronic fatigue syndrome.

- For more information, see <http://orwh.od.nih.gov/cfs.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html>
- For more information, see <http://orwh.od.nih.gov/cfs/2006NIHfundedCFSstudies.html>
- For more information, see <http://orwh.od.nih.gov/cfs/cfsFundingGMWs.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (ORWH, NIAID, NIAMS, NIAAA, NIA, NICHD, NIDA, NIDDK, NINDS, NCRR, CSR, NIEHS, NIDCR, NINR, NHLBI, NIMH, NCCAM, FIC, ODS, OBSSR)

**Mechanisms of HIV Neuropathogenesis: Domestic and Global Issues:** Neurological manifestations, including HIV dementia and opportunistic infections and tumors, are among the most threatening complications of HIV infection. Emerging data indicate that the prevalence of HIV-related neurological disease differs across regions of the world, suggesting that different subtypes of HIV may be more or less capable of causing neuropathology, or that genetic variance among people in various regions of the world could affect susceptibility to HIV's neuropathological effects. NIH sponsored a meeting in the spring of 2007 to address these issues, resulting in the release of a funding announcement.

- For more information, see <http://synapse.neurology.unc.edu/venice>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-030.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIMH, NINDS, OAR)

**National NeuroAIDS Tissue Consortium (NNTC):** The NNTC is a repository of brain tissue and fluids from highly characterized HIV-positive individuals. Established as a resource for the research community, NNTC includes information from more than 2,000 individuals, including

approximately 641 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

- For more information, see <http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-08-021.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E/I) (NIMH, NINDS)

**NIH Countermeasures Against Chemical Threats (CounterACT) Research Network:**

CounterACT Research Network, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The network, which has collaborated with the U.S. Department of Defense (DoD) from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DoD researchers identified as a potential countermeasure against chemical agent-induced seizures, is entering clinical trials in epilepsy patients through the NINDS Neurological Emergency Clinical Trials Network, and NIH is collaborating with DoD to complete animal studies necessary for its FDA approval as a nerve agent treatment.

- For more information, see <http://www.ninds.nih.gov/funding/research/counterterrorism/index.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NINDS, NEI, NIAID, NIAMS, NIEHS, NIGMS)

**Specialized Program of Translational Research in Acute Stroke (SPOTRIAS):** The objective of SPOTRIAS is to serve as an incubator for translational and early-phase clinical research studies. SPOTRIAS sites are located at medical centers where staff have the capacity to evaluate and treat stroke patients very rapidly after symptom onset. NIH supports seven SPOTRIAS sites, which have made substantial progress, including impressive increases in the use of the “clot buster” tPA (tissue plasminogen activator) to treat acute stroke; the establishment of three interlinked repositories for protein and DNA tissue samples, neuroimages, and clinical data; enrollment of more than 640 individuals with acute stroke into treatment protocols; the management of 17 early-phase clinical trials; and the training of 25 research fellows.

- For more information, see <http://www.spotrias.com>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E/I) (NINDS)

**The SMA Project:** A decade ago, spinal muscular atrophy (SMA) was one of hundreds of poorly understood inherited disorders that affect the nervous system, and the outlook for developing treatments was bleak. The discovery of the gene defect that causes SMA dramatically improved prospects, revealing a rational strategy to develop drugs. The SMA Project is a novel approach to preclinical drug development and may serve as a model for other disorders. The project has brought together expertise from industry, academia, the FDA, and NIH to generate a detailed drug development plan. A “virtual pharma organization” develops and applies the resources to carry out the plan through subcontracts to companies that serve the pharmaceutical



industry. The project created a new drug through extensive modification of indoprofen, a drug with known activity in experimental settings that was not suitable for clinical application. Through repeated modification and evaluation cycles in laboratory tests, the project produced hundreds of chemical compounds related to indoprofen and has made encouraging progress. In 2007, preclinical studies began to evaluate the two best candidates for clinical readiness. The best of these will likely be ready for early stage clinical testing in 2008 or 2009. In early 2008, the project also began two new drug development projects that could yield additional drug candidates for SMA.

- For more information, see <http://www.smaproject.org>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NINDS)

**The NIH Toolbox for Assessment of Neurological and Behavioral Function:** The NIH Blueprint for Neuroscience Research supports this contract awarded to the Evanston Northwestern Healthcare Research Institute. The project entails the development of a set of standardized neurological and behavioral measures of cognition, emotion, sensation, and motor function. The toolbox will foster uniformity among the basic measures used and allow comparisons or data compilations across multiple studies. This innovative approach to measurement will be responsive to the needs of researchers in a variety of settings and will place particular emphasis on measuring outcomes in clinical trials and functional status in large cohort studies, such as epidemiological and longitudinal studies.

- For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-AG-06-008.html>
- For more information, see <http://www.enh.org/aboutus/press/article.aspx?id=4358>.
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (OBSSR, NCCAM, NCCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR)

**The NIH Rapid Access to Intervention Development (RAID) Pilot Program:** The NIH-RAID Pilot program makes available, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new small-molecule drugs, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving research findings from bench to bedside. Among the projects approved are drugs for hepatic fibrosis, the blood diseases beta-thalassemia and sickle cell anemia, brain tumors, and the neurological disorders Friedreich's ataxia and Alzheimer's disease. The NIH-RAID Pilot program is part of the NIH Roadmap for Medical Research.

- For more information, see <http://nihroadmap.nih.gov/raid/index.aspx>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (Roadmap—all ICs participate)

**Gene Influences Antidepressant Response:** Whether depressed patients will respond to an antidepressant depends, in part, on which version of a gene they inherit. In an NIH-supported study, investigators found that having two copies of one version of a gene that codes for a component of the brain's mood-regulating system increased the odds of a favorable response to

an antidepressant by up to 18 percent, compared to having two copies of the other, more common version.

- For more information, see <http://www.nimh.nih.gov/press/stardgene.cfm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
- (E) (NIMH)

### **Genetic Roots of Bipolar Disorder Revealed by First Genome-Wide Study of Illness:**

According to NIH-funded research, the likelihood of developing bipolar disorder depends in part on the combination of small effects of variations in many different genes in the brain, none of which is powerful enough to cause the disease by itself.

- For more information, see <http://www.nimh.nih.gov/press/mcmahon-bipolar-genetics.cfm>
- This example also appears in Chapter 3: *Genomics*.
- (E) (NIMH)

### **Other Notable Activities**

**Advances in Treatment Development:** NIH continues to fund research into the development of new, targeted medications and treatments for mental disorders.

- ▷ *Drug Development for Cognitive Impairments in Schizophrenia:* The Treatment Unit for Research on Neurocognition in Schizophrenia program is a network that is testing the safety and efficacy of new therapeutic compounds for treating the cognitive deficits of schizophrenia.
  - (E) (NIMH)
- ▷ *Studies of Fragile X Syndrome:* NIH has entered into a public-private partnership to study and test possible medications for treating fragile X syndrome, the most common cause of inherited mental impairment. Fragile X syndrome is caused by a single gene mutation that ultimately results in exaggerated activity of a brain protein called mGluR5. Researchers will study, in animals, the safety of chemical compounds known to block this mGluR5 activity. If this phase goes well, researchers will move forward with clinical studies.
  - (E) (NIMH, NINDS, NICHD)
- ▷ *Faster-acting depression treatments:* A recent NIH-funded study found that people with treatment-resistant depression experienced relief in as little as 2 hours after a single intravenous dose of ketamine, a medication usually used in higher doses as an anesthetic. Used in very low doses, ketamine is important for depression research but at higher doses could have side effects that may limit its clinical use. Nevertheless, this research could inform the development of faster and longer acting medications for treating depression.
  - For more information, see <http://www.nimh.nih.gov/press/ketamine.cfm>
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
  - (I) (NIMH)

**Clinical Research and Trials in Neurological Disease:** NINDS provides extramural funding for more than 1,000 clinical research studies. Nearly 1 million people participate in these projects, and it is essential to assess the return on this investment in improving quality of life. NINDS contracted an independent evaluation of the costs and benefits of its Phase III clinical trials. Investigators found that, although the total cost of clinical trials in the study was \$335 million, the cumulative benefits over a 10-year period exceeded \$15 billion and added 470,000 healthy years of life to people in the United States. NINDS is extending this evaluation approach by developing a computer model that will estimate the public health impact of any given clinical trial in neurology or neurosurgery. This model will be publicly available for use by researchers and the Institute to facilitate decision-making. NINDS is also assessing ways to further improve its trials. To this end, the Institute has funded a Neurological Emergencies Treatment Trials (NETT) Network to facilitate high-quality clinical trials in acute neurological disorders and accelerate the implementation of new therapies into practice in emergency departments.

- [Johnston SC, et al. \*Lancet\* 2006;367:1319-27](#), PMID: 16631910
- For more information, see <http://www.nett.umich.edu/nett/welcome>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NINDS)

**Scientific Basis of the Placebo Effect:** The placebo effect can be defined as the measurable, observable, or felt changes that occur during, but are not directly attributable to, a specific health intervention. It is a ubiquitous and frequently powerful phenomenon that operates in all forms of medicine, so good clinical research is designed to account for its effects as well as those of the intervention under study. Because of the power of the placebo effect, it is equally important to understand the mechanisms by which it operates and to explore how its benefits might be maximized to enhance the quality and effectiveness of all forms of health care. An ongoing NIH initiative is examining multiple aspects of the placebo effect through interdisciplinary investigations employing molecular, physiological, biochemical, immunological, genetic, behavioral, and social science approaches. This work is beginning to shed light on many facets of the placebo effect. For example, one recently published study showed that placebo-associated pain relief was correlated with activation of areas of the brain that are associated with pain relief that occurs through both innate mechanisms and with use of opioid narcotics. Other ongoing studies are examining the role and importance of the placebo effect in the relationship between patient and health care provider.

- [Zubieta JK, et al. \*J Neurosci\* 2005;25:7754-62](#), PMID: 16120776
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**Reducing Disparities in Stroke:** NIH is actively engaged in a number of research projects designed to identify risk factors for stroke in minority populations and enhance prevention and treatment in these groups. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is an observational study to explore the role of race and geographic differences on the prevalence of risk factors for stroke and on stroke incidence and mortality. To date, researchers have recruited approximately 27,000 of a projected 30,000 individuals (about 50 percent African American and 50 percent White) and have already published a number of

important findings on their baseline data. NIH has also established an acute stroke research and care center at the Washington Hospital Center, a community hospital in Washington, DC, where more than 75 percent of stroke patients are African American or Hispanic. The center will collect data to aid in stroke prevention programs and will run two clinical trials, one on secondary stroke prevention and another on increasing the use of tissue plasminogen activator among minorities. The program directly addresses GPRA Goal SRO-8.9.2: “By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities.”

- For more information, see <http://www.regardsstudy.org/index.htm>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (NINDS)

**Blending Initiative: Bench to Bedside to Community:** Efforts to systematically move science-based interventions and practices into community settings are exemplified in the testing of drug abuse treatment approaches in the community settings where they will be used by drug treatment professionals who are trained to implement them. This work is occurring through the National Drug Abuse Treatment Clinical Trials Network at NIH, which involves practitioners from community treatment programs in formulating research protocols and provides real-world feedback on their success and feasibility. The adoption of the addiction medication buprenorphine by a growing number of community treatment programs that treat patients with opioid addiction is an example of real culture change issuing from NIH clinical research. A similar approach is under way to enhance treatment for drug-addicted individuals involved with the criminal justice system through research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) initiative. CJ-DATS seeks to achieve better integration of drug abuse treatment for criminal offenders with other public health and public safety forums and is a collaborative effort by NIH and multiple Federal agencies and health and social service professionals. These initiatives are helping to change the culture of how drug abuse treatment is delivered in this country.

- For more information, see <http://www.drugabuse.gov/CTN>
- For more information, see <http://www.cjdats.org>
- For more information, see <http://www.drugabuse.gov/Blending>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Clinical and Translational Research*, and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NIDA) (GPRA Goal)

**Hearing Aids and Directional Microphones:** Approximately 32.5 million American adults report some degree of hearing loss, according to data from the National Center for Health Statistics 2003 National Health Interview Survey. Although almost 95 percent of Americans with hearing loss could have their hearing treated with hearing aids, only about 20 percent of Americans with hearing loss have hearing aids, and many who wear them are dissatisfied with them. Hearing in noisy environments is a major unsolved problem faced by hearing aid users, and of all available technologies, directional microphones currently show the most promise for addressing this problem. NIH-supported scientists have been studying the tiny fly *Ormia ochracea*, which has such sensitive directional hearing that it has inspired ideas for a new generation of hearing aids. The fly’s ear structure, which permits ultrasensitive time coding and localization of sound, provides a model for scientists and engineers in developing new miniature

directional microphones for hearing aids that can focus sound amplification on speech. To improve hearing aid technology so that users can better understand speech in a noisy background, NIH-supported scientists successfully completed a prototype of a low-power, highly directional microphone small enough to fit into a hearing aid. The use of improved directional microphones in hearing aids will improve the quality of life for individuals with hearing loss who depend on hearing aids to understand spoken language.

- [Miles RN, Hoy RR. \*Audiol Neurootol\* 2006;11:86-94](#), PMID: 16439831
- This example also appears in Chapter 3: *Technology Development*.
- (E) (NIDCD) (GPRA Goal)

**Visual Processing in Neuroscience Blueprint:** Much of the cerebral cortex of the brain is devoted to processing the images that flood our eyes. The visual cortex also connects with many regions of the brain that govern memory, language, movement, and a myriad of other cognitive abilities. NIH's visual processing research portfolio prioritizes understanding of how the brain processes visual information, how brain activity results in visual perception, and how the visual system interacts with other cognitive systems.

- For more information, see <http://www.neuroscienceblueprint.nih.gov>
- For more information, see [www.nei.nih.gov/funding/app.asp#1b](http://www.nei.nih.gov/funding/app.asp#1b)
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NEI)

**Centers on Suicide Prevention:** In response to the 2002 Institute of Medicine Report "Reducing Suicide: A National Imperative," NIH issued an RFA and funded three centers focused on suicide intervention and prevention. Now in their third year of support, the centers have conducted pilot intervention studies with patients suffering from mental and substance use disorders.

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIMH, NIAAAA, NIDA)

**Understanding How Prefrontal Cortex Affects Cognitive Function:** In FY 2008, NIH will support an RFA to stimulate research on how a brain region called the prefrontal cortex interacts with other parts of the brain to give rise to sophisticated behavior and cognitive function. Abnormal functioning of the prefrontal cortex is associated with mental disorders such as schizophrenia and depression.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-110.html>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIMH)

**Brain Tumor:** The NIH Brain Tumor Progress Review Group identified many priorities for the field. Research on understanding and preventing brain tumor dispersal was one of the group's highest scientific priorities, and NIH funds a number of projects in this area, many of which were submitted in response to a Program Announcement with set-aside funds issued in 2004. NIH also funds clinical studies investigating therapy delivery to the brain and evaluating the safety and tolerability of various therapies, including immunological therapies, vaccine therapy, monoclonal

antibodies, and combination therapies. The Surgical and Molecular Neuro-Oncology Unit within the NIH Division of Intramural Research investigates basic mechanisms of brain tumor development and chemotherapy resistance to find new therapeutic strategies, particularly for malignant gliomas.

- For more information, see [http://www.ninds.nih.gov/find\\_people/groups/brain\\_tumor\\_prg/index.htm](http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm)
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NINDS, NCI)

**Know Stroke in the Community Educational Campaign:** In 2004, NIH entered a first-time partnership with CDC to launch a new grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders, called “Stroke Champions,” who worked to educate communities about the signs and symptoms of stroke. The program focuses on reaching African Americans, Hispanics, and seniors in communities that have the health care systems in place to treat stroke. In 2005-2006, the program had been implemented in 11 cities, educating 168 Stroke Champions who have conducted more than 600 community events.

- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (NINDS)

**Peripheral Neuropathies:** NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. In October 2006, NIH held a workshop that looked across different peripheral neuropathies to focus on steps needed for therapy development. The workshop brought together researchers in inherited and acquired peripheral neuropathies, representatives from voluntary disease groups, and NIH staff.

- (E) (NINDS, NIDDK)

**Rare Disorders:** NIH supports research to uncover the causes of and develop treatments for the hundreds of rare disorders that affect the nervous system while also promoting research on topics such as stem cells, gene therapy, and neuroimaging that will impact multiple rare disorders. New NIH-funded grants in FY 2006 and 2007 focused on rare diseases, such as Friedreich’s ataxia, ALS, transmissible spongiform encephalopathies, and Rett syndrome. NINDS also collaborates with the Office of Rare Diseases (ORD) and patient voluntary organizations to stimulate research via workshops or grant solicitations. For example, lysosomal storage disorders, such as Fabry, Niemann-Pick, and Gaucher diseases, are rare genetic diseases with neurological manifestations. NINDS, ORD, and a patient voluntary group cosponsor an initiative to spur new research on the delivery of therapies for lysosomal storage disorders across the blood-brain barrier.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAS-06-202.html>
- For more information, see [http://www.ninds.nih.gov/about\\_ninds/plans/a-t\\_plan.htm](http://www.ninds.nih.gov/about_ninds/plans/a-t_plan.htm)
- (E) (NINDS, NCI, NCCR, NEI, NHGRI, NHLBI, NIA, NIAID, NICHD, NIDDK, NIEHS, NIGMS, ODP/ORD)



**Translational Research:** To meet the special needs of translational research across neurological disorders, NINDS has developed a program to support pilot projects, full-scale collaborative teams in academia and small businesses, and training efforts. Investigator-initiated proposals are rigorously peer reviewed, and expertise and criteria are tailored to translational research objectives. Funding is milestone driven, and the program fosters collaborative research. Ongoing projects are developing drug, stem cell, or gene therapies for ALS, Batten disease, epilepsy, Huntington's disease, Duchenne and other muscular dystrophies, Parkinson's disease, tuberous sclerosis, and stroke and other disorders. In 2008 the program will expand to include molecular diagnostics, which are critical for catching disease early, when intervention is most likely to succeed.

- For more information, see <http://www.ninds.nih.gov/funding/research/translational/index.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NINDS)

**Acupuncture for Osteoarthritis of the Knee:** Clinical trials supported by NIH and others suggest that acupuncture may have a useful role in treating a variety of chronic painful conditions, hypertension, and obesity. For example, in 2006 NIH-funded investigators reported findings from the longest, largest, randomized, controlled clinical trial of acupuncture ever conducted. The results demonstrated that acupuncture is an effective adjunct to conventional treatment for osteoarthritis, the most common form of arthritis and a major cause of pain, limitation of activity, and health care utilization among the elderly. Study participants receiving acupuncture had significantly reduced disability and improved quality of life. The innovative trial design resulted from an interdisciplinary collaboration of rheumatologists, licensed acupuncturists, and biostatisticians, ensuring that the research methodology was scientifically sound and accurately reflected acupuncture as traditionally practiced.

- [Manheimer E, et al. \*Acupunct Med\* 2006;24:S7-14](#), PMID: 17308513
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**How We Detect Taste at the Molecular Level:** Taste is critical for discriminating between nutritious and spoiled foods. Taste disorders can lead to reduced appetite and poor nutrition. Scientists are trying to increase their understanding by identifying proteins that we produce to help detect taste. Taste cells are clustered in taste buds on the tongue and palate. NIH-supported scientists have identified a new protein, PKD1L3, found specifically in taste cells. The PKD1L3 protein forms a channel that allows tastants, such as sodium ions or protons, to enter through taste cell membranes so that tastes can be detected. Another group of NIH-supported scientists determined that the protein is located in taste pores and is activated by acids (sour) but not other tastants. A third group of NIH-supported scientists reports that mice lacking PKD2L1-expressing cells cannot detect sour tastants, but can detect all others. Together, these three reports suggest that PKD1L3 channels detect sour tastants in food. Scientists can now explain how humans detect the flavors sweet, sour, bitter, and umami, or savory, at the cellular level. This advance in understanding taste may help scientists treat taste impairments and could also lead to the



development of better salt and sugar substitutes for the millions of Americans on restricted diets to control high blood pressure, diabetes, and obesity.

- [Lopez-Jimenez ND, et al. \*J Neurochem\* 2006;98:68-77](#), PMID: 16891422
- [Huang AL, et al. \*Nature\* 2006;442:934-8](#), PMID: 16929298
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E/I) (NIDCD)

**Stuttering:** Stuttering is a communication disorder with notable physical and emotional challenges to the speaker and sometimes to the listener. It is estimated that approximately 3 million Americans stutter. Stuttering affects individuals of all ages but occurs most frequently in young children between the ages of 2 and 6 who are developing speech and language. Boys are three times more likely to stutter than girls. Most children, however, outgrow their stuttering. It is estimated that less than 1 percent of adults stutter. NIH-supported scientists identified a specific location for a gene on chromosome 12 that seems to be an important contributor to stuttering in a series of 40 highly inbred families of Pakistani origin. Determining the underlying molecular causes of stuttering may lead to improved diagnosis and treatment.

- [Riaz N, et al. \*Am J Hum Genet\* 2005;76:647-51](#), PMID: 15714404
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCD)

**Discovering the Molecular Mechanisms of Pain:** Nociception, the sensory component of pain, depends in part on the intricate network of sensory transmission within our bodies, stretching from our extremities to the spinal cord and onward to the brain. But on its most fundamental level, nociception involves molecules and chemical mechanisms. NIH scientists have reported progress in understanding precisely how individual molecules in our nerve cells generate, transmit, and sustain sensory signals. They discovered that a much-studied protein called cyclin-dependent kinase 5 (Cdk5) plays a regulatory role in pain signaling between sensory nerves in the spinal cord and nerve ganglia. Their results offer the first direct evidence of this regulatory role for Cdk5. The authors also reported the first evidence from animal studies of the importance of Cdk5 activity in inflammation. These findings point the way for additional research, suggesting that new analgesic drugs that alter Cdk5 activity one day may be beneficial in treating pain.

- [Pareek TK, Kulkarni AB. \*Cell Cycle\* 2006;5:585-8](#), PMID: 16552189
- [Pareek TK, et al. \*Proc Natl Acad Sci U S A\* 2006;103:791-6](#), PMID: 16407116
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (I) (NIDCR)

**DNA Test for Charcot-Marie-Tooth Disease:** Charcot-Marie-Tooth disease, one of the most common inherited neurological disorders, affects 1 in 2,500 people in the United States. Its symptoms start in early adulthood and include progressive arm and leg pain that leads to difficulty walking and manipulating objects. Using a special strain of mice, new genomic technologies, and information from the mouse and human genome sequences, NIH-funded researchers rapidly identified a mutation that causes a subtype of the disease. Knowledge of the

specific gene defect will enable development of a DNA test to confirm the diagnosis in patients and predict risk for family members.

- [Chow CY, et al. \*Nature\* 2007;448:68-72](#), PMID: 17572665
- For more information, see <http://www.med.umich.edu/opm/newspage/2007/charcot.htm>.
- This example also appears in Chapter 3: *Genomics*.
- (E) (NIGMS, NINDS)

## NIH Strategic Plans Pertaining to Neuroscience and Disorders of the Nervous System

### National Institute of Neurological Disorders and Stroke (NINDS)

- [Neuroscience at the New Millennium](#)
- [Benchmarks for Epilepsy Research](#)
- [Report of the Stroke Progress Review Group](#)

### National Eye Institute (NEI)

- [National Plan for Eye and Vision Research](#) (2004)
- [Vision Research—A National Plan 1999-2003: A Report of the National Eye Advisory Council](#)
- [Progress in Eye and Vision Research 1999-2006](#)
- [Ocular Epidemiology Strategic Planning Panel Report—Epidemiological Research: From Populations Through Interventions to Translation](#) (2007)
- [Age-Related Macular Degeneration Phenotype Consensus Meeting Report](#)
- [Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration Workshop Report](#)

### National Institute on Aging (NIA)

- [Living Long and Well in the 21st Century: Strategic Directions for Research on Aging](#)

### National Institute on Deafness and Other Communication Disorders (NIDCD)

- [FY 2006-FY 2008 NIDCD Strategic Plan](#)

### National Institute of Mental Health (NIMH)

- [NIMH Strategic Plans and Priorities](#)
- [Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research](#)
- [Pathways to Health: Charting the Science of Brain, Mind, and Behavior](#)

### National Institute on Drug Abuse (NIDA)

- [NIDA Draft Strategic Plan](#)

### National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- [National Institute on Alcohol Abuse and Alcoholism Five Year Strategic Plan FY 08-13](#)
- [Mechanisms of Alcohol Addiction](#)

### National Center for Complementary and Alternative Medicine (NCCAM)

- [Expanding Horizons of Health Care: Strategic Plan 2005-2009](#)

### **National Institute of Child Health and Human Development (NICHD)**

- [Neuroscience research at NICHD](#)
- Branch Reports to Council with Future Research Directions:
  - National Center for Medical Rehabilitation Research NICHD, Report to the National Advisory Child Health and Human Development (NACHHD) Council, January 2006
  - [National Center for Medical Rehabilitation Research \(NCMRR\), NICHD, Report to the NACHHD Council, January 2006](#)
  - [Developmental Biology, Genetics, and Teratology Branch, Report to the NACHHD Council, September 2006](#)
  - [Mental Retardation and Developmental Disabilities Branch, NICHD, Report to the NACHHD Council, June 2005](#)

### **Fogarty International Center (FIC)**

- [Pathways to Global Health Research](#) (Draft)

### **Office of AIDS Research (OAR)**

- [FY 2008 Trans-NIH Plan for HIV-Related Research](#)

### **Other Trans-NIH Plans**

- [NIH Blueprint for Neuroscience Research](#)  
(NCCAM, NCCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, **NIMH**, **NINDS**, NINR, OBSSR)
- [The 2006 Parkinson's Disease Research Plan](#)  
(NCCAM, NCCR, NHGRI, NIA, NICHD, NIDA, NIDCD, NIEHS, NIMH, **NINDS**, NINR)
- [Research Plan for Tuberous Sclerosis](#)  
(NCI, NHLBI, NIAMS, NICHD, NIDDK, NIMH, **NINDS**, **ORD**)
- [Muscular Dystrophy Research and Education Plan for the NIH](#)  
(**NINDS**, NIAMS, **NICHD** [co-leads])
- [Action Plan for the Muscular Dystrophies](#)  
(**NINDS**, NIAMS, **NICHD** [co-leads])
- [Report of the Brain Tumor Progress Review Group](#)  
(**NCI**, **NINDS**)
- [Research Plan for Ataxia-Telangiectasia](#)  
(NCI, NCCR, NEI, NHLBI, NHGRI, NIA, NIAID, NICHD, NIEHS, NIGMS, **NINDS**, **ORD**)
- [The Autism Research Matrix](#)  
(**NIMH**; NICHD; NIDCD; NINDS; NIEHS; CDC; ACF; HRSA; CMMS; SAMHSA; NIDDK)
- [NIH Research Plan on Down Syndrome](#)  
(**NICHD**, NCI, NHLBI, NIA, NIAID, NIDA, NIDCD, NIDCR, NIMH, **NINDS**)
- [Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan](#)  
(CC, CSR, NCCAM, NCI, NCMHD, NCCR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, **NINDS**, NINR, NLM)

## **INFECTIOUS DISEASES AND BIODEFENSE**

*By 1986, there were 5,833 reported AIDS cases in the United States and the 1-year mortality was 51 percent. It was a period often described as the “dark ages,” where desperate attempts were being made to find something—anything—that would slow disease progression. The seminal discovery for the first class of anti-HIV drugs was that an enzyme called reverse transcriptase was necessary for the virus to replicate. Agents were then screened to find candidate drugs that inhibited the enzyme. Drs. Robert Yarchoan, Hiroaki Mitsuya, and Sam Broder found that zidovudine (AZT) had this property. AZT was then quickly placed in a placebo-controlled clinical trial in patients with late-stage disease. The first review of data in September 1986 showed 19 deaths in the placebo group compared with 1 death in the AZT treatment group. The study was stopped and the FDA approved the drug in record time. It was 21 months from trial initiation to drug approval—an FDA record that has never been broken.*

### **Introduction**

The goals of NIH-supported research on infectious diseases and biodefense rest on two core components. NIH builds and maintains a base of fundamental knowledge about infectious and immune-related diseases and uses that knowledge to develop new and improved diagnostics, therapeutics, and preventive measures, including vaccines. At the same time, NIH continues to develop a flexible domestic and international infrastructure that allows it to respond to newly emerging and re-emerging threats wherever they occur, thereby protecting public health in the United States and abroad.

### **Infectious Diseases**

Infectious diseases are caused by microbial pathogens—bacteria, viruses, fungi, protozoa, and helminths (worms)—that invade the body and multiply, causing physiological damage and illness. Pathogens cause a range of diseases from nonserious to life threatening and can be transmitted in many ways. Influenza and TB can be transmitted from person to person via airborne inhalation; HIV, which causes AIDS, is transmitted through exposure to blood or other body fluids, during sexual intercourse, and from mother to child at birth or during breast-feeding; and malaria is caused by a microscopic parasite that is transmitted by an insect “vector,” in this case a mosquito. Unlike chronic and degenerative illnesses, transmissible infectious diseases can rapidly devastate large human populations and easily cross international borders.

### **Biodefense and Emerging and Reemerging Infectious Diseases**

Public health threats that could cause large-scale disruption and devastation include the deliberate or accidental release of pathogenic agents such as anthrax or smallpox, biological toxins, chemical weapons such as nerve gas, or radioactive substances. The NIH biodefense strategy is designed to protect all civilian populations and integrates basic, applied, and clinical research knowledge and capabilities into a flexible and adaptable “network.” Other threats to

public health change continually as new pathogens emerge and as familiar microbes reemerge with new properties or in unusual settings. Examples of recent emerging and reemerging public health threats include naturally occurring infectious diseases such as Ebola hemorrhagic fever and severe acute respiratory syndrome (SARS). The overall goal of research on biodefense and emerging and reemerging infectious diseases is to develop the knowledge and tools to respond quickly and effectively as public health threats emerge, whether they occur naturally, accidentally, or deliberately.

Although NIAID has primary responsibility for infectious diseases and biodefense research, many other NIH ICs play critical roles, including FIC, NICHD, NINDS, and the NIH Office of AIDS Research (OAR). Nearly every NIH IC supports AIDS-related research activities, consistent with their individual missions. The ICs that conduct most of the research on AIDS and related co-infections, malignancies, cardiovascular and metabolic complications, and behavioral and social science issues are NIAID, NIDA, NCI, NIMH, the National Center for Research Resources (NCRR), NICHD, and NHLBI. All NIH AIDS research is coordinated by OAR.

In addition, the NIH Office of Science Policy manages and supports the National Science Advisory Board for Biosecurity (NSABB). The NSABB provides advice on strategies for the efficient and effective oversight of dual-use biological research—research that has a legitimate scientific purpose but could be misused to pose a threat to public health or national security—taking into consideration both national security concerns and the needs of the research community.

NIH-wide research on infectious diseases and biodefense includes basic research to understand fundamental mechanisms by which microorganisms cause disease, the host response to pathogens, and mechanisms by which insects and other vectors transmit infectious diseases. Translational research builds on basic research findings with the aim of developing new and improved diagnostics, therapeutics, vaccines, and other preventive measures. NIH conducts and supports clinical research to assess the efficacy and safety of new drugs, vaccines, and other products. As NIH pursues these goals, an overarching priority is to reduce health disparities and improve health for all people.

Infectious diseases and biodefense are inherently global concerns. NIH engages in international partnerships to improve means for detecting and controlling the spread of infectious diseases and supports international programs to foster research and research capacity in low- and middle-income countries. Within the United States, NIH seeks strategic partnerships with other governmental and nongovernmental organizations.

NIH supports research on HIV/AIDS, TB, malaria, emerging and reemerging infectious diseases (such as hemorrhagic fevers caused by Ebola and other viruses, West Nile virus, SARS, Lyme disease, prion diseases, and H5N1, a virus that causes avian influenza), sexually transmitted infections, and influenza and other respiratory infections. In addition, NIH funds research on many less familiar but still important diseases that exact an enormous global toll.<sup>24</sup>

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<sup>24</sup> For more information, see <http://www3.niaid.nih.gov/Biodefense>

NIH research on biodefense and emerging and reemerging infectious diseases is necessarily intertwined and includes the development of infrastructure and capacity-building, that is, facilities and human resources needed to conduct research on dangerous pathogens safely and effectively; basic research on microbes and host immune defenses; and the targeted development of medical countermeasures, including vaccines, therapeutics, and diagnostics that would be needed in the event of a biological, chemical, or radiological weapons attack.

## **Burden of Illness and Related Health Statistics**

Infectious diseases cause approximately 26 percent of all deaths worldwide. Each year, more than 11 million people die from infectious diseases, the vast majority of deaths occurring in low- and middle-income countries. The top infectious disease killers in those countries for people ages 15 to 59 are HIV/AIDS, TB, and lower respiratory infections. HIV causes nearly 2.1 million total deaths each year,<sup>25</sup> TB kills 1.6 million each year, and lower respiratory infections in 2005 caused an estimated 3.7 million deaths.<sup>26</sup> Malaria is a serious problem, especially in Africa, where one in every five childhood deaths is due to the effects of the disease.<sup>27</sup> The infectious diseases that today cause the greatest number of human deaths worldwide are (in order) lower respiratory infections, HIV/AIDS, diarrheal diseases, malaria, and TB.<sup>28</sup>

Each year infectious diseases kill approximately 6.5 million children, most of whom live in developing countries. For children younger than age 14, infectious diseases account for 7 of the top 10 causes of death. In this age group, the leading infectious diseases are lower respiratory infections, diarrheal diseases, and malaria. Among children younger than age 5, infectious diseases cause about two-thirds of all deaths.<sup>29</sup>

The burden of infectious diseases is not evenly shared, even among developing nations. People who live in sub-Saharan Africa are most affected, particularly by HIV/AIDS, which accounts for one in five deaths in that region. Africa and the most populous countries of Asia harbor the largest number of TB cases. Together, Bangladesh, China, India, Indonesia, and Pakistan account for half of new TB cases each year.<sup>30</sup>

In the United States, infectious diseases add significantly to the overall burden of illness. Together, influenza and pneumonia account for more than 60,000 deaths annually.<sup>31</sup> More than a million cases of sexually transmitted diseases occur each year, and more than 42,000 new cases of AIDS were reported in 2004.<sup>32</sup>

Also, many infectious diseases are increasingly difficult to treat because pathogens are developing resistance to antimicrobial drugs. For example, in recent years there have been

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<sup>25</sup> For more information, see <http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate?epiUpdArchive/2007default.asp>

<sup>26</sup> For more information, see <http://www.dcp2.org/main/Home.html>; <http://www.who.int/entity/mediacentre/factsheets/fs310.pdf>

<sup>27</sup> For more information, see <http://www.who.int/features/factfiles/malaria/en/index.html>

<sup>28</sup> For more information, see <http://www.dcp2.org/pubs/GBD/3/Table/3.14>

<sup>29</sup> For more information, see <http://www.dcp2.org/main/Home.html>

<sup>30</sup> For more information, see <http://www.dcp2.org/main/Home.html>

<sup>31</sup> For more information, see <http://www.cdc.gov/nchs/fastats/deaths.htm>

<sup>32</sup> For more information, see <http://www.cdc.gov/nchs/fastats/infectis.htm>

dramatic increases in antiretroviral drug resistance in HIV, chloroquine resistance in malaria, the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), and methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

## **NIH Funding for Infectious Disease and Biodefense Research**

FYs 2006 and 2007, NIH funding for infectious diseases research was \$3.132 billion and \$3.059 billion respectively. Funding for biodefense research was \$1.766 billion and \$1.735 billion. There is substantial overlap in these funding figures. The table at the end of this chapter indicates some of the research areas involved in this investment (see “Estimates of Funding for Various Diseases, Conditions, and Research Areas”).

### **Summary of NIH Activities**

NIH programs on infectious diseases and biodefense encompass a broad range of basic, translational, preclinical, and clinical research. These activities include developing critical research resources and infrastructure domestically and abroad that allow NIH to respond effectively to existing and emerging infectious diseases wherever they occur.

#### **Basic Research**

Basic research on infectious diseases and biodefense seeks to increase understanding of how pathogens cause disease and how hosts respond to infection; it provides the foundation for improvements in the prevention, diagnosis, and treatment of infectious diseases. For example, NIH researchers recently discovered how a surface protein of the virus that causes chicken pox and shingles attaches to a host cellular protein. That finding, in turn, has opened the door to designing and developing new treatments that block the virus-attachment process.

Many challenges remain in basic research on infectious diseases. These include further definition of the mechanisms by which the immune system protects against infection and of the intricate interactions that occur between pathogens and their hosts; more precise identification of the driving forces behind changing global patterns of infectious diseases; uncovering additional links between infectious diseases (and the immune responses to them) and the development of some cancers, as well as some autoimmune, cardiovascular, and neurological disorders; and discovering how and why genetic changes arise that make pathogens more dangerous. For example, HIV, H5N1 influenza, and Ebola virus originated in animals but mutated and acquired the ability to infect humans. Also, microbes that cause TB, AIDS, and influenza are mutating and acquiring resistance to antimicrobial drugs, which has prompted NIH to develop research initiatives and programs to expand investigations of the basis of antimicrobial resistance, including how bacteria develop and share resistance genes.

Many advances in understanding infectious diseases are the result of the revolution in genomic sequencing that has occurred in the past decade. In FYs 2006 and 2007, NIH-funded researchers and their collaborators completed a range of genome-sequencing projects that help reveal how microbes evolve, infect host cells, cause disease, develop drug resistance, and spread. The studies include sequencing the complete or partial genomes of 54 different samples of the



malaria parasite, *Plasmodium falciparum*; a common sexually transmitted parasite, *Trichomonas vaginalis*; an oral bacterium; and more than 2,800 samples of avian and human influenza viruses.<sup>33</sup> Several of the genome-wide association studies funded by NIH examine genetic variations and explore susceptibility to infection or responses to smallpox, anthrax, typhoid, and cholera vaccinations (see also the section “Genomics” in Chapter 3).

## **Major Infectious Diseases**

NIH conducts research on hundreds of infectious diseases, placing special emphasis on those that claim large numbers of lives each year and cause widespread suffering. NIH also explores how human behaviors as well as social, cultural, economic, and geographic factors affect disease transmission. Additionally, NIH conducts studies to evaluate and ensure the health of special populations, including minorities, individuals who are immunocompromised, the elderly, adolescents, young children, and infants. The ultimate goal is to translate knowledge gained through basic research into interventions that improve public health.

### ***Tuberculosis***

TB is an old disease but still ranks high among the foremost microbial killers of the 21st century and is particularly common among people with HIV. NIH supports a large portfolio of research to develop new drugs, vaccines, and diagnostics for TB and to evaluate improved treatment and prevention regimens. New drugs currently in clinical trials include SQ-109, a promising candidate therapy being developed in a private-public partnership. After a hiatus of 60 years in which no new TB vaccines were clinically tested, at least 9 candidates are now in human trials and at least 10 more are in preclinical development.

The rapid emergence of drug-resistant forms of TB poses an increasing and dangerous public health threat. Both MDR-TB and XDR-TB are classified as emerging infectious diseases and are increasingly difficult to treat. NIH supports the development of new and improved diagnostic tools to more accurately diagnose early TB disease, help optimize therapy by identifying drug-resistant strains, and track the spread of TB in communities. To ensure that research continues to contribute effectively to the global response to the increasing TB threat, in 2007 NIH developed a comprehensive [TB research agenda](#). The plan incorporates NIH collaborations with other U.S. Government agencies and multilateral organizations worldwide and supports public-private partnerships to benefit people who have TB, including individuals who are co-infected with HIV.

### ***Malaria***

The age-old scourge of malaria claims millions of lives every year, mostly among children. The broad NIH malaria research portfolio and the malaria research agenda currently under development are designed to improve understanding of malaria parasites, host responses, and vector biology, thereby accelerating the development of new and improved public health interventions, including vaccines, therapeutics, and vector management. NIH is collaborating with strategic partners to develop vaccines for malaria and is currently testing several candidate

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<sup>33</sup> For more information, see <http://www.niaid.nih.gov/dmid/genomes/mcs/influenza.htm>

vaccines in malaria-endemic areas. In 2007, NIAID began a new initiative entitled “NIAID Partnerships with Public-Private Partnerships.” This initiative seeks to support the role of public-private partnerships in the development of new drugs, vaccines, and diagnostics for diseases such as malaria, trypanosomiasis, leishmaniasis, and other neglected tropical diseases.

### ***HIV/AIDS***

In the countries hardest hit by HIV/AIDS, the disease has lowered life expectancy, orphaned millions of children, lowered family income, reduced worker productivity, and diminished the supply of teachers and health care workers.<sup>34</sup> NIH plays many critical roles in the global effort to conquer HIV. Antiretroviral therapies made possible by NIH-supported research have resulted in improved quality of life and life expectancy for people who have access to these drugs. A recent study concluded that, since 1996, these antiretroviral medications have saved at least 3 million years of life in the United States alone. Worldwide, more than 2 million people receive antiretroviral therapy, more than half of them with support from the President’s Emergency Plan for AIDS Relief (PEPFAR). However, the use of these antiretroviral therapies is associated with a range of side effects and long-term complications that may have a negative impact on mortality rates. The appearance of multidrug-resistant strains of HIV presents an additional serious public health concern. NIH AIDS research programs are addressing these and other complications.

The broad effort to extend the availability and use of anti-HIV drugs to regions most affected by HIV/AIDS continues. NIH is funding research to develop therapeutic regimens that are easier to use in resource-limited settings, as well as new antiretroviral drugs that target HIV in novel ways. In one of the largest HIV/AIDS treatment trials ever conducted, NIH-funded scientists participating in an international collaboration involving 318 clinical sites in 33 countries showed that HIV-positive individuals who receive episodic treatment with anti-HIV drugs have twice the risk of disease progression, including death from AIDS, than do those who receive continuous therapy with antiretroviral drugs. In addition, the recently concluded [Children with HIV Early Antiretroviral Therapy study](#) in South Africa showed that treating HIV-infected children early with antiretroviral drugs helps them live longer.

Another key research priority is prevention and treatment of HIV-associated co-infections, such as TB and hepatitis C, and comorbidities, such as HIV-associated malignancies, cardiovascular disease, and neurological complications. Studies are evaluating the incidence and treatment of metabolic and cardiovascular disease in people who receive long-term antiretroviral therapy. In addition, the AIDS Malignancy Consortium has launched several clinical studies to identify appropriate treatment regimens for HIV-infected individuals with cancer.

Successful efforts to prevent the spread of HIV and improve adherence and access to treatment are also driven by research in behavioral and social sciences that extends understanding of decision-making, drug abuse, and sexual behavior. As people changed risky behaviors, new AIDS cases in the United States were nearly halved from a peak of over 80,000/year in 1993,<sup>35</sup>

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<sup>34</sup> For more information, see <http://www.kff.org/hiv/aids/7661.cfm>

<sup>35</sup> For more information, see <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2004report/pdf/2004SurveillanceReport.pdf>

to 42,000/year in 2005.<sup>36</sup> Previously 1,650 babies were born infected with HIV each year but today that number is less than 50.<sup>37</sup> Whether preventing transmission, engendering trust to encourage testing and early treatment, or increasing adherence and access to the latest medications and health services, slowing the spread of HIV/AIDS involves understanding (basic behavioral and social science) and changing human behavior at individual, group and community levels.

NIH continues to place a high priority on HIV prevention research, including research to develop vaccines, microbicides, strategies to prevent mother-to-child transmission, antiretroviral therapy as a pre-exposure prophylaxis strategy, treatment for drug addiction, and behavioral interventions. NIH-sponsored studies recently demonstrated that the use of antiretroviral prophylaxis can reduce the rate of mother-to-child transmission of HIV from approximately 25 percent to less than 2 percent. NIH also supports research to develop and test other prevention strategies, such as circumcision. For example, NIH-supported clinical trials in Kenya and Uganda showed that medically supervised circumcision of adult males can significantly lower their risk of contracting HIV through heterosexual intercourse by approximately 50 percent. In countries hit hard by HIV, adult male circumcision serves as another prevention strategy that could result in fewer HIV infections.

Topically applied microbicides for women and men are another promising avenue for preventing HIV transmission. Several microbicides have entered large-scale efficacy trials, the results of which are expected in the next few years. In 2006, NIH established the [Microbicide Trials Network](#) to develop safe and effective microbicides to prevent HIV transmission. In addition to basic and clinical research, studies of cultural and behavioral factors related to acceptability and adherence of prevention interventions are under way.

The ultimate prevention tool, and what is considered the best hope to end the HIV/AIDS pandemic, is a safe and effective vaccine that could prevent HIV infection. NIH-supported researchers around the world have developed candidate vaccines against HIV, some of which are now being tested in various phases of clinical trials. One example is the large-efficacy HIV vaccine trial in Thailand that is being conducted with support from NIH. The [NIH Vaccine Research Center](#), as well as the NIH-supported [HIV Vaccine Trials Network](#), is also dedicated to developing and testing new HIV vaccine candidates, including some that target different HIV types (called clades). To overcome key scientific roadblocks to HIV vaccine development and facilitate the design and testing of HIV vaccine candidates, NIH established the [Center for HIV/AIDS Vaccine Immunology](#), an international consortium of scientists. NIH is a member of the Partnership for AIDS Vaccine Evaluation, a consortium of U.S. Government agencies and key U.S. Government-funded organizations involved in the development and evaluation of HIV vaccines. NIH also recently reissued a notice of program project awards for the HIV Vaccine Research and Design Program, which supports multiproject, multidisciplinary HIV/AIDS vaccine-related studies.

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<sup>36</sup> For more information, see <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2005report/>

<sup>37</sup> For more information, see <http://www.cdc.gov/hiv/topics/perinatal/resources/factsheets/perinatal.htm>

## **Emerging Infectious Diseases and Biodefense**

NIH has mounted a comprehensive and vigorous research program to address critical challenges posed by naturally emerging and reemerging infectious diseases, as well as to mitigate the threats of [biological, chemical, or nuclear/radiological terrorism](#). The goals of these overlapping programs are to develop the capacity to respond rapidly to public health threats; better understand the patterns and means by which pathogens spread and how they cause disease; decipher the mechanisms by which pathogens that infect animals mutate and acquire the ability to infect humans; and develop safe and effective medical countermeasures against naturally occurring, accidental, and deliberately introduced public health threats.

Influenza is a classic example of a reemerging infectious disease. The influenza viruses that caused the pandemic World War I-era Spanish flu and the current avian flu (caused by the H5N1 influenza virus) began in birds, mutated and spread to mammals (pigs, cats, etc.), and then mutated further and acquired the ability to infect humans. Thus, the spread of H5N1 from birds to humans underscores the urgent need to develop better vaccines and drugs to protect against pandemic influenza, as well as the seasonal epidemics that claim an average of 36,000 lives per year in the United States alone.

In 2006, NIH undertook a comprehensive examination of its influenza portfolio and convened a [Blue Ribbon Panel on Influenza Research](#) to identify areas of influenza research in which progress is needed. To help implement the panel's recommendations and facilitate a broad spectrum of influenza research, NIH has adopted several strategies. In 2007, NIH made multiple awards to support innovative influenza research to advance the development of promising vaccines, adjuvants, therapeutics, immunotherapeutics, and diagnostics. NIH also established six [Centers of Excellence for Influenza Research and Surveillance](#) to expand its ability to conduct research on different strains of animal and human influenza viruses collected in other countries or the United States. NIH researchers are collaborating extensively with other Department of Health and Human Services (DHHS) agencies, across other Federal agencies, with private industry, and internationally and are working with strategic partners to develop DNA-, recombinant virus-, and recombinant protein-based candidate influenza vaccines. NIH also leads an international collaborative effort to analyze national and global epidemiological patterns associated with influenza virus circulation.

To date, NIH research has laid the foundation for improved influenza vaccine manufacturing methods, new categories of vaccines that may work against multiple influenza strains, and the next generation of anti-influenza drugs. The inactivated-virus H5N1 vaccine currently stockpiled by HHS has been shown in NIH-sponsored clinical trials to be safe and capable of inducing an immune response predictive of being protective against the H5N1 virus in healthy adults, children, and seniors.

### ***Biological Countermeasures Research***

NIH supports research on a range of emerging and reemerging pathogens that are also considered potential agents of bioterrorism, including Marburg and Ebola hemorrhagic fever viruses, smallpox, and anthrax. NIH-supported researchers are probing the ecology of how these

infections arise, identifying the natural hosts and modes of natural transmission of pathogens and developing safe and effective vaccines and treatments. For example, NIH-funded scientists recently developed promising candidate vaccines for Ebola and Marburg hemorrhagic fever viruses. The Marburg vaccine has been tested in rhesus monkeys and helped all of them survive a later challenge with live virus. An [experimental Ebola vaccine](#) has entered human clinical trials.

### ***Chemical Countermeasures***

Within DHHS, NIH is leading the development of new and improved medical countermeasures designed to prevent, diagnose, and treat the conditions caused by chemical agents that could be released either accidentally or deliberately. To guide this research, NIH has prepared the “Strategic Plan and Research Agenda on Medical Countermeasures Against Chemical Threats.” Under this plan and in collaboration with DoD, NIH has established the trans-agency [CounterACT Research Network](#). The network has established four Centers of Excellence in Medical Chemical Research; funded more than two dozen research projects focusing on nerve agents, sulfur mustard and other blister-causing agents, cyanide and other metabolic poisons, and pulmonary agents; and awarded several Small Business Innovation Research grants for therapeutics and diagnostics development.

### ***Nuclear/Radiological Countermeasures***

To enhance readiness in the event of a radiological or nuclear threat, NIH has developed a [strategic plan and research agenda](#). To help implement the plan, NIH has issued an RFA to conduct research to validate existing biodosimetry tools that evaluate radiation doses to which individuals have been exposed and to develop new [biodosimetry assays and tools](#). NIH also issued RFAs to support the research and development of [medical countermeasures to enhance survival after radiation exposure](#).

NIH works closely with DHHS to periodically update and prioritize the research development activities of its strategic plan and ensure its integration as a key component of the larger national biodefense research agenda. The [Radiation Event Medical Management Program](#) (REMM) provides online guidance to health care providers about diagnosis and treatment for radiation-induced injuries. Further, in collaboration with the DHHS Office of the Assistant Secretary for Preparedness and Response, NIH has prepared a downloadable, online diagnostic and treatment tool kit to guide health care providers during a mass casualty radiation event.

## **Infrastructure and Research Resources**

NIH continues to develop the infrastructure necessary to carry out pioneering research on infectious diseases. As research capabilities (e.g., genomics, proteomics, microarray technology) have evolved and research needs have changed, new facilities and research resources have been designed, implemented, and enhanced. However, since the U.S. anthrax attacks of 2001, the emergence of severe acute respiratory syndrome (SARS) in southeast Asia, repeated outbreaks of hemorrhagic fever viruses in Africa, the threat of pandemic influenza, and other actual and potential public health emergencies, there is an increased need to develop the ability to respond

rapidly to public health threats. To this end, NIH has established or expanded reagent and tissue repositories, data centers, and centralized analytical laboratories and is expanding the number of extramural research facilities nationwide. The latter include the 6 Centers of Excellence for Influenza Research and Surveillance mentioned above, 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, 2 National Biocontainment Laboratories (with BSL-4 capacity, the highest level of containment), 13 Regional Biocontainment Laboratories with BSL-3 capacity, 8 Human Immunology Centers, 10 centers to study host immunity in special populations (children, pregnant women, elderly, immunosuppressed individuals), clinical trials networks at domestic and international sites, and nonhuman primate research centers. In addition, three intramural biocontainment laboratories—on the NIH campus in Bethesda, Maryland (BSL-3); on the National Interagency Biodefense Campus at Fort Detrick in Frederick, Maryland (BSL-4); and at the NIAID Rocky Mountain Laboratories in Hamilton, Montana (BSL-4)—are operational or nearing completion.

## **International Collaboration**

Much of NIH infectious disease and biodefense research is collaborative, interdisciplinary, and—increasingly—international. NIH supports research and training programs to develop and test safe and effective interventions for preventing and treating infectious diseases, exchanging scientific information, and building research capacity in other countries (see also the section “Research Training and Career Development” in Chapter 3). These efforts include programs to establish research resources and infrastructure, for example, to help train scientists from developing countries to engage in infectious disease research, including clinical, operational, and health services research, and to help establish sustainable research capacity in those countries. Because HIV/AIDS and TB take such an enormous global toll, NIH is strengthening the capacity for clinical, operational, and health services research in low- and middle-income countries where HIV/AIDS, TB, or both are significant problems. NIH has established critical global partnerships with the World Health Organization and other United Nations agencies, governmental and nongovernmental organizations, international foundations, and private-sector organizations. Additionally, NIH is establishing international collaborations to develop a safe, effective vaccine against malaria and to gather and analyze national and global epidemiological patterns associated with influenza virus circulation, including data on mortality, virus surveillance, genomics, and control strategies.

## **Notable Examples of NIH Activity**

### **Key for Bulleted Items:**

E = Supported through **Ex**tramural research

I = Supported through **I**namural research

COE = Supported through a congressionally mandated **C**enter of **E**xcellence program

GPRA = Relates to progress toward a goal tracked under the **G**overnment **P**erformance and **R**esults **A**ct

## **Basic Research**

**Microbial Genomics:** NIH has made significant investments in large-scale, whole-genome sequencing of pathogens over the last decade. Sequenced pathogens include hundreds of



bacteria, fungi, parasites, invertebrate vectors of diseases, and viruses (including the pathogens that cause anthrax, influenza, aspergillosis, TB, gonorrhea, chlamydia, and cholera and many that are potential agents of bioterrorism). NIH also provides comprehensive genomic, bioinformatic, and proteomic resources and reagents to the scientific community. These include the (1) Microbial Genome Sequencing Centers, which rapidly produce high-quality genome sequences of human pathogens and invertebrate vectors of diseases; (2) Pathogen Functional Genomics Resource Center, which provides functional genomic resources; (3) Bioinformatics Resource Centers, which provide access to genomic and related data in a user-friendly format; and (4) Proteomics Research Centers, which support research on the full set of proteins encoded in a microbial genome. The NIH Influenza Genome Sequencing Project has sequenced more than 2,800 human and avian isolates (as of November 28, 2007); NIH scientists recently exploited these data to explain the global spread of resistance to adamantanes, a first-generation class of anti-influenza drug.

- For more information, see <http://www3.niaid.nih.gov/research/topics/pathogen/default.htm>
- This example also appears in Chapter 3: *Genomics*.
- (E/I) (NIAID) (GPRA Goal)

**Scientists Complete Full Sequence of Opportunistic Oral Bacterium:** Over the last decade, scientists have assembled the complete DNA sequences of several important oral bacteria. Now NIH-funded investigators have decoded and added another important bacterium, *Streptococcus sanguinis*, a key player in the formation of the oral biofilm, to the list. Although not regarded as a pathogen in the mouth, *S. sanguinis* is known to enter the bloodstream, where it can colonize heart valves and contribute to bacterial endocarditis, a condition that kills an estimated 2,000 Americans each year. With the bacterium's genetic blueprint now publicly available online, scientists can better study the dynamics of biofilm formation and possibly tease out new leads to prevent tooth decay and periodontal disease. They can also now systematically identify and target sequences within the DNA of *S. sanguinis* that are critical to the infectious process, invaluable information in designing more effective treatments for endocarditis.

- [Xu P, et al. \*J Bacteriol\* 2007;189: 3166-75](#), PMID: 17277061
- This example also appears in Chapter 3: *Genomics*.
- (E) (NIDCR)

## Major Infectious Diseases

**Malaria Vaccine Research:** Malaria continues to be one of the most devastating diseases throughout the world today. The number of cases of the disease ranges from 350 million to 500 million each year, resulting in more than 1.1 million deaths, primarily among young children in Africa (World Health Organization [WHO]). To address this important public health issue, the WHO Initiative for Vaccine Research reports that, as of August 2005, there are at least 45 candidate vaccines in preclinical development and 26 in clinical trials. NIH plays a valuable role in funding a number of these activities, supporting 15 of the candidates in preclinical development and 5 of the candidates in clinical trials. Examples of NIH-supported activities include the following:



- ▷ NIH researchers have applied an innovative technology, tested in mice, that may prompt an individual's immune system to eliminate the malaria parasite from the mosquito. Because the vaccine targets the parasite instead of conferring protection to the individual, it has the potential to eradicate malaria from large geographic regions.
- ▷ NIAID, in collaboration with the Walter Reed Army Institute of Research, GlaxoSmithKline Biologicals, the U.S. Agency for International Development, and others, has completed a Phase I adult trial in Mali of a novel candidate vaccine that works by blocking the replication of malaria parasites in the blood. Additional studies in children (who have the highest death toll among malaria cases) are under way.
  - For more information, see [http://www.who.int/vaccine\\_research/diseases/soa\\_parasitic/en/index4.html](http://www.who.int/vaccine_research/diseases/soa_parasitic/en/index4.html)
  - (NIAID, NICHD, NIDDK)

**Value of Early HIV Screening, Testing, and Counseling:** HIV/AIDS disproportionately affects several minority groups, particularly African Americans. Although adult and adolescent African Americans make up approximately 13 percent of the population, they accounted for half of the new HIV/AIDS diagnoses in 2001-2005. This disparity is particularly striking because African Americans do not have higher rates of addiction or intravenous drug use than Whites. One contributing factor is that African Americans are often diagnosed with HIV infection at a later point in the illness, increasing their likelihood of progressing to AIDS and of transmitting the disease. As part of efforts to prevent late diagnosis and HIV spread, NIH is working to identify and address the cultural barriers to making HIV screening more acceptable and to strengthen the links among education, testing and counseling, and treatment within all ethnic groups. Indeed, NIH-supported modeling research has shown that routine HIV screening, even among populations with prevalence rates as low as 1 percent, is as cost-effective as screening for other conditions such as breast cancer and high blood pressure. The CDC has recognized that these findings have important public health implications and has called for increased HIV screening as part of its recommended guidelines. NIH is eager to advance new HIV rapid-screen technologies and counseling in community drug treatment programs and in criminal justice settings.

- For more information, see <http://www.drugabuse.gov/ResearchReports/hiv/hiv.html>
- For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm>.
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDA)

**Special Journal Issue: “Cultural Dynamics in HIV Prevention Among Young People”:**

Twenty-five years of behavioral and biomedical research have led to breakthroughs in the prevention and treatment of HIV disease; however, young people have not fully benefited from these advances. In September 2005, NIH held a workshop, “Cultural Dynamics in HIV/AIDS Biobehavioral Research Among Young People.” In March 2007, a special issue of the *Journal of the Association of Nurses in AIDS Care* presented a series of papers developed from this

workshop. These papers are focused on current research into preventing the spread of HIV infection among youths from many cultures across the United States and around the world.

- [Hare ML, Villarruel AM. \*J Assoc Nurses AIDS Care\* 2007;18:1-4](#), PMID: 17403490
- For more information, see <http://www.ninr.nih.gov/NewsAndInformation/JANAC/>
- (E) (NINR)

**Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN):** Although one-third to one-half of new HIV infections occur among adolescents and young adults, researchers know little about how the complex physiological changes associated with adolescence impact the transmission dynamics and course of HIV infection. NIH is supporting a national clinical research network to address the unique challenges and clinical management needs of HIV-positive youth and those at risk of infection. Researchers in this network are building the capacity to develop and conduct selected biomedical, behavioral, and community-based studies, including vaccine and microbicide trials to ensure that the needs of high-risk teens (e.g., alcohol- or drug-abusing adolescents) have access to the most promising treatment and prevention interventions as they are being developed.

- For more information, see <http://www.atnonline.org>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NICHD, NIDA, NIMH)

**Diagnosis of Malaria by Microscopy:** Virtually all clinical decisions, epidemiological surveys, field trials of drugs and vaccines, and evaluations of intervention programs in malaria depend on diagnoses made by microscopy. NIH has undertaken the first systematic analysis of errors and sources of error in malaria microscopy. This multiyear study includes the best malaria clinics in the tropical world and found 13 percent false-negative and 24 percent false-positive rates. Follow-up work is analyzing the accuracy and effect of different microscopy techniques, using different blood samples from the same patient, different microscope slides from the same blood sample, aspects of parasite and patient biology, microscopist training, and other factors.

- [O’Meara WP, et al. \*Malaria J\* 2006;5:118](#), PMID: 17164007
- (FIC)

**Microbicides:** With more than 19.2 million women worldwide living with HIV/AIDS and more than 80 percent of HIV infections spread through heterosexual activity, NIH collaborative research is developing new ways to help women protect themselves from the virus. This includes the development and testing of agents that, if applied topically to genital areas, inactivate the virus or otherwise prevent susceptible cells from being infected with HIV. Scientists are working to develop, standardize, and validate innovative ways to rapidly screen large numbers of potential antimicrobial agents for irritation and safety. In addition, work is under way to examine the behavioral and social factors influencing whether individuals or couples would adopt and use new antimicrobial products consistently and effectively.

- (E) (NICHD, NIAID)

**Culturally Appropriate Research to Prevent HIV Infection:** Great strides have been made in the past 25 years in treatment and prevention strategies to combat the spread of HIV/AIDS in the United States. However, many populations in the United States and around the world have not benefited from these developments, and this is especially true for young people. One possible reason for such disparities is the influence of cultural differences on the effectiveness of prevention and treatment strategies. In fall 2006, NIH solicited proposals for innovative research to design and test interventions to prevent HIV transmission among young people. Areas of research interest include developing prevention/treatment interventions for young people with HIV/AIDS that take into account the cultural differences of those infected, determining the influence of cultural differences on how young people view living with HIV/AIDS and how these differences affect their views on preventing the spread of the disease, and examining challenges in transferring successful interventions across cultures, especially to other parts of the world.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-003.html>
- (E) (NINR)

**The Program in HIV/AIDS & Cancer Virology:** The mission of this program is to facilitate and rapidly communicate advances in the discovery, development, and delivery of antiviral and immunologic approaches for the prevention and treatment of HIV infection, AIDS-related malignancies, and cancer-associated viral diseases. This includes basic laboratory, translational, and clinical studies of disease pathogenesis and the development of novel targeted treatment approaches for cancers in HIV-infected individuals, as well as HIV infection itself, and drug resistance. Recent advances include a new prophylactic vaccine for HPV and promising candidates for prophylactic and therapeutic vaccines for HIV.

- For more information, see <http://ccr.nci.nih.gov>
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NCI)

**The NCI Vaccine Program:** NCI's vaccine program develops novel vaccines for cancer immunotherapy and prevention and HIV. The program encourages collaborations, identifies organizational and reagent needs for the community, and develops the optimal infrastructure for vaccine development and novel clinical trial approaches. Gardasil<sup>®</sup>, the first vaccine to prevent cervical cancer induced by HPV, is now available and can potentially save more than 5,000 U.S. women's lives each year. This FDA-approved vaccine resulted from the basic research performed at NIH that produced a prototype vaccine and the observation that linked HPV and cervical cancer.

- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NCI)

**Retrovirus Epidemiology Donor Study (REDS):** REDS was begun by NIH in 1989 to determine the prevalence and incidence of HIV infection among blood donors and the risks of transmitting HIV and other viruses via transfusions. In 2004, NIH launched REDS-II to monitor the appearance of newly discovered infectious agents in the blood supply, evaluate the characteristics and behaviors of voluntary blood donors, determine the causes of transfusion

reactions of unknown etiology, assess the results of new donor screening methods, assess the effects of new blood-banking technologies, and evaluate the donation process. In 2005, an international component was added to REDS-II to conduct research on blood donors in selected countries seriously affected by the AIDS epidemic to ensure the safety and availability of blood for transfusion.

- For more information, see <http://clinicaltrials.gov/ct/show/NCT00097006;jsessionid=7A9763F65A8C734DA771CDB5210D4877?order=7>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NHLBI)

**Improved Management of Antiretroviral Therapy for Adults and Children:** Two recent NIH studies transformed the management of antiretroviral therapy by extending the survival of adults and children with HIV/AIDS. Results from the Strategies for Management of Antiretroviral Therapy (SMART) study, one of the largest HIV/AIDS treatment trials ever conducted, showed that episodic use of antiretroviral therapy based on CD4+ cell levels is inferior to the use of continuous therapy for treatment-experienced patients and that deliberately interrupting antiretroviral therapy more than doubles the risk of developing AIDS or dying from any cause. The Children with HIV Early Antiretroviral Therapy (CHER) Study examined early antiretroviral therapy in South African children. Interim data showed a 96 percent increase in survival among infants who received immediate antiretroviral therapy compared with infants who received therapy later.

- [SMART Study Group et al. \*N Engl J Med\* 2006;355:2283-96](#), PMID: 17135583
- For more information, see <http://www3.niaid.nih.gov/news/newsreleases/2006/smart06.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIAID)

**New Approaches to Diagnostics:** Recognizing the urgent need for rapid, highly sensitive, and specific clinical diagnostics that can diagnose individuals exposed to or infected by human pathogens, NIH has developed a comprehensive research program that is taking advantage of genomic information and emerging technologies, such as nanotechnology, to develop new and improved diagnostic tools. The program covers a broad range of activities, including the development of improved sample preparation and processing, platform development, enhanced detection methods, and clinical validation. Program priorities include development of tools that can distinguish between a variety of pathogens or that can determine pathogen subtypes and their sensitivity to drug treatments.

- (E) (NIAID)

**NIAID HIV Vaccine Research Education Initiative (NHVREI):** This new national initiative is designed to educate the public about HIV vaccine research, especially at-risk populations such as African Americans, Hispanics, men who have sex with men, and women at high risk of HIV infection. The goal is to increase awareness about the urgent need for an HIV vaccine within the communities that are most affected by HIV/AIDS, create a supportive environment for current and future volunteers in HIV vaccine trials, and improve the public's perceptions and attitudes

toward HIV vaccine research. The NHVREI Local Partnership Program provides support to partner organizations in targeted communities to help achieve the initiative's goals.

- For more information, see <http://www3.niaid.nih.gov/news/newsreleases/2006/bethegeneration.htm>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NIAID)

**Research Agenda for MDR-TB/XDR-TB:** Diagnosing, treating, and controlling the spread of TB has become increasingly complicated by the HIV/AIDS co-epidemic and the emergence of MDR-TB and XDR-TB, which together threaten to set TB control efforts back to the pre-antibiotic era. In response to this urgent situation, in June 2007, NIH released its research agenda, *Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis*. The research priorities identified in the agenda build on a foundation of ongoing NIH-supported TB research, which currently comprises more than 300 research projects worldwide. This Web-based “living document,” identified as such because of NIH's ability to modify, amend, or update it as scientific and public health needs and opportunities evolve, was prepared in close collaboration with other Government and non-Government organizations and reviewed by TB specialists in academia, advocacy groups, international organizations, and other Government agencies. It identifies six critical areas for additional investigation: (1) new TB diagnostic tools, (2) improved therapies for all forms of TB, (3) basic biology and immunology of TB, (4) MDR-TB and XDR-TB epidemiology, (5) clinical management of MDR-TB and XDR-TB in people with and without HIV infection, and (6) TB prevention, including vaccines.

- For more information, see <http://www3.niaid.nih.gov/topics/tuberculosis>
- (E/I) (NIAID)

**The Evolving HIV Epidemic: Beyond Intravenous Drug Use:** The nature of the HIV epidemic in this country is changing. Effective medications and HIV risk reduction interventions in intravenous drug abusers have helped to curb the spread of HIV through injection drug use to a point where it now accounts for a smaller percentage of new infections. However, drug abuse continues to play a major role in the spread of HIV through other mechanisms: drug abusers proffer sexual behaviors to obtain drugs or money to support their addiction, and drugs of abuse can worsen the course of the illness and produce intoxication, which can alter judgment and decision-making and lead to impulsive and risky sexual behaviors. Recognition of this link is critical for developing more integrated and effective prevention strategies. A critical aspect of this message is that treatment of drug abuse *is* HIV prevention, an idea being furthered by NIH in concert with other Federal agencies, such as CDC.

- For more information, see <http://www.drugabuse.gov/ResearchReports/HIV/HIV.html>
- (E) (NIDA)

**Understanding Factors Affecting the Use of Microbicides:** NIH is planning an initiative on research directed toward understanding the complex interplay among individual, dyadic, social, and other contextual factors that may influence the initiation and sustained use of microbicides that are proven to be efficacious in reducing the risk of acquiring or transmitting HIV. In addition, the initiative will address research on prevention strategies that incorporate the use of microbicides and on the development of behavioral and social tools to assess product

acceptability, initiation, and sustained use in a manner that will directly inform microbicide product development and improvement.

- (E) (NIMH)

**OAR-Sponsored Initiatives Targeting Scientific Needs in AIDS Research:** OAR, through its planning process, identifies scientific areas that require focused attention and facilitates innovative, cross-institute, multi-institute, multidisciplinary activities to address those needs. OAR fosters these efforts by designating resources to jump-start program areas through funds for grant supplements to the ICs, establishing working groups or committees, sponsoring workshops or conferences to highlight a particular research topic, and sponsoring reviews or evaluations of research program areas. Examples include a Microbicide Innovation Program to accelerate the discovery of single and/or combination microbicides against HIV and STDs and a Prevention Science Initiative to foster innovative research in HIV prevention. OAR also supports initiatives to enhance dissemination of research findings, including sponsorship of a group of scientific panels that develop AIDS treatment and prevention guidelines, and the distribution of those guidelines through *AIDSinfo*, a Web-based service to provide up-to-date information for caregivers and patients about AIDS treatment and prevention.

- For more information, see <http://www.oar.nih.gov>
- (OAR)

**Trans-NIH Management and Coordination of HIV/AIDS Research:** NIH is the world's leader in AIDS research, representing the largest and most significant public investment in AIDS research in the world. Our response to the pandemic requires a unique and complex multi-institute, multidisciplinary, global research program. NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection and its associated co-infections, opportunistic infections, malignancies, and other complications. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every NIH IC. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds. OAR, located within the NIH Office of the Director, coordinates the scientific, budgetary, and policy elements of NIH AIDS research. Through its unique, trans-NIH planning, budgeting, and portfolio assessment processes, OAR ensures that AIDS research dollars are invested in the highest priority areas of scientific opportunity, allowing NIH to pursue a united research front against the pandemic.

- For more information, see <http://www.oar.nih.gov>
- (OAR)

**Development of New TB Diagnostic Tool:** By detecting TB as early as possible, health providers can more effectively treat and control the disease in a population. An NIH-funded investigator working in Lima, Peru, has developed a new assay for TB. This simple and relatively inexpensive diagnostic test offers faster, more sensitive detection of TB and drug-resistant TB than the currently used method and cuts diagnostic time from an average of 28 days



to 7 days. The new, inexpensive method is appropriate for countries with limited resources, and several countries are in the process of incorporating it into TB control protocols.

- [Moore DA, et al. \*N Engl J Med\* 2006;355:1539-50](#), PMID: 17035648
- (E) (FIC, NIAID)

**Adult Male Circumcision Significantly Reduces Risk of Acquiring HIV:** NIH-supported scientists announced an early end to two clinical trials of adult male circumcision because an interim review of trial data revealed that medically performed circumcision, with appropriate care in the postoperative period, significantly reduces a man's risk of acquiring HIV through heterosexual intercourse. The trials, which enrolled 2,784 men in Kisumu, Kenya, and 4,996 men in Rakai, Uganda, showed that HIV acquisition in circumcised men relative to uncircumcised men was reduced by roughly half. Although the initial benefit will be fewer HIV infections in men, ultimately adult male circumcision could lead to fewer infections in women in those areas of the world where HIV is spread primarily through heterosexual intercourse. Circumcision remains only part of a broader HIV prevention research agenda that includes development of vaccines, microbicides, behavioral interventions, and prevention of mother-to-child transmission.

- [Auvert B, et al. \*PLoS Med\* 2005;2:e298](#), PMID: 16231970
- For more information, see [http://www3.niaid.nih.gov/news/newsreleases/2006/AMC12\\_06.htm](http://www3.niaid.nih.gov/news/newsreleases/2006/AMC12_06.htm)
- (E) (NIAID)

## **Emerging Infectious Diseases and Biodefense**

**Biodefense Vaccines:** NIH is the lead Federal agency within DHHS for conducting research on potential agents of bioterrorism that directly affect human health. The terrorist attacks of September 11, 2001, and the deliberate exposure of civilians to anthrax spores prompted DHHS to emphasize the importance of advancing vaccines for specific pathogens that could be used in bioterrorist attacks. In response, in February 2002, NIH convened the Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research. This panel was brought together to provide objective expertise on NIH's future biodefense research agenda in both the short and the long term. As expected, one of the identified areas of research emphasis was the development of new and improved vaccines against agents of bioterrorism, with the initial focus on smallpox and anthrax. Since that time, substantial progress has been made in biodefense vaccine research and development, which has resulted in the following advances:

- ▷ Modified Vaccinia Ankara, a new, safer smallpox vaccine that is the outcome of several years of NIH-sponsored research and development, has been purchased for the Strategic National Stockpile.
- ▷ An Ebola vaccine has been developed and is currently being tested in humans at NIH.
- ▷ A promising new anthrax vaccine candidate made with a purified protein has been developed and will enable researchers to determine the minimum level of protein needed to confer protection and minimize side effects.

- For more information, see <http://www.hhs.gov/news/press/2007pres/06/pr20070604a.html>
- For more information, see <http://www3.niaid.nih.gov/news/newsreleases/2003/ebolahumantrial.htm>
- (NIAID, NICHD)



**Microneedle-Based Immunization Against Pandemic Influenza:** NIH is supporting a team of investigators under the Bioengineering Research Partnership grant mechanism to develop a low-cost, room temperature-stable, microneedle-based transdermal vaccine patch against pandemic influenza that could be rapidly distributed through pharmacies, fire stations, or the U.S. mail and painlessly self-administered. This dose-sparing delivery system will not produce any sharp, biohazardous waste and would avoid the expensive and time-consuming hypodermic vaccination process administered by medical personnel, thus allowing for a rapid response to pandemic influenza. This innovative application impacts the “HHS Pandemic Influenza Plan” and NIH’s directives on high-priority influenza research areas.

- For more information, see <http://www.hhs.gov/pandemicflu/plan>
- This example also appears in Chapter 3: *Technology Development*.
- (E) (NIBIB)

**Probes and Cell Arrays for Detection of Bacterial Toxins:** Microarray technology offers an opportunity for simultaneous monitoring the behavior of multiple markers within a mammalian cell and ultimately could be used for detection and elucidation of mechanisms of action of different biologically active agents, including those that are considered a threat in the biodefense area. The ultimate goal of this research project is to provide a general and robust approach for the detection of biologically active agents, especially when these agents have been engineered to elude currently available immunoassays. Cell arrays offer a new opportunity for sensitive and precise monitoring of biologically active substances. The goal of this project is to develop a system for the identification of regulatory elements that will allow a substantial extension of the discriminative abilities of cell arrays and the creation of cell arrays that are capable of detection and identification of potential biowarfare agents.

- (E) (NIEHS)

**Antimicrobial Resistance Research:** Antimicrobial resistance, which is caused by factors such as overuse of antibiotics, is severely jeopardizing the utility of many “first-line” antimicrobial agents and has emerged as a major public health threat. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. NIH is also pursuing translational and clinical research in this area, including clinical studies to test interventions for community-acquired MRSA infection, and to evaluate the efficacy of off-patent antimicrobial agents. NIH will continue to address high-priority research questions regarding resistance to help public health officials hold the line against drug-resistant microbes.

- For more information, see <http://www.niaid.nih.gov/factsheets/antimicro.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIAID) (GPRA Goal)

**Ecology of Infectious Diseases (EID):** Jointly administered by NIH and the National Science Foundation (NSF), the EID program uniquely fills a critical gap in our national effort to protect public health against the threat of emerging infectious diseases. Most emerging diseases are initially transmitted from animals to humans, and some are capable of becoming pandemics. This program supports the discovery of the principles that govern the relationships between ecological

disturbances and transmission of infectious agents, and the use of those principles to develop predictive models of epidemics. Potential benefits of the program include an increased capacity to forecast outbreaks and to improve understanding of how diseases emerge and reemerge.

- [Eaton BT, et al. \*Nat Rev Microbiol\* 2006;4:23-35](#), PMID: 16357858
- For more information, see [http://www.fic.nih.gov/programs/research\\_grants/ecology/index.htm](http://www.fic.nih.gov/programs/research_grants/ecology/index.htm)
- (E) (FIC, NIAID, NIEHS)

**Biodefense Therapeutics Development:** Treatments against NIAID Category A-C priority pathogens, microbes, and toxins, which are considered to be the most significant threats to the Nation's well-being, are either nonexistent, of limited utility, or threatened by the emergence of antimicrobial resistance or intentional engineering to increase virulence or decrease drug susceptibility. Given the absence of a substantial commercial market, regulatory hurdles, and extensive clinical trial requirements, the private sector has little incentive to invest in antimicrobial countermeasures. To remedy this situation, NIH supports unique partnerships among Government, industry, small businesses, and academia to facilitate the movement of promising products through all stages of the drug research and development pipeline, with the goal of developing therapeutics against diseases such as smallpox, botulism, and Ebola and West Nile virus infection. These projects range from preclinical services (such as performing medicinal and analytical chemistry, custom drug synthesis, formulation, clinical manufacturing, microbiology and virology screening, pharmacokinetics, and safety testing) to the development and testing of DAS 181 (Fludase), which is potentially a broad-spectrum therapeutic agent for use against all annual and pandemic variations of influenza.

- For more information, see [http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/funding/FY2006+Awards/therapeutic\\_awards.htm](http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/funding/FY2006+Awards/therapeutic_awards.htm)
- (E/I) (NIAID)

**Developing New Adjuvants to Boost Vaccine Effectiveness:** The NIH Innate Immune Receptors and Adjuvant Discovery initiative encourages the discovery of novel adjuvants to meet the growing need to boost the effectiveness of vaccines against potential agents of bioterrorism and emerging infectious diseases. Adjuvants activate the body's innate immune system—microbe-engulfing phagocytes and soluble immune stimulators—leading to effective adaptive immune responses by B cells, which make antibodies, and T cells, which can directly kill infected cells. Using high-throughput screening, several groups of researchers have identified, optimized, and developed adjuvants that are now in preclinical development.

- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAID)

**Medical Countermeasures Against Nuclear and Radiological Threats:** NIH is leading the DHHS effort to sponsor and coordinate research to develop a means to counter the detrimental effects of a range of radiological threats. Most medical countermeasures to treat radiation injury are still in the early stages of development but are progressing. NIH-funded researchers recently (1) screened more than 40,000 candidate compounds and identified 52 candidates for evaluation as protective agents against the toxic effects of ionizing radiation, (2) developed improved forms of the chelating agent diethylenetriaminepentaacetic acid (DTPA), which animal testing data

suggest can effectively clear the radionuclide americium-241 from the blood, and (3) studied 29 candidate drugs that are active against a broad range of radionuclides and might be useful in treating victims of radiological dispersion devices (“dirty bombs”).

- For more information, see <http://www3.niaid.nih.gov/research/topics/radnuc>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIAID)

**Pandemic and Seasonal Influenza Vaccine Research:** In FYs 2006 and 2007, NIH made significant progress toward the development of new and more effective vaccines for the control of both seasonal and pandemic influenza. For example, an NIH-supported clinical trial provided the scientific data on which the FDA based its recent licensure of the first pandemic influenza vaccine against H5N1 virus (“bird flu”) in the United States. NIH also developed and conducted clinical trials of whole-inactivated and live-attenuated vaccines against H5N1 influenza and developed DNA, recombinant virus, and recombinant protein-based influenza vaccines. NIH also supports activities to expand and accelerate the development of additional manufacturing methods; evaluate various strategies to optimize a limited vaccine supply, including intradermal vaccines and the use of adjuvants; and explore the concept of developing a vaccine that raises immunity to parts of the influenza virus that vary little from season to season and from strain to strain, thereby potentially reducing or eliminating the need for annual immunization against seasonal influenza. Such a vaccine might also strengthen protective immunity against an emerging pandemic strain of influenza virus.

- For more information, see <http://www3.niaid.nih.gov/healthscience/healthtopics/Flu/Research/ongoingResearch/Prevention/default.htm>
- For more information, see <http://www3.niaid.nih.gov/healthscience/healthtopics/Flu/PDF/InfluenzaBlueRibbonPanel2006.pdf>
- (E/I) (NIAID)

**Radiation Event Medical Management (REMM):** As a part of an effort to improve public health emergency preparedness and response, NIH and the DHHS Office of the Assistant Secretary for Preparedness and Response announced in 2007 a new downloadable online diagnostic and treatment toolkit to guide health care providers during a mass casualty radiation event. The REMM toolkit includes easy-to-follow procedures for diagnosis and management of radiation contamination and exposure, guidance for the use of radiation medical countermeasures, and a variety of other features to facilitate medical responses to radiation emergencies.

- For more information, see <http://remm.nlm.gov>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (I) (NLM)

## Infrastructure and Research Resources

**Biodefense Research Infrastructure:** NIH has invested substantially in the intellectual and physical infrastructure needed to build the Nation’s capacity for research on biodefense and

emerging infectious diseases. This effort draws scientists from many disciplines to conduct research and development activities and to train future researchers. It also provides facilities that will greatly enhance the safe and efficient conduct of research on infectious agents. The NIH-funded infrastructure includes (1) 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, which use a multidisciplinary approach to research and development, (2) two National Biocontainment Laboratories (with BSL-4 capacity, the highest level of containment) and (3) 13 Regional Biocontainment Laboratories with BSL-3 capacity.

- For more information, see <http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PublicMedia/BioLabs.htm>
- (E/I) (NIAID) (GPRA Goal)

**The National Science Advisory Board for Biosecurity (NSABB):** NSABB was established to advise the U.S. Government on strategies for the efficient and effective oversight of dual-use biological research, taking into consideration both national security concerns and the needs of the research community. The term “dual use” in conjunction with life sciences research is an acknowledgment that some of the information and technologies used to advance human, animal, and plant health can also be used to threaten public health and safety. NSABB brings together 25 voting non-Federal members who represent the scientific, biosafety, security, legal, ethics, scientific publishing, and intelligence communities. In addition, there is active participation by 14 major Federal departments, agencies, and offices across the Government. NSABB has issued two sets of reports and recommendations. The first is focused on the biosecurity issues raised by the rapidly increasing ability to synthesize select agents and other dangerous pathogens. The report identifies a number of biosecurity considerations; assesses whether the current Federal regulations, policies, and guidelines afford adequate oversight in this arena; and provides recommendations for addressing the issues. The second report is a proposed framework for local and Federal oversight of dual-use research. It is intended as a springboard for the development of Federal guidelines and procedures for oversight of dual-use research and includes guidance for identifying dual-use research of concern, considerations for developing codes of conduct for life scientists, and considerations and tools for the responsible communication of dual-use research. NSABB is currently developing strategies for fostering international engagement of dual-use life sciences issues and for education and outreach regarding these issues.

- For more information, see <http://www.biosecurityboard.gov>
- (OD)

**HIV/AIDS Research Network Restructuring:** To better address the evolving scientific challenges of the HIV/AIDS epidemic, in FY 2006 NIH restructured its HIV/AIDS clinical research infrastructure into six research networks: the AIDS Clinical Trials Group (ACTG), the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network (HVTN), the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Group, the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), and the Microbicide Trials Network (MTN). Each network consists of a leadership group that provides administrative and technical support, as well as a number of the 73 HIV/AIDS Clinical Trials Units NIH funds in the United States and abroad (some Clinical Trials Units belong to more than

one network). The reorganization will improve the efficiency, flexibility, and coordination of HIV/AIDS clinical research.

- For more information, see <http://www3.niaid.nih.gov/news/newsreleases/2007/ctu07.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIAID) (GPRA Goal)

**Translational Research at Primate Research Centers:** Nonhuman primates are critical components for translational research because of their close physiological similarities to humans. Nonhuman primates are widely used for both hypothesis-based and applied research directly related to human health, such as the development and testing of vaccines and therapies. The NIH-supported National Primate Research Centers and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. In FY 2007, more than 1,000 research projects used nonhuman primates from these resources. Highlights of research activities include:

- ▷ Use of the simian immunodeficiency virus for AIDS-related research, including development of novel microbicides to prevent infection by the AIDS virus and testing of AIDS vaccines
  - ▷ Identification of the central role of specific genes and molecules in drug addiction and neurological conditions and diseases, studies of the biochemistry and physiology of drug and alcohol addiction, and development of stem cell-based therapies for neurodegenerative diseases
  - ▷ Sponsored scientific workshops in FYs 2006 and 2007 that further defined the genetic tools necessary for translational research using nonhuman primates
- For more information, see [ncrr.nih.gov/comparative%5Fmedicine/resource\\_directory/primates.asp](http://ncrr.nih.gov/comparative%5Fmedicine/resource_directory/primates.asp)
  - This example also appears in Chapter 3: *Clinical and Translational Research*.
  - (E) (NCRR)

**Centers of Excellence for Influenza Research and Surveillance:** Six Centers of Excellence for Influenza Research and Surveillance, established in 2007, significantly expand the ability of NIH to conduct research on different strains of animal and human influenza viruses collected internationally or in the United States. The centers will lay the groundwork for the development of new and improved control measures for emerging and reemerging influenza viruses, help determine the prevalence of avian influenza viruses in animals in close contact with humans, and extend understanding of how influenza viruses evolve, adapt, and are transmitted. The centers will also bolster research on questions such as how influenza viruses cause disease and how the human immune system responds to infection and will inform public health strategies to control and minimize the impact of seasonal and pandemic influenza.

- For more information, see <http://www3.niaid.nih.gov/research/resources/ceirs>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAID)

**Urinary Tract Infections:** NIH supports a Specialized Center of Research on Sex and Gender Factors Affecting Women's Health. This program advances new understanding of host-pathogen

interactions that occur throughout the infectious cycle, including host defense response in the bladder and the virulence mechanisms by which bacterial pathogens subvert the defenses.

- For more information, see <http://clinicaltrials.gov/ct/show/NCT00068120>
- Justice SS, et al. *Proc Natl Acad Sci U S A* 2006;103:19884-9, PMID: 17172451
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK)

**NIH Countermeasures Against Chemical Threats (CounterACT) Research Network:**

CounterACT, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The network, which has collaborated with DoD from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DoD researchers identified as a potential countermeasure against chemical agent-induced seizures, is entering clinical trials in epilepsy patients through the NINDS Neurological Emergency Clinical Trials Network, and NIH is collaborating with DoD to complete animal studies necessary for its FDA approval as a nerve agent treatment.

- For more information, see <http://www.ninds.nih.gov/funding/research/counterterrorism/index.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NINDS, NEI, NIAID, NIAMS, NIEHS, NIGMS)

**Influenza Virus Resource:** This database of more than 40,000 influenza virus sequences allows researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic and vaccine targets. The resource was developed by NCBI using data obtained from NCBI's Influenza Virus Sequence Database and from NIAID's Influenza Genome Sequencing Project, which has contributed sequences of the complete genomes from more than 2,500 influenza samples. In FY 2006 more than 11,000 influenza virus sequences were entered into the database, and new search and annotation tools were added to assist researchers in their analyses.

- Wolf YI, et al. *Biol Direct* 2006;1:34, PMID: 17067369
- Chang S, et al. *Nucleic Acids Res* 2007;35:D376-80, PMID: 17065465
- For more information, see <http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>
- For more information, see <http://www.niaid.nih.gov/dmid/genomes/mscs/influenza.htm>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*, Chapter 3: *Genomics*, and Chapter 3: *Molecular Biology And Basic Sciences*
- (I) (NLM)

**Wireless Information System for Emergency Responders (WISER<sup>®</sup>):** WISER is a system designed to assist first responders in hazardous material incidents by providing a wide range of information on hazardous substances, including substance identification support, physical characteristics, human health information, and containment and suppression advice. In 2007, several important features were added to WISER, including radiological support with data for more than 20 isotope substances and tools/reference materials for radiological incidents. A new partnership with the U.S. Department of Transportation (DoT) enabled integration of the DoT's



Emergency Response Guidebook (ERG) 2004 with WISER and the development of a stand-alone ERG 2004 Mobile version. Widely used by first responders, WISER is available for downloading onto electronic handheld devices and Windows-based platforms or for browsing on the Web.

- For more information, see <http://wiser.nlm.nih.gov>
- This example also appears in Chapter 3: *Technology Development*.
- (I) (NLM)

**HIV/AIDS Epidemiological and Long-Term Cohort Studies:** NIH supports epidemiological HIV research through a wide range of cohort studies that contribute to our understanding of risk factors that lead to HIV transmission and disease progression. Established in 2005, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) compiles data from NIH-funded international HIV research to answer population-level questions about HIV variants and resistance, HIV pathogenesis in different settings, success of antiretroviral therapy, treatment history of HIV in different populations, success of prevention strategies, and vaccines. The Pediatric HIV/AIDS Cohort Study (PHACS), established in 2005, addresses two critical pediatric HIV research questions: the long-term safety of fetal and infant exposure to prophylactic antiretroviral chemotherapy and the effects of perinatally acquired HIV infection in adolescents. The Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) are the two largest observational studies of HIV/AIDS in women and homosexual or bisexual men, respectively, in the United States. These studies exceed standard clinical care diagnostics and laboratory analysis on both HIV-infected, and, importantly, HIV-negative controls, which allows for novel research on how HIV spreads, how the disease progresses, and how it can best be treated. The studies focus on contemporary questions such as the interactions among HIV infection, aging, and long-term treatment; cardiovascular disease; and host genetics and their influence on susceptibility to infection, disease progression, and response to therapy.

- For more information, see <http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIAID, NICHD)

**National NeuroAIDS Tissue Consortium (NNTC):** The NNTC is a repository of brain tissue and fluids from highly characterized HIV-positive individuals. Established as a resource for the research community, NNTC includes information from more than 2,000 individuals, including approximately 641 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

- For more information, see <http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-08-021.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E/I) (NIMH, NINDS)



## **International Collaboration**

**Success in Treating Drug Addiction Internationally:** International efforts to disseminate effective drug abuse treatments have seen success in countries with epidemic opiate addiction/HIV problems. Because of NIH research demonstrating that addiction is a chronic, relapsing disease that can be effectively treated, a culture change is starting to occur in these countries. For example, despite experiencing severe drug problems, Malaysia lagged behind in the treatment of drug addiction and related disorders, even as it coped with having the second-highest HIV prevalence rate among adult populations and the highest proportion of HIV cases from injection drug use. Historically, drug abusers were “rehabilitated” involuntarily in correctional facilities. Although 60 percent of prisoners had drug-related offenses, no or minimal treatment was available in prison, and no medications were permitted. This primarily criminal treatment approach had limited effectiveness, which led to widespread public dissatisfaction and the recent introduction of medications for addiction. These include naltrexone (1999), buprenorphine (2001), and methadone (2003). These drug treatment programs, which were rapidly embraced by the country’s medical community, have resulted in tens of thousands of opiate-dependent patients receiving medical treatment. Now, the Ministry of Health rather than the Ministry of Security has authority for providing medical treatment for heroin addiction. This shift signals a remarkable change in Malaysian policies and approaches to addiction and an important opportunity to develop, implement, and disseminate effective treatments. A similar success story is starting to unfold in China as well.

- [Mazlan M, et al. \*Drug Alcohol Rev\* 2006;25:473-8](#), PMID: 16939945
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDA, NIAID)

**Multinational Influenza Seasonal Mortality Study:** NIH is leading an international collaborative effort to analyze national and global epidemiological patterns associated with influenza virus circulation. Twenty countries have contributed data on mortality, virus surveillance, genomics, and control strategies. The goals of this large-scale collaboration are to evaluate and compare public health strategies to alleviate the impact of seasonal influenza in different countries and to understand the global circulation patterns of influenza and their impact on populations. A better understanding of influenza epidemiology worldwide can inform vaccine strain selection and strategies to mitigate future influenza pandemics.

- For more information, see <http://origem.info/misms>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (FIC)

**HIV Vaccine Development:** NIH supports research around the world to find a safe and effective vaccine against HIV. Since the first HIV vaccine trial in 1987, NIH has worked with its partners in academia, Government, the private sector, and non-Government organizations to conduct more than 100 HIV vaccine clinical trials that have enrolled more than 26,000 volunteers. In 2005, NIH formed the Center for HIV/AIDS Vaccine Immunology (CHAVI), a consortium of scientists committed to overcoming key scientific roadblocks to HIV vaccine development and to designing and testing HIV vaccine candidates. NIH is also involved in the Global HIV Vaccine

Enterprise and the Partnership for AIDS Vaccine Evaluation (PAVE). Several clinical trials are testing vaccine candidates around the globe. Recently, however, two large vaccine trials stopped immunizations upon recommendation of a Data Safety Monitoring Board review. However, the new large-scale trial, called PAVE 100, is still under discussion and may begin in 2008. This trial will test whether an NIH-developed candidate vaccine can prevent acquisition of infection or progression of disease (using viral load as a surrogate marker) in those who become infected.

- For more information, see <http://www3.niaid.nih.gov/research/topics/HIV/vaccines/default.htm>
- (E/I) (NIAID) (GPRA Goal)

**Global Infectious Disease Research Training:** A major barrier to improved treatment and control of infectious diseases is the scarcity in endemic countries of scientists with expertise in infectious disease research. This program supports institutions in the United States and developing countries to train scientists from developing countries to engage in research on infectious disease other than HIV/AIDS. The program is contributing to the long-term goal of building sustainable research capacity in endemic infectious diseases in institutions in developing countries to enhance prevention, treatment, and control of infectious diseases that cause major morbidity and mortality in the developing world.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/gid.htm](http://www.fic.nih.gov/programs/training_grants/gid.htm)
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (FIC, NIAID)

**HIV Research Training Programs:** The AIDS International Training and Research Program (AITRP) builds institutional, national, and regional HIV research capacity in low- and middle-income countries. Over the past 19 years, this program has been responsible for many of the first generation of research scientists from these countries, with many more in the pipeline. The program offers multidisciplinary biomedical, behavioral, and social science research training to a wide range of professionals. Building on the AITRP, the Clinical, Operational and Health Services Research Training Program for HIV/AIDS and TB (ICOHRTA AIDS/TB) began in 2002 to strengthen the capacity for clinical, operational, and health services research in low- and middle-income countries where AIDS, TB, or both are significant problems. Through training health professionals that reach across the spectrum of clinical and public health research, this program is strengthening the capacity of scientists, program managers, and policymakers to evaluate and better implement large-scale prevention, treatment, and care interventions that are locally relevant and effective. Many local leaders of programs supported by the President's Emergency Plan for AIDS Relief have received or are receiving their research training through the AITRP and the ICOHRTA AIDS/TB programs.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/aitrp/index.htm](http://www.fic.nih.gov/programs/training_grants/aitrp/index.htm)
- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/icohrta/aids\\_tb.htm](http://www.fic.nih.gov/programs/training_grants/icohrta/aids_tb.htm)
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Research Training and Career Development*.
- (E) (FIC, NCI, NIAID, NHLBI, NIDA, NIDCR, NIMH, NINDS, NINR, OAR, ORWH)

**Mechanisms of HIV Neuropathogenesis: Domestic and Global Issues:** Neurological manifestations, including HIV dementia and opportunistic infections and tumors, are among the most threatening complications of HIV infection. Emerging data indicate that the prevalence of

HIV-related neurological disease differs across regions of the world, suggesting that different subtypes of HIV may be more or less capable of causing neuropathology or that genetic variance among people in various regions of the world could affect susceptibility to HIV's neuropathological effects. NIH sponsored a meeting in the spring of 2007 to address these issues, resulting in the release of a funding announcement.

- For more information, see <http://synapse.neurology.unc.edu/venice/>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-030.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH, NINDS, OAR)

**HIV Virus Transmission From Primates to Humans:** Through the International Research Scientist Development Award (IRSDA), FIC provides career development and research support to U.S. postdoctoral scientists in the formative stages of their careers to solidify their commitment to global health research. For example, under this program, FIC supported the career development of Dr. Nathan Wolfe, whose work in Cameroon advanced our understanding of how retroviruses enter into human populations and determined that the likely point of transmission of the HIV occurred between primates and bushmeat hunters. Dr. Wolfe has now received the NIH Director's Pioneer Award. Co-funded by FIC and NIAID, this award builds on Dr. Wolfe's IRSDA-supported research and is enabling the establishment of the first global network to monitor the transmission of new viruses, including those causing pandemic disease threats such as Ebola, anthrax, and monkeypox, from animals into human populations. This hunter cohort distributed throughout key habitats will provide a framework for a range of research projects aimed at predicting and preventing disease emergence, including studies of risk factors associated with primary and secondary infections with zoonotic microorganisms, anthropological studies of hunting and meat processing practices that lead to exposure, and ecological studies of the animal and human populations that influence transmission among and between groups.

- [Wolfe ND, et al. \*Proc Natl Acad Sci U S A\* 2005;102:7994-9](#), PMID: 15911757
- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/irsda.htm](http://www.fic.nih.gov/programs/training_grants/irsda.htm)
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (FIC)

## **NIH Strategic Plans Pertaining to Infectious Disease and Biodefense Research**

### **National Institute of Allergy and Infectious Diseases (NIAID)**

- [NIAID: Planning for the 21st Century \(2000\)](#)

### **HIV/AIDS**

- [NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis \(2001\)](#)
- [Vaccine Research Center Strategic Plan: Research Toward Development of an Effective AIDS Vaccine \(2001\)](#)

### **Infectious Diseases (non-biodefense, non-AIDS)**

- [Blueprint for Tuberculosis Vaccine Development \(1997\)](#)

**Biodefense and Emerging Infectious Diseases**

- [NIAID Strategic Plan for Biodefense Research \(2007 update\)](#)
- [NIAID Strategic Plan for Biodefense Research \(2002\)](#)
- [NIAID Biodefense Research Agenda for CDC Category A Agents \(2002\)](#)
- [NIAID Biodefense Research Agenda for Category B and C Priority Pathogens \(2003\)](#)
- [NIAID Expert Panel on Immunity and Biodefense \(2002\)](#)
- [NIAID Expert Panel Review of Medical Chemical Defense Research \(2003\)](#)
- [NIAID Expert Panel on Botulinum Toxins \(2002\)](#)
- [NIAID Expert Panel on Botulinum Diagnostics \(2003\)](#)
- [NIAID Expert Panel on Botulinum Neurotoxins Therapeutics \(2004\)](#)
- [Report of the Blue Ribbon Panel on Influenza Research \(2006\)](#)
- [NIAID Research Agenda Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis \(2007\)](#)

**Special Populations**

- [Women's Health in the U.S.: Research on Health Issues Affecting Women \(2004\)](#)

**National Institute of Dental and Craniofacial Research (NIDCR)**

- [NIDCR Strategic Plan](#)
- [NIDCR Implementation Plan](#)

**National Institute of Child Health and Human Development (NICHD)**

**Branch Reports to Council with Future Scientific Directions**

- [Pediatric, Adolescent, and Maternal AIDS Branch \(PAMAB\), NICHD, Report to the NACHHD Council, June 2007](#)

**National Institute on Drug Abuse (NIDA)**

- [Bringing the Power of Science to Bear on Drug Abuse and Addiction](#) (under revision)

**National Institute on Alcohol Abuse and Alcoholism (NIAAA)**

- [National Institute on Alcohol Abuse and Alcoholism Five-Year Strategic Plan, FY08-13](#)
- Recommendations of the NIAAA Extramural Advisory Board (EAB)
- [Developing an NIAAA Plan for HIV-Related Biomedical Research](#)

**National Center for Complementary and Alternative Medicine (NCCAM)**

- [Expanding Horizons of Health Care: Strategic Plan 2005-2009](#)

**John E. Fogarty International Center (FIC)**

- [Pathways to Global Health Research](#) (Draft)

**Office of AIDS Research (OAR)**

- [FY 2008 Trans-NIH Plan for HIV-Related Research](#)  
CC, CSR, FIC, NCCAM, NCI, NCMHD, NCR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, **OAR**, OBSSR, OIR, ORD, ORWH

**Other Trans-NIH Strategic Plans**

- [\*NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats\*](#)  
NCI, NHLBI, **NIAID**, NIEHS

## AUTOIMMUNE DISEASES

*The immune system has always been thought of as the body's protector against disease-causing organisms and foreign bodies. The idea that a person's immune system could launch an attack against itself was so unthinkable that, in 1900, bacteriologist and immunologist Paul Ehrlich coined the term horror autotoxicus. Ehrlich theorized that the body is averse to forming antibodies against itself. More than 40 years later, Mac Burnet postulated that a so-called "thymic censor" blocked the creation of auto-antibodies—antibodies that, instead of attacking foreign bodies, attack the self. Burnet suggested that these auto-antibodies might be produced if the "thymic censor" malfunctioned. Now we know that autoimmunity is the failure of the immune system to differentiate between the self (the body's own cells, tissues, and organs) and the non-self (disease-causing organisms and other foreign substances). When this happens, the immune system reacts as though the body is nonself and acts accordingly—it attacks. Burnet went on to win the Nobel Prize for subsequent work in immunology. He and Peter Medawar won the prize by demonstrating that the body can learn to not attack a foreign presence (e.g., a transplanted organ). This concept, called immune tolerance, is central to many of today's most important advances in immunology.*

### Introduction

Autoimmune diseases are a group of more than 80 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues, and cells. The causes of autoimmune disease remain unknown, although genetic factors play major roles in susceptibility. Some of these diseases may be triggered by an infectious agent or an environmental exposure, especially in individuals who have inherited a heightened susceptibility. Some of the more common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, multiple sclerosis, systemic lupus erythematosus, and inflammatory bowel disease. Organ-specific autoimmune diseases are characterized by immune-mediated injury localized to a single organ or tissue, for example, the pancreas in type 1 diabetes and the central nervous system in multiple sclerosis. In contrast, non-organ-specific diseases, such as systemic lupus erythematosus, are characterized by immune reactions against many different organs and tissues, which may result in widespread injury.

Autoimmune diseases can affect any part of the body and have myriad clinical manifestations that can be difficult to diagnose. At the same time, autoimmune diseases share some features related to their onset and progression. In addition, overlapping genetic traits enhance susceptibility to many of these diseases, so that a patient may suffer from more than one autoimmune disorder, or multiple autoimmune diseases may occur in the same family. Furthermore, because most autoimmune diseases are more common in women than in men, hormones are suspected of playing a role. For these and other reasons, the autoimmune diseases are best recognized as a family of related disorders that must be studied together as well as individually.

Most autoimmune diseases disproportionately affect women and, as a group, are among the leading causes of death for young and middle-aged women.<sup>38</sup> Although treatments are available for many autoimmune diseases, cures have yet to be discovered and patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, and hospitalization. The social and financial burden of these diseases is immense and includes poor quality of life, high health care costs, and substantial loss of productivity.

NIH supports research and promotes progress toward conquering autoimmune diseases through a wide range of research projects and programs. Because autoimmune diseases span many organ systems and clinical disciplines, multiple NIH institutes, including NIAID, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIDDK, NCI, NIDCR, NINDS, the National Human Genome Research Institute (NHGRI), and NIEHS, collaborate with professional and patient advocacy organizations to support [autoimmune disease research](#). The [Autoimmune Diseases Coordinating Committee](#) (ADCC) facilitates inter-Institute collaboration and coordination in the development, review, award, and post-award monitoring of solicited autoimmune diseases research programs.

Several decades of intensive research have produced a wealth of information that has transformed conceptual understanding of autoimmune diseases. This research has helped set the stage for major advances in diagnosis, treatment, and prevention interventions. However, NIH recognizes that more needs to be done to close the gaps in knowledge and achieve the overall goal of reducing the rising toll of autoimmune diseases. The major tasks facing researchers in autoimmune diseases are:

- Development of a mechanism-based, conceptual understanding of autoimmune diseases
- Translation of this knowledge into new, broadly applicable strategies for treatment and prevention of multiple diseases
- Development of sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals

NIH supports an array of programs to accomplish these tasks, including research and activities to:

- Advance understanding of the distribution of autoimmune diseases through epidemiological studies
- Apply the knowledge provided by the Human Genome Project toward elucidating the hereditary risks of autoimmune diseases
- Extend understanding of genetic and environmental factors contributing to autoimmune diseases and then develop effective prevention strategies that arrest the autoimmune process before it can irreversibly damage the body
- Enhance the translation of scientific advances in autoimmune disease to clinical practice through the conduct of training and education activities for researchers and clinicians in collaboration with nonprofit and advocacy organizations and through effective information dissemination to patients, their families, and the public

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<sup>38</sup> [Walsh SJ, Rau LM. \*Am J Public Health\* 2000;90:1463-6](#), PMID: 10983209



In autoimmune diseases, a major goal of contemporary research is to “re-educate” the immune system by using tolerance induction strategies that aim to selectively block or prevent deleterious immune responses while leaving protective immunity intact. Immune tolerance will be evaluated by integrating mechanistic studies of tolerance induction and suppression of disease into clinical research studies and by conducting clinical trials of a variety of agents and strategies through dedicated clinical networks.

Overarching priority areas that promise to accelerate autoimmune disease research include biomarker development, bioinformatics, and application of new technologies. The development of biomarkers holds great promise for earlier and more accurate diagnosis of autoimmune diseases, better prediction of disease flare-ups, and improved monitoring of disease progression and response to treatment. New technologies such as genomics and proteomics provide scientists with the tools to identify susceptibility genes and to study gene and protein patterns in tissue samples. They also make it possible to characterize antibodies in serum, which may provide vital insights into the mechanisms of onset and progression of autoimmune disease. Bioinformatics tools, which help scientists to assemble and analyze large amounts of data, will be particularly important. Many of these research areas intersect with initiatives planned under the NIH Roadmap, which fosters trans-Institute and multidisciplinary collaboration as a way to address complex challenges in biomedical research.

## **Burden of Illness and Related Health Statistics**

Although many individual autoimmune diseases are rare, collectively they affect millions of Americans, and for unknown reasons, their prevalence is rising. Examples of prevalence and incidence statistics for some autoimmune diseases are:

- An estimated 2.1 million people in the United States (about 1 percent of the population) , including about 30,000 to 50,000 children, have rheumatoid arthritis.<sup>39</sup>
- About 730,000 to 1.5 million people have type 1 diabetes ([National Diabetes Fact Sheet, 2005](#)). About 15,000 people younger than age 20 are diagnosed annually with type 1 diabetes.<sup>40</sup>
- An estimated 250,000 to 350,000 people in the United States have been diagnosed with multiple sclerosis.<sup>41</sup>
- In the United States, 239,000 people have been diagnosed with or are suspected to have systemic lupus erythematosus.<sup>42</sup>
- As many as 1.4 million people in the United States have inflammatory bowel disease.<sup>43</sup>

For more information, see <http://www.niaid.nih.gov/publications/pdf/ADCCFinal.pdf>

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<sup>39</sup> [Lawrence RC, et al. \*Arthritis Rheum\* 1998;41:778-99](#), PMID: 9588729

<sup>40</sup>For more information, see <http://jama.ama-assn.org/cgi/content/abstract/297/24/2716>

<sup>41</sup> [Anderson DW, et al. \*Ann Neurol\* 1992;31:333-6](#), PMID: 1637140

<sup>42</sup> [Lawrence RC, et al. \*Arthritis Rheum\* 1998;41:778-99](#), PMID: 9588729

<sup>43</sup> [Loftus EV Jr. \*Gastroenterology\* 2004;126:1504-17](#), PMID: 15168363

## **NIH Funding for Autoimmune Disease Research**

In FYs 2006 and 2007, NIH funding for autoimmune diseases research was \$598 million and \$587 million respectively. The table at the end of this chapter indicates some of the research areas supported by this investment (see “Estimates of Funding for Various Diseases, Conditions, and Research Areas”).

### **Summary of NIH Activities**

NIH seeks to understand the onset and progression of autoimmune diseases and to use that knowledge to develop better interventions for disease prevention, diagnosis, and treatment. With more than 80 distinct autoimmune diseases, this may seem to be a daunting task. However, the many commonalities in the mechanisms that cause autoimmune disorders means that research on one autoimmune disease often advances our understanding of others.

### **Providing Research Resources and Infrastructure**

#### *Disease Registries*

Many autoimmune diseases are rare, and researchers often must engage in national and international collaborative research to ensure access to sufficient numbers of patients and tissue samples to conduct their studies. NIH provides resources to facilitate these research efforts. For example, disease registries provide an important epidemiological resource for tracing the natural history of autoimmune diseases, assessing its burden in different populations, and identifying and tracking trends in incidence and prevalence. NIH supports patient registries for numerous autoimmune diseases, including alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, epidermolysis bullosa acquisita, juvenile and adult-onset rheumatoid arthritis, lupus, neonatal lupus, and scleroderma. Some of these registries also contain relevant clinical data linked to tissue samples.

#### *Other Research Resources*

NIH-supported research resources also include programs for the preclinical development of therapeutic agents, such as the [Type 1 Diabetes-Rapid Access to Intervention Development Program](#); biological specimen repositories; animal models; provision of genetic, genomic, and other molecular assays for specific projects; clinical trials infrastructure; and assistance in identifying collaborators. Some of these resources are mentioned in more detail in the “Notable Examples” later in this section.

### **Identifying Environmental Triggers of Autoimmune Diseases**

Two large-scale projects that are searching for environmental triggers of autoimmune diseases are the [Carolina Lupus Study](#) and [The Environmental Determinants of Diabetes in the Young \(TEDDY\)](#) study. The Carolina Lupus Study, initiated in 1997, was the first population-based epidemiological study to examine the influence of hormonal and occupational exposures on lupus. The investigators found a striking association between occupational exposure to silica dust

and lupus in individuals living in North and South Carolina. They also found that, compared with people who did not have lupus, patients with lupus were more likely to self-report occupational exposure to mercury, agricultural work that involved mixing pesticides, or work in a dental office or laboratory.<sup>44</sup> These and similar findings are expected to lead to improved prevention strategies for lupus and other autoimmune diseases and suggest possibilities for studies of the molecular development of lupus.

TEDDY is pinpointing environmental factors—such as infectious agents or diet—that can trigger type 1 diabetes in genetically susceptible individuals. This international consortium is following individuals who are at high genetic risk for type 1 diabetes from birth until age 15 to discover how environmental factors after birth contribute to the development of prediabetic autoimmunity and type 1 diabetes. Because type 1 diabetes and celiac disease share similar genetic predispositions, TEDDY investigators also are examining environmental triggers of celiac disease. The dataset and biologic samples amassed in TEDDY will provide a valuable resource for future studies.

## Understanding the Genetics of Autoimmune Diseases

NIH-supported scientists are identifying the genetic underpinnings of autoimmune disorders, research that can elucidate molecular pathways of disease and possible therapeutic targets. For example, investigators recently showed that a gene called *PSORS1* plays a role in determining who gets psoriasis. Individuals with a particular form of this gene (the HLA-Cw6 allele) are more likely to develop early-onset psoriasis.<sup>45</sup> Scientists hope that further research will lead to a treatment that interferes with the disease by targeting the *PSORS1* gene. Researchers also have discovered genes that variously appear to play roles in lupus, rheumatoid arthritis, inflammatory bowel disease, and alopecia areata, bringing us a step closer to understanding the mechanisms of these diseases.<sup>46</sup>

Recent technological advances have led to the development of genome-wide association studies that compare the genomes of people with an illness to those of people without the illness. Through this comparison, it becomes possible to identify even subtle genetic differences between affected and unaffected people (see the “Genomics” section in Chapter 3 for more information about genome-wide association studies). Genome-wide analysis is beginning to yield important results in the study of autoimmune diseases. For example, recent studies have led to the identification of key genes involved in type 1 diabetes<sup>47</sup> and inflammatory bowel disease.<sup>48</sup> Recent technological advances have led to the development of genome-wide association studies that compare the genomes of people with an illness to those of people without the illness. Through this comparison, it becomes possible to identify even subtle genetic differences between affected and unaffected people (see the *Genomics* section for more information about genome-

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<sup>44</sup> Cooper GS, et al. *J Rheumatol* 2004;31:1928-33, PMID: 15468355

<sup>45</sup> Nair RP, et al. *Am J Hum Genet* 78:827-51, PMID: 16642438

<sup>46</sup> Haan CK, Geraci SA. *Science* 2006;312:1665-9, PMID: 12022585, Haas CS, et al. *Arthritis Rheum* 2006;54:2047-60, PMID: 16804865, Martinez-Mir A, et al. *Am J Hum Genet* 2007;80:316-28, PMID: 17236136, Duerr RH, et al., *Science* 2006;314:1461-3, PMID: 17068223

<sup>47</sup> Lowe CE, et al., *Nat Genet* 2007;39:1074-82, PMID: 17676041

<sup>48</sup> Duerr RH, et al., *Science* 2006;314:1461-3, PMID: 17068223

wide association studies). Genome-wide analysis is beginning to yield important results in the study of autoimmune diseases, including the identification of key genes involved in type 1 diabetes and IBD. In other research, investigators using a large familial dataset the first new genes linked to MS in more than 20 years. These genes code for proteins that influence the way T cells patrol the body for pathogens, shedding light on a possible mechanism of MS onset and progression.<sup>49</sup> In a similar quest to identify disease genes, the [Type 1 Diabetes Genetics Consortium](#) is studying families with two or more siblings with type 1 diabetes. In addition, NIH supports the [Genetic Association Information Network](#) (GAIN), which provides genotyping services, including genome-wide association studies to enhance and extend the utility of existing of research efforts. Through GAIN, NIH supports a long-term collaboration in which investigators are seeking to identify new genetic susceptibility factors for the development of psoriasis.”

## Understanding the Mechanisms of Autoimmune Disease Onset and Progression

NIH sponsors research to illuminate the causes of autoimmune diseases and the regulatory mechanisms that control autoantibody production and function. For example, researchers recently used a mouse model to show that toll-like receptors, a set of immune receptors involved in the earliest immune responses to infection and long thought to play a key role in autoimmune responses, are indeed implicated. They showed that even minor mutations in toll-like receptors can spark autoimmunity, suggesting that this family of proteins could be an important therapeutic target for lupus or other autoimmune diseases.<sup>50</sup> Related research showed that a recently identified joint protein, cadherin 11, plays a role in rheumatoid arthritis in a mouse model of the disease. The investigators showed that a treatment that targets this protein prevents the abnormal adhesion and cartilage destruction typical of rheumatoid arthritis in mice, revealing a potential new therapeutic target in humans.<sup>51</sup>

NIH supports a range of initiatives such as the following to better understand the mechanisms of autoimmune disease onset and progression and to develop effective interventions.

The [Cooperative Study Group for Autoimmune Disease Prevention](#), established in 2001, is a collaborative network of investigators devoted to understanding the functioning of the immune system in both health and autoimmune disease. The Study Group works to develop the knowledge base necessary to design safe and effective interventions for the prevention of autoimmune disorders. Participating centers support preclinical research, innovative pilot projects, and noninterventional clinical studies, with an emphasis on type 1 diabetes. The Study Group, renewed recently for another 5 years, includes six cooperative agreements among researchers across the Nation.

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<sup>49</sup> [International Multiple Sclerosis Genetics Consortium. \*N Engl J Med\* 2007;357:851-62](#), PMID: 17660530

<sup>50</sup> [Pisitkun P, et al. \*Science\* 2006;312:1669-72](#), PMID: 16709748

<sup>51</sup> [Lee DM, et al. \*Science\* 2007;315:1006-10](#), PMID: 17255475

The [Beta Cell Biology Consortium](#) (BCBC) is a team science initiative established in 2001 and competitively continued in 2005. This program facilitates interdisciplinary approaches to advance the understanding of insulin-producing pancreatic beta cell development and function. Currently, BCBC consists of 29 scientists, the majority of whom participate as investigators on 10 cooperative agreements. Scientists from two intramural NIH laboratories also are involved. In addition to conducting research, the Consortium develops research resources, such as antibodies, mouse models, and gene arrays, for use by the scientific community.

Scientists studying autoimmune diseases are excited about the emerging research approach known as systems biology that seeks to understand the overall behavior of biological systems. Systems biology uses computational methods to analyze data or simulate the system of interest and requires collaboration among researchers from bioinformatics, computer science, molecular biology, genomics, and other disciplines. NIH-supported researchers are applying a systems biology approach to better understand Sjögren's syndrome, an autoimmune disorder in which immune cells attack and destroy the glands that produce tears and saliva, and other salivary gland disorders. Salivary gland biology is conducive to systems biology because researchers already have extensively catalogued the genes and proteins expressed in salivary glands. The scientific opportunity is to create an integrative, quantitative, and dynamic model encompassing every known aspect of the molecular and cellular biology of salivary glands and to translate this model into precise and practical ways to treat Sjögren's syndrome.

## **Improving the Diagnosis and Prognosis of Autoimmune Diseases**

Biomarker research is one area of investigation that may lead to better techniques for diagnosing autoimmune disorders. Biomarkers, clinical signs that correlate with the onset or progression of disease, already are commonly used to help diagnose some diseases, including prostate cancer and certain types of heart disease. With the rise of technologies to identify and test biomarkers more quickly, this area of research holds great promise for earlier and more accurate autoimmune disease diagnosis, better prediction of disease flare-ups, and improved monitoring of disease progression and response to treatment.

Recent progress in identifying biomarkers for lupus provides an example of NIH's work in this area. For example, researchers have identified biomarkers that can be detected in the urine of patients with kidney disease and that provide information about the type and severity of disease.<sup>52</sup> If validated with further research, these biomarkers may provide the basis for a noninvasive test to replace repeated kidney biopsies in patients with lupus, who are at increased risk for potentially severe kidney disease.

The [Biomarkers Consortium](#), of which NIH is a founding partner, recently approved the concept for a systemic lupus erythematosus Biomarkers Working Group. The Consortium is a public-private partnership that endeavors to discover, develop, and qualify biomarkers to identify risk for disease, make a diagnosis, and guide treatment. The systemic lupus erythematosus Biomarkers Working Group will focus on identifying and validating biomarkers for prognosis and assessment of lupus disease activity, with the goal of speeding drug discovery and evaluation

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<sup>52</sup> [Varghese SA, et al., J Am Soc Nephrol 2007;18:913-22](#), PMID: 17301191

of new therapies in a disease that has not had a new drug approved in 40 years. This work also may lead to the identification of common biomarkers for other autoimmune diseases.

## **Developing Evidence-Based Treatment and Prevention Interventions**

NIH supports the development of effective clinical strategies to prevent and treat autoimmune diseases and the translation of successful strategies to clinical application. The following programs and initiatives highlight NIH's work in this area.

[The Autoimmunity Centers of Excellence](#) (ACEs) encourage and enable collaborative research—across scientific disciplines and medical specialties, and between basic and clinical scientists—to test prevention and treatment interventions. Nine ACEs focus on strategies that induce immune tolerance or regulate the immune system. Researchers also explore the molecular mechanisms underlying the agents evaluated in ACE trials. The enhanced interactions between basic and clinical researchers help to accelerate the translation of research findings into medical applications. ACE currently is supporting 10 active clinical trials studying treatments for lupus, multiple sclerosis, pemphigus vulgaris, rheumatoid arthritis, and Sjögren's syndrome.

[The Clinical Islet Transplantation Consortium](#) develops and implements a program of single- and multicenter clinical studies, with accompanying mechanistic studies, in islet transplantation for the treatment of type 1 diabetes. The Consortium is focused on improving the safety and long-term success of methods for transplanting islets, the insulin-producing cells of the pancreas, in people whose own islets have been destroyed by the autoimmune process that characterizes type 1 diabetes. Some studies will focus on improving combined islet and kidney transplants in patients with type 1 diabetes who have kidney failure, a common diabetes complication.

[The Immune Tolerance Network](#) (ITN) is a collaborative research effort to study and test new drugs and therapies for autoimmune diseases and other immune-related disorders. ITN studies are based on stimulating immunological tolerance, the mechanism by which the immune system naturally avoids damage to self.

Today, autoimmune diseases are commonly managed with immunosuppressive agents. Because these agents broadly reduce the immune response, they place patients at increased risk for infection. The ITN supports four clinical studies with the goal of identifying and developing interventions that selectively target harmful autoimmune responses, avoiding the burdensome and dangerous side effects of global immunosuppression. For example, researchers are evaluating agents that suppress the activity of proteins known to be involved in the pathology of many autoimmune diseases. These proteins include the major histocompatibility complex, large protein clusters that are heavily involved in immune function; T cell receptors, which help lymphocytes (a type of immune cell) recognize foreign material; and autoantigens, normal proteins or other molecules that are mistakenly recognized by the immune system.

The development of therapeutic vaccines is a promising approach being taken by ITN scientists. One therapeutic vaccine in development, called the “universal” major histocompatibility complex (MHC) class II peptide vaccine, might be used to treat a wide variety of autoimmune disorders. The vaccine's target peptide—a short portion of a protein—is present in many of the



molecules known to be associated with the pathology of rheumatoid arthritis. Because of this “universality,” one vaccine can be used to simultaneously disrupt multiple molecular pathways of rheumatoid arthritis, increasing the likelihood of treatment success.

One clinical trial of special note is the [Scleroderma: Cyclophosphamide or Transplantation \(SCOT\)](#) trial. The SCOT trial will compare the potential benefits of stem cell transplant and high-dose monthly cyclophosphamide (Cytosan) in the treatment of scleroderma. This approach differs from current organ-specific treatments by seeking to treat the immune system as a whole.

## Addressing the Comorbidities of Autoimmune Diseases

Another strategy for reducing the burden of disease is to support research to understand, prevent, diagnose, and treat comorbidities that affect many patients with autoimmune diseases. Comorbidities range from the presence of more than one autoimmune disease to conditions arising from immune attack on various body tissues or the interventions necessary to treat autoimmune disease. For example, a study of families with vitiligo, a pigmentation disorder in which white patches of skin appear on different parts of the body, found that family members of patients with vitiligo are predisposed to other, potentially more serious, autoimmune diseases.<sup>53</sup> This finding may increase the ability to diagnose autoimmune diseases earlier, which could lead to better treatment.

Patients with type 1 diabetes are at increased risk for eye disorders, nerve and kidney damage, and heart disease. The landmark [Diabetes Control and Complications Trial \(DCCT\)/Epidemiology of Diabetes Interventions and Complications \(EDIC\)](#) study has shown that intensive control of blood glucose levels reduces the development of these long-term and often life-threatening diabetes complications.<sup>54</sup> In other research, investigators have identified potential molecular targets for prevention or treatment of chronic periodontitis, which can be a complication of diabetes.<sup>55</sup>

## Notable Examples of NIH Activity

### Key for Bulleted Items:

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

COE = Supported through a congressionally mandated **C**enter of **E**xcellence program

GPRA = Relates to progress toward a goal tracked under the **G**overnment **P**erformance and **R**esults **A**ct

## Providing Research Resource and Infrastructure

**Type 1 Diabetes–Rapid Access to Intervention Development (T1D-RAID):** Many investigators who have discovered promising therapeutic agents in the laboratory do not have the

<sup>53</sup> [Laberge G. et al., \*Pigment Cell Res\* 2005;18:300-5](#), PMID: 16029422

<sup>54</sup> [Nathan DM. et al., \*N Engl J Med\* 2005;353:2643-53](#), PMID: 16371630; For more information, see <http://diabetes.niddk.nih.gov/dm/pubs/control/#study>

<sup>55</sup> [Muthukuru M, Cutler CW. \*Infect Immun\* 2006;74:1431-5](#), PMID: 16428799



resources to ready the agents for use in human clinical trials. Therefore, NIH supports the T1D-RAID program to provide resources for preclinical development of agents to test in clinical trials. For example, the drug lisofylline, which was prepared and tested under the T1D-RAID program, will be studied in an upcoming pancreatic islet transplantation clinical trial.

- For more information, see <http://www.t1diabetes.nih.gov/T1D-RAID/index.shtml>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK, NCI)

## Identifying Environmental Triggers of Autoimmune Diseases

**Carolina Lupus Study:** Since 1997, NIH has supported the Carolina Lupus Study, the first population-based epidemiological study to examine the influence of hormonal and occupational exposures, as well as the genetic factors that affect immune function and metabolism, on systemic lupus erythematosus. Lupus is a severe, disabling autoimmune disease that can lead to morbidity and mortality from renal and cardiovascular disease. African Americans are two to three times more likely than Whites to develop the disease, for unknown reasons. The study included 265 patients and 355 people without lupus living in 60 counties in North and South Carolina. The results of analysis of occupational exposure to silica dust in relation to risk for systemic lupus erythematosus were striking. Other associations were seen with self-reported occupational exposure to mercury, in mixing pesticides for agricultural work, and among dental workers. Weaker associations were seen between systemic lupus erythematosus and shift work and among health care workers with patient contact.

- For more information, see <http://www.niehs.nih.gov/research/atniehs/labs/epi/studies>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIEHS)

## Understanding the Genetics of Autoimmune Diseases

**Multiple Sclerosis:** While the exact cause of multiple sclerosis is unknown, research suggests a strong genetic component. NIH funds a number of studies to determine the underlying genetic causes of multiple sclerosis, including a project to identify regions of the genome containing multiple sclerosis susceptibility genes by using a large familial dataset and genomic analysis tools. NIH also funds clinical trials to test therapies for multiple sclerosis, including the CombiRx trial, a randomized, controlled clinical trial comparing the efficacy of treatment combining interferon-beta and glatiramer acetate versus treatment with a single agent for relapsing forms of multiple sclerosis. A study conducted in conjunction with CombiRx by NIH intramural researchers (BioMS) is assessing multiple sclerosis biomarkers by using genomic and proteomic technology and relating the information obtained back to clinical and MRI data generated by the CombiRx clinical trial.

- [Gregory SG, et al. \*Nat Genet.\* 2007;39:1083-91](#), PMID: 17660817
- [International Multiple Sclerosis Genetics Consortium, et al. \*N Engl J Med.\* 2007;357:851-62](#), PMID: 17660530
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NINDS)

**Autoimmune Diseases and Genetics:** With the advancement of genomic science, more information has been gained about the genetic component of autoimmune diseases. Susceptibility genes have been identified for rheumatoid arthritis, lupus, psoriasis, and alopecia areata. Understanding the genetic influence of these diseases provides essential information for the design of new therapies.

- [Kumar KR, et al. \*Science\* 2006;312:1665-9](#), PMID: 16778059
- [Nair RP, et al. \*Am J Hum Genet\* 78:827-51](#), PMID: 16642438
- [Haas CS, et al. \*Arthritis Rheum\* 2006;54:2047-60](#), PMID: 16804865
- [Martinez-Mir A, et al. \*Am J Hum Genet\* 2007;80:316-28](#), PMID: 17236136
- [Remmers EF, et al. \*N Engl J Med.\* 2007 Sep 6;357:977-86](#), PMID: 17804842
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/lupus\\_susceptibility\\_gene.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/lupus_susceptibility_gene.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/psoriasis\\_gene.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/psoriasis_gene.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/three\\_genes\\_ra.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/three_genes_ra.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2007/alopecia\\_areata.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/alopecia_areata.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Press\\_Releases/2007/09\\_06.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/09_06.asp)
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NIAMS, NCRR, NHLBI, NIAID, NIMH)

**Genetic Susceptibility for Alopecia Areata:** Scientists supported by NIH have identified loci on four chromosomes that appear to play a role in the development of alopecia areata, an autoimmune disease characterized by hair loss that can affect the whole scalp or, in rarer cases, the entire body. Many U.S. families recruited for the study were identified through the Alopecia Areata Registry.

- [Martinez-Mir A, et al. \*Am J Hum Genet\* 2007;80:316-28](#), PMID: 17236136
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2007/alopecia\\_areata.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/alopecia_areata.asp)
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NIAMS, NIMH)

## Understanding the Mechanisms of Autoimmune Disease Onset and Progression

**The Cooperative Study Group for Autoimmune Disease Prevention:** In 2006, NIH renewed the Cooperative Study Group for Autoimmune Disease Prevention, which was established in 2001. This collaborative network is devoted to understanding immune homeostasis in both health and autoimmune diseases and to developing interventions to prevent autoimmune disease. The six participating Centers support preclinical research, innovative pilot projects, and noninterventional clinical studies, with an emphasis on type 1 diabetes. By the end of 2006, grantees had published 109 original research papers, and 5 of 48 pilot projects had matured into investigator-initiated grants. Of note, the Centers are collaborating on the “Roadmap to

Inflammation in the NOD [non-obese diabetic] Mouse” project, which will identify and characterize genes and proteins involved in the development of diabetes and study the mechanisms by which diabetes develops.

- For more information, see [http://fathmanlab.stanford.edu/roadmap\\_study\\_design.html](http://fathmanlab.stanford.edu/roadmap_study_design.html)
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAID, NIDDK)

**Systems Biology Approach to Salivary Gland Physiology:** Previous research has catalogued the genes and proteins expressed in the salivary glands. This initiative puts those catalogues into context by defining when and where genes and proteins are expressed and how they function as parts of a fully integrated biological system. The initiative combines the power of mathematics, biology, genomics, computer science, and other disciplines to translate this highly detailed information into more precise and practical leads to treat Sjögren’s syndrome, a debilitating autoimmune disorder that affects millions of Americans. The initiative also will help in learning to use saliva as a diagnostic fluid for a variety of conditions, from AIDS to cancer to diabetes.

- For more information, see <http://grants2.nih.gov/grants/guide/rfa-files/RFA-DE-08-001.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (NIDCR)

**Beta Cell Biology Consortium (BCBC):** The BCBC is collaboratively pursuing key challenges relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development to understand how insulin-producing beta cells are made, exploring the potential of stem cells as a source for making islets, and determining the mechanisms underlying beta cell regeneration. The BCBC has generated key research resources, such as animal models, microarrays, and antibodies, which are available to the scientific community.

- For more information, see <http://www.betacell.org>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*
- (E) (NIDDK)

**Promising New Route to Rheumatoid Arthritis Therapy:** Rheumatoid arthritis is a debilitating autoimmune disease that is characterized by joint inflammation and affects approximately 2.1 million Americans. In this disease, a thin membrane of the joint, the synovium, overgrows and attaches abnormally to cartilage, leading to its erosion. A recently identified joint protein, cadherin 11, mediates the disease in a mouse model. Blocking synovium attachment to cadherin 11 prevents this abnormal adhesion and cartilage destruction in mice and reveals a potential new therapeutic target for the disease in humans.

- [Lee et al. \*Science\* 2007;315:1006-10](#), PMID: 17255475
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2007/cad\\_11.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cad_11.asp)
- (E) (NIAMS)

**New Molecular Targets to Halt Periodontal Bone Loss:** Approximately 80 percent of American adults have some form of periodontal disease. Chronic periodontitis erodes supporting structures of the tooth, leading to tooth loss. The risk of periodontal diseases is higher in smokers and individuals with diabetes; 18 million Americans suffer from diabetes and related complications, including increased incidence and severity of periodontitis. This higher incidence and severity are associated with increased cell death in bone- and tissue-forming cells called osteoblasts and fibroblasts. The loss of these cells results in decreased capacity to repair tissue and bone. NIH-supported investigators published two separate papers describing the mechanisms by which the diabetic state enhances cell death. The papers suggest that diabetes-induced cell death and compromised tissue repair are mediated by the TNF- $\alpha$  pro-apoptotic pathway, and the major effector is caspase-3. Inhibition of TNF- $\alpha$  or caspase-3 activity reduces cell death and restores repair capacity. Discrimination between harmful microbes and commensal species is a critical property of the mucosal immune system, which is essential for maintaining health. Host immune cells have surface receptors that recognize bacterial species such as those known to be associated with periodontitis. Host immune cells can selectively learn to respond strongly or to tolerate endotoxin produced by recognized bacteria. NIH-supported scientists found that patients with chronic periodontitis overproduce a molecule known as SHIP, which plays an important regulatory role in signaling immune cells to tolerate endotoxin. The data from these studies suggest possible targets for developing new ways to treat or prevent chronic periodontitis.

- [Al-Mashat HA, et al. \*Diabetes\* 2006;55:487-95](#), PMID: 16443785
- [Liu R, et al. \*Am J Pathol\* 2006;168:757-64](#), PMID: 16507891
- [Muthukuru M, Cutler CW. \*Infect Immun\* 2006;74:1431-5](#), PMID: 16428799
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)

**Trans-NIH Initiative for Translational Research in Immunology, Autoimmunity, and Inflammation:** A new, trans-NIH initiative is being developed by the intramural research program to facilitate the translation of advances in basic immunology to improved therapies and clinical care for immune-mediated diseases. The translation of basic immunology to the clinic has been impeded by separations between basic immunologists, physicians, and epidemiologists and by barriers among clinicians who address diseases that share pathophysiologic mechanisms but are historically separated in different specialty practices. The new program will integrate research efforts not only across the basic, clinical, and population sciences but also across conventional medical subspecialties. Research will focus on a variety of autoimmune diseases, congenital and acquired immunodeficiency syndromes, processes in which inflammation or altered immunity has a pathogenic role, and malignant diseases influenced by the immune system. Studies will address the underlying role of the immune system and the similarities and differences of the inflammatory response in many seemingly unrelated immune-mediated diseases. The initiative is expected to advance understanding of the causes of the diseases and to promote the development of new therapies. It also is expected to serve as a model for future trans-NIH translational research efforts to facilitate more rapid development and testing of new therapies and enhance interdisciplinary training.

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I) (NHLBI, NIAID, NIAMS, NIDDK)

## Improving the Diagnosis and Prognosis of Autoimmune Diseases

**Monitoring Organ Rejection Using MRI:** Organ transplants give patients a new lease on life. However, preventing the immune systems from rejecting the transplanted organ sometimes presents a challenge. Physicians must strike a balance between suppressing the immune system so that it does not reject the organ and maintaining enough immune activity to ward off infections. Tracking how the body accepts the new organ is critical to this process. The current “gold standard” for monitoring organ rejection is tissue biopsy, an invasive procedure in which a physician removes a small sample of the transplanted organ for testing. Biopsy has two drawbacks: patient discomfort (the physician must perform the procedure multiple times) and poor selectivity (biopsy removes tissue from only a limited number of sites and can miss rejection starting elsewhere in the organ). To overcome these limitations, NIH-supported researchers are developing a new method to monitor organ rejection with MRI. They label macrophages (immune cells) with polymer-coated, micron-sized iron oxide particles. These magnetic particles allow the migration of the macrophages to rejection sites in the transplanted organ to be clearly tracked by MRI. At present, this work is being performed on rats, but the investigators are extending it to large animals and humans. If successful, the approach could be used to optimize the administration of immunosuppressant drugs in clinical situations.

- [Wu YL, et al. \*Proc Natl Acad Sci U S A\*. 2006;103:1852-7. PMID: 16443687](#)
- For more information, see <http://www.nibib.nih.gov/HealthEdu/PubsFeatures/eAdvances/25Sep06>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIBIB)

## Developing Evidence-Based Treatment and Prevention Intervention

**The Immune Tolerance Network:** In 2007, NIH renewed support for the Immune Tolerance Network (ITN), a consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN studies and tests new drugs and therapies for autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based on stimulating immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to “re-educate” the immune system to eliminate harmful immune responses and graft rejection while preserving protective immunity against infectious agents. The ITN has established state-of-the-art core laboratory facilities to study the underlying mechanisms of candidate therapies and to monitor tolerance. In 2006, the ITN reported that a novel DNA-based ragweed allergy therapy could achieve long-lasting symptom reduction after only 6 weeks of therapy, compared with current methods that require years of biweekly injections. Current ITN studies include pancreatic islet transplantation for type 1 diabetes, approaches to slow or reverse the progression of autoimmune diseases, approaches to treat and prevent asthma and allergic disorders such as food allergy, and therapies to prevent liver and kidney transplant rejection without causing harmful suppression of immunity.

- For more information, see <http://www.immunetolerance.org/>
- For more information, see <http://content.nejm.org/cgi/content/abstract/355/14/1445>

- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAID)

## Addressing the Comorbidities of Autoimmune Diseases

**Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC):** The DCCT demonstrated that intensive control of blood glucose levels reduced complications of the eyes, nerves, and kidneys in type 1 diabetes patients. Long-term findings from the follow-on EDIC study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients should begin intensive therapy as early as possible. EDIC recently found that recurrent hypoglycemia associated with intensive control does not affect patients' long-term cognitive function. After more than 20 years of studying this patient cohort, crucial insights continue to emerge.

- For more information, see <http://www.bsc.gwu.edu/bsc/studies/edic.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK)

**Comorbidities:** Many autoimmune diseases affect multiple organ systems. Recent studies have identified the basis of concurrent diseases at a molecular level, as well as clinically. A biomarker for lupus-related kidney disease has led to a noninvasive diagnostic breakthrough. Patients with the skin pigmentation disease vitiligo are at increased risk for other autoimmune diseases. In addition, recent studies document an increased risk for cardiovascular disease among patients with rheumatoid arthritis.

- [Laberge G, et al., \*Pigment Cell Res\* 2005;18:300-5](#), PMID: 16029422
- [Giles GT, et al. \*Arthritis Res Ther\* 2005;7:195-207](#), PMID: 16207349
- [Varghese SA, et al., \*J Am Soc Nephrol\* 2007;18:913-22](#), PMID: 17301191
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/lupus\\_kidney.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/lupus_kidney.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/vitiligo\\_risk.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/vitiligo_risk.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/journal\\_special\\_text.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/journal_special_text.asp)
- (E) (NIAMS, NCRR, NHLBI, NIAID)

**Vitiligo:** Vitiligo is a skin disease characterized by a loss of pigment in all people who are affected. The psychological and social consequences can be particularly profound in affected people of color. A study of 133 families with vitiligo found that family members—even those who do not have vitiligo—are also predisposed to other, potentially more serious autoimmune diseases.

- [Jin Y, et al. \*N Engl J Med\* 2007;356:1263-6](#), PMID: 17377159
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Press\\_Releases/2007/04\\_10.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/04_10.asp)
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIAMS, NIAID, NIDDK)



## NIH Strategic Plans Pertaining to Autoimmune Diseases

### National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

- [NIAMS Long-Range Plan: Fiscal Years 2006-2009](#)
- [The Future Directions of Lupus Research](#)

### National Institute of Dental and Craniofacial Research (NIDCR)

- [NIDCR Strategic Plan](#)
- [NIDCR Implementation Plan](#)

### National Institute of Allergy and Infectious Diseases (NIAID)

- [NIAID: Planning for the 21st Century \(2000\)](#)
- [NIAID Plan for Research on Immune Tolerance \(1998\)](#)
- [Report of the Expert Panel on Food Allergy Research \(2006\)](#)
- [Women's Health in the U.S.: Research on Health Issues Affecting Women \(2004\)](#)

### National Center for Complementary and Alternative Medicine (NCCAM)

- [Expanding Horizons of Health Care: Strategic Plan 2005-2009](#)

### Trans-NIH Plans

- [NIH Autoimmune Diseases Coordinating Committee: Autoimmune Diseases Research Plan](#)  
CSR, FIC, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, ORD, ORWH
- [NIH Action Plan for Transplantation Research \(2007\)](#)  
NCI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NIDA, NIDCR, NIDDK, NIMH, NINDS
- [Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan](#)  
CSR, NCCAM, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM



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## CHRONIC DISEASES AND ORGAN SYSTEMS

*Two-year-old Hannah's<sup>56</sup> great-grandmother, who was born in 1900, died of tuberculosis in her thirties. Polio crippled her grandfather, and other family members died at young ages of influenza and typhoid fever. Dramatic improvements in public health and medical practice have made it considerably less likely that these and many other infectious diseases will pose the same threat to Hannah that they did to her ancestors. However, she and her family will almost certainly be affected by one or more chronic diseases and conditions -- for example, type 2 diabetes, and obesity -- whose incidence has risen dramatically in the United States as the burden of infectious disease has diminished. Even more worrisome is that although we think of many chronic diseases as more often affecting adults, such conditions are increasingly appearing in the young. For example, some 16 percent of American children between the ages of six and 19 are overweight<sup>57</sup> -- a number unprecedented in history -- placing them at greatly increased risk of type 2 diabetes, depression, and, as they grow to adulthood, heart disease and a host of other life-threatening conditions. In fact, former Surgeon General Richard Carmona has said that today's obese children could be the first generation of Americans with a life expectancy less than that of their parents, to say nothing of the effects of obesity-related conditions on their quality of life. As the burden of chronic disease in children and adults continues to grow in the United States and around the world, biomedical research to understand, predict, prevent, and treat chronic disease is critical.*

### Introduction

A chronic disease is one that lasts 3 months or longer. In general, chronic diseases cannot currently be prevented by vaccine or cured by medication, nor do they resolve on their own. Not all chronic diseases are fatal, and not all fatal conditions are chronic. Nonetheless, 7 of every 10 Americans who die each year—more than 1.7 million people—succumb to a chronic disease. Health-damaging behaviors, such as tobacco use, lack of physical activity, poor eating habits, and excessive alcohol use contribute to many chronic diseases, whereas others may represent the long-term effect of early exposure to toxins and/or other environmental factors, especially in individuals with a higher genetic risk of disease. A shared aspect of many chronic diseases is chronic pain and other disease-associated disability that interferes with quality of life.

Many of the most burdensome chronic diseases develop over time and become more prevalent with age; less commonly, chronic disease may manifest from birth as a result of one or more faulty genes. Chronic diseases can be common in the U.S. population (e.g., heart disease, the leading cause of death), relatively rare (e.g., cystic fibrosis, which affects approximately 30,000 Americans), or represent a growing medical problem (e.g., type 2 diabetes and obesity).

Most chronic diseases and conditions affect one or more organs. Thus, research to combat chronic illness involves significant trans-NIH collaboration in addition to the mission-specific

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<sup>56</sup> A composite.

<sup>57</sup> [Hedley AA, et al. JAMA 2004;291:2847-2850](#), PMID: 15199035

work of each IC. NIH supports basic research on both normal and disease states of organ systems to understand the initiation and progression of chronic diseases, as well as translational and clinical research on new biomedical and behavioral strategies to prevent, preempt, diagnose, treat, and cure these diseases. The ultimate goal is to reduce or eliminate morbidity and mortality while improving the quality of life for those living with these often debilitating conditions.

This section focuses primarily on a number of major chronic diseases within NIH's purview. Additional major chronic diseases are discussed in this chapter in the sections "Cancer" (cancers of all organs and tissues, including blood), "Neuroscience and Disorders of the Nervous System" (e.g., Parkinson's disease, Alzheimer's disease), "Autoimmune Diseases" (e.g., lupus, multiple sclerosis), and "Infectious Diseases and Biodefense" (e.g., HIV/AIDS). Because some people with certain chronic diseases require transplantation to replace a diseased organ or tissue, organ transplantation research is highlighted in this section. Research on complementary and alternative medicine (CAM) approaches to combating chronic disease also is discussed. Finally, NIH supports research to reduce the pain associated with long-term diseases and to find innovative and effective forms of palliative care to relieve disease symptoms. Some of these efforts are highlighted in this section; more information on NIH pain research can also be found at the [NIH Pain Consortium](#) Web site.

## **Burden of Illness and Related Health Statistics**

The prevalence and burden of chronic diseases are substantial. In fact, the burden of chronic diseases is rapidly increasing worldwide. In 2005, chronic diseases contributed approximately 60 percent of the 58 million total reported deaths in the world and almost three-quarters of the burden of disease (measured in disability-adjusted life-years) in those age 30 or older. By 2015, deaths from chronic disease will be the most common cause of death even in the poorest countries.<sup>58</sup> Considering the totality of chronic diseases in the United States, more than 7 percent of adults age 45 to 54 have three or more chronic conditions and 36 percent of adults age 75 and older have three or more chronic conditions. Chronic disease disables or limits activity for almost 12 percent of all adults and more than 34 percent of adults age 65 and older. Moreover, annual mortality from chronic diseases in the United States is more than 1.7 million. For details on the depth and breadth of this burden, see the table of data, presented by disease and condition, at the end of this section.

### **ABOUT VARIOUS CHRONIC DISEASES AND CONDITIONS**

Links to detailed information on many specific chronic health conditions can be found at <http://health.nih.gov>. Following are examples of chronic diseases and conditions addressed by NIH-funded research, with links to major associated research programs and NIH research fact sheets.

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<sup>58</sup> [Quam L, et al. \*Lancet\* 2006;368:1221-3](#), PMID: 17027712

**Cardiovascular Diseases:** Heart disease is the leading cause of death in the United States.<sup>59</sup> Coronary heart disease, the most common type of [heart disease](#), occurs when the arteries that supply blood to the heart muscle become hardened and narrow. Coronary heart disease can cause angina (chest pain) or a heart attack and, over time, contribute to serious disability or death. Other chronic, serious cardiovascular conditions include hypertension, heart failure, atrial fibrillation, and peripheral arterial disease. Rare cardiovascular disorders include Marfan syndrome, a connective tissue disorder that affects growth and development, including the heart and blood vessels; long QT syndrome, a disorder of the heart's electrical activity that may cause a sudden, uncontrollable, and dangerous heart rhythm; and congenital heart defects.

**Lung Diseases:** Chronic obstructive pulmonary disease, the fourth leading cause of death in the United States,<sup>60</sup> causes airflow obstruction in the lungs that makes breathing difficult. [Asthma](#), the most common chronic disease of childhood, is characterized by inflamed or swollen airways. Asthma can be controlled so that individuals have fewer and less frequent symptoms or can be more active. Rare lung diseases include cystic fibrosis, an inherited disease that affects multiple organs, and idiopathic pulmonary fibrosis, in which lung tissue becomes thick and stiff, resulting in loss of function.<sup>61</sup>

**Diabetes Mellitus:** Diabetes is characterized by abnormally high levels of glucose (sugar) in the blood. It can be caused by either autoimmune destruction of cells in the pancreas ([type 1](#)) or the inability of tissues such as the muscles and liver to properly use insulin ([type 2](#)). Diabetes can result in complications such as heart disease, stroke, hypertension, and nerve damage. It is also the leading cause of kidney failure and nontraumatic lower limb amputation in the United States and of new cases of blindness among working-age Americans.

**Obesity:** Obesity, which has risen to epidemic levels in the United States, is a chronic, relapsing health problem caused by an interaction of genes, [environment](#), and behavior. A common measure of overweight and obesity in adults is body mass index (BMI) a calculation based on height and weight. For most people, BMI correlates with their amount of body fat, and it is used as an indicator of weight-related health risks. An adult with a BMI between 25 and 29.9 is considered overweight, whereas an adult with a BMI of 30 or higher is considered obese. BMI numbers are interpreted differently for children; however, as with adults, rates of overweight and obesity have risen dramatically for children in recent years. Obesity increases the risk of other chronic conditions, including type 2 diabetes, heart disease, certain cancers, osteoarthritis, liver and gallbladder disease, urinary incontinence, sleep apnea, and depression.

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<sup>59</sup> For more information, see <http://www.cdc.gov/nchs/products/pubs/pubd/hestats/leadingdeaths03/leadingdeaths03.htm>

<sup>60</sup> For more information, see <http://www.cdc.gov/nchs/products/pubs/pubd/hestats/leadingdeaths03/leadingdeaths03.htm>

<sup>61</sup> For more information, see <http://heal.niehs.nih.gov/about.htm>; <http://www3.niaid.nih.gov/research/topics/allergies/default.htm>; <http://www.nhlbi.nih.gov/about/factpdf.htm>

**Kidney Diseases:** [Chronic kidney disease](#) is the progressive, permanent loss of kidney function that can result from physical injury or from a disease that damages the kidney, such as diabetes, high blood pressure, or polycystic kidney disease. Patients with advanced chronic kidney disease may progress to irreversible kidney failure and require immediate, life-saving dialysis or a kidney transplant. Chronic kidney disease is a growing problem in the United States; between 1990 and 2000, the number of people with kidney failure requiring dialysis or transplantation doubled.

**Digestive and Urologic Diseases:** [Diseases of the digestive system](#) involve many organs (e.g., intestine, stomach, liver, gallbladder, and pancreas) and include disorders such as irritable bowel syndrome, ulcerative colitis, Crohn's disease, celiac disease, peptic ulcer disease, gallstones, gastroesophageal reflux disease, and chronic pancreatitis. [Illnesses of the genitourinary tract](#) are similarly diverse and include chronic prostatitis, benign prostatic hyperplasia, interstitial cystitis and painful bladder syndrome, urinary incontinence, and urinary tract infections.

**Liver Diseases:** Chronic forms of liver disease include chronic viral hepatitis (B and C), alcoholic and nonalcoholic fatty liver disease, genetic diseases such as hemochromatosis, and autoimmune diseases such as primary sclerosing cholangitis. Significant liver injury can sometimes result from adverse reactions to medical drugs and other compounds. Although many organ systems may be damaged by chronic alcohol use, alcoholic liver disease is the leading cause of death from excessive and long-term alcohol consumption.

**Blood Diseases:** Chronic anemias result from a deficiency of red blood cells or an abnormality in hemoglobin production, as is the case with [sickle cell disease](#) and Cooley's anemia. Patients can experience pain, fatigue, and other, serious health problems. Chronic inherited bleeding disorders such as hemophilia and von Willebrand disease leave patients at risk for uncontrollable bleeding. Conversely, clotting disorders such as deep vein thrombosis can lead to the formation of life-threatening blood clots.<sup>1</sup>

**Musculoskeletal Diseases:** [Osteoarthritis](#), the most common form of arthritis, is a degenerative disease caused by the breakdown of cartilage, leading to pain, swelling, and stiffness in joints. [Osteoporosis](#), another musculoskeletal disease that causes significant disability, occurs when bones become thin, weak, and fragile. Other chronic bone diseases include osteogenesis imperfecta, a genetic disease that causes bones to become brittle and break for no known reason, and Paget's disease of bone, in which bones grow larger and weaker than normal.

**Skin Disorders:** Skin, the largest organ of the body, separates the internal organs from the outside environment, protects against bacteria and viruses, regulates body temperature, and provides sensory information about surroundings. The most common type of eczema—inflammation of the skin—is atopic dermatitis, which is characterized by dry, itchy skin. Chronic wounds on the skin or impaired [wound healing](#) are common in elderly, bed-ridden, and diabetic populations.

**Eye Diseases and Deafness:** Diseases of the eyes and ears can lead to chronic impairment or loss of vision and hearing. Middle ear infections (otitis media) can cause temporary hearing loss in children that can become permanent. [Age-related macular degeneration](#) (loss of cells in the retina) or hearing loss can reduce independence and quality of life in the elderly. Uveitis (inflammation of the eye) and glaucoma (damage to the optic nerve) are significant causes of new blindness in adults.

**Dental and Craniofacial Disorders:** [Periodontal disease](#) is a disorder of the gingiva and tissues around the teeth. It varies in severity but can lead to bleeding, pain, infection, tooth mobility, and tooth loss. Periodontal disease can affect other organs and has been linked to cardiovascular disease, diabetes, and pulmonary disease. Temporomandibular joint and muscle disorders, commonly called TMJD, are a group of conditions that cause pain and dysfunction in the jaw joint and the muscles that control jaw movement. The primary symptom of these disorders is pain, which can become permanent and debilitating.

**Mental Illness and Addiction:** Mental disorders are the leading cause of disability in the United States and Canada. Mental illness can also coexist with a number of other chronic diseases. For example, unipolar depressive disorder, a major contributor to disability worldwide, can be triggered by chronic diseases such as cancer or stroke in those who are prone to the disorder. Conversely, depression is associated with an increased risk for other diseases, such as coronary heart disease. Mental disorders often co-occur with alcohol dependence and other substance abuse, making treatment of either disorder more difficult. [Addictions to alcohol](#) and other [drugs](#) of abuse also are chronic diseases that have both physiological and behavioral components.<sup>62</sup>

## NIH Funding for Chronic Diseases and Organ Systems Research

Currently, NIH does not collect the data necessary to provide an aggregate figure for expenditures on chronic diseases and organ systems research. The table at the end of this chapter provides funding estimates for many of the areas of research associated with chronic diseases and organ systems (see “Estimates of Funding for Various Diseases, Conditions, and Research Areas”). Because of overlap among the areas of research listed in the table, and because research on chronic disease and organ systems may account for only a portion of the funding for a given area, the figures in that table cannot be used to provide an aggregate number.

### Summary of NIH Activities

To alleviate the public health burden of chronic diseases, NIH supports research on the development and progression, detection and diagnosis, prevention, and treatment and management of these diseases. Because of the impact such diseases have on public health and the national economy, NIH directs significant resources toward the study of common chronic diseases, such as asthma, heart disease, diabetes, and many others. However, NIH also supports

<sup>62</sup> For more information, see <http://www.nih.gov/about/researchresultsforthepublic/MoodDisorders.pdf>; <http://www.nih.gov/about/researchresultsforthepublic/AlcoholDependenceAlcoholism.pdf>; <http://www.nih.gov/about/researchresultsforthepublic/DrugAbuseandAddiction.pdf>; <http://www.nih.gov/about/researchresultsforthepublic/Tobaccoaddiction.pdf>

research on many less common chronic conditions. This research has the potential to improve the health and quality of life of thousands of Americans who suffer with these “rare” diseases but also can yield fundamental information on normal physiology as well as the pathophysiology of other, more common diseases. For example, long QT syndrome, which results from genetic mutations that lead to disruption of the normal electrical rhythms of the heart, affects an estimated 1 in 5,000 individuals and results in 3,000 deaths per year in the United States. However, studies of long QT syndrome also have shed light on the causes and treatments of more common, nongenetic cardiac arrhythmias that contribute to 300,000 sudden deaths each year.

This section highlights some key examples of challenges, progress, and emerging opportunities in NIH-supported research on chronic diseases and organ systems. Through its multifaceted research efforts, NIH is providing a solid foundation for improved patient health and well-being.

## **Understanding Fundamental Mechanisms of Organ Health and Disease**

Basic research supported by NIH provides the foundation for understanding and addressing chronic diseases. Understanding fundamental biological mechanisms at the molecular, cellular, tissue, and organ levels provides the basis for formulating new theories of disease causation, identification of novel treatment targets, and development of innovative strategies for disease prevention, diagnosis, or treatment. For example, NIH has made advances in understanding the mechanisms of chronic periodontitis, a disease that leads to tooth loss and affects 80 percent of the U.S. adult population. NIH-supported scientists have discovered that patients with chronic periodontitis have elevated levels of SHIP, a protein that impairs their ability to mount a robust immune attack on bacteria associated with the disease. In another study, NIH-supported scientists identified two pathways associated with chronic periodontitis in diabetic patients who experience increased incidence and severity of this disease. Although studied in different contexts, each of these advances paves the way for potential new targets for preventing or treating this highly prevalent disease. In another effort to increase understanding of the mechanisms of a chronic disease, NIH has initiated a Specialized Center of Clinical Research focused on understanding the key structural and regulatory processes mediating mucus clearance and their dysfunction in cystic fibrosis and COPD. The concepts emerging from the center are expected to stimulate development of new therapies to enable treatment early in the course of disease.

Some diseases, such as drug and alcohol addiction, affect nearly every organ system. NIH supports research to uncover fundamental mechanisms of alcohol-induced tissue injury that are common to many organs and tissues throughout the body, including the brain and liver. Program initiatives to elucidate the underlying mechanisms of alcohol-induced tissue injury will lead to the identification of biomarkers for early detection of disease and new strategies for treatment. Other diseases, such as osteoporosis, have a more limited but still significant impact on the body by affecting key tissues or organs. Because bone loss occurs without symptoms, people may not know that they have osteoporosis until a sudden strain, bump, or fall causes a disabling fracture. NIH supports a number of research projects aimed at elucidating the underlying mechanisms of osteoporosis and other bone diseases. Still other chronic diseases, such as diabetes, affect multiple organs and body systems but might be effectively treated or even cured by replacing a



single type of tissue. For example, death of the insulin-producing beta cells of the pancreas results in type 1 diabetes, whereas type 2 diabetes arises when beta cells are present but not working properly. The NIH-supported [Beta Cell Biology Consortium](#) is studying how beta cells are made during development, maintained in sufficient numbers in healthy individuals, and function to release insulin in precise response to the body's needs. This research will provide the foundation for strategies to replace beta cells in patients with type 1 diabetes and to repair defective beta cells in those with type 2 diabetes.

A related line of inquiry is the study of processes that may either contribute to or signify the presence of chronic disease. For example, inflammation is a normal and necessary reaction of the body to infections, chemical irritants, and other harmful substances or injury. However, unresolved or chronic inflammation underlies or contributes to many chronic diseases. Researchers are working to elucidate the role of inflammation in a number of chronic diseases; for example, using a mouse model of glaucoma, researchers have discovered that a key inflammation marker, TNF- $\alpha$ , might be the link between elevated eye pressure and damage to the optic nerve. Another team found that resolvin E1, a form of omega-3 fatty acid, can alter the course of inflammation associated with periodontitis. In addition, researchers are building on advances in the fundamental biology of inflammation to investigate age-related inflammatory processes in the elderly, such as vascular inflammation and neurotoxicity in the brain and inflammatory responses to sleep loss.

A critical dimension of basic research on chronic diseases and organ systems is the development of innovative technologies, research tools, and materials that are revolutionizing our understanding of the human body and laying the groundwork for cutting-edge therapies. Heart and vascular diseases represent only one example of many chronic diseases that benefit from technology research. Use of new, noninvasive imaging techniques in the [Jackson Heart Study](#), a longitudinal study of heart and cardiovascular disease in African Americans in Mississippi, is expected to provide important new insights into the origins of heart disease in this population. Likewise, advances from disciplines such as materials science, tissue engineering, bioengineering, and computational sciences are providing a foundation for the development of replacements for damaged or diseased small blood vessels, from which thousands of patients with vascular disease could benefit each year.

## **Detecting and Diagnosing Chronic Disease**

Early detection and diagnosis of a chronic disease or of damage to an organ allows patients to seek appropriate care and, in some cases, improve their outcomes or prevent progression of the disease. NIH fosters research on disease detection and diagnosis through the identification of biomarkers that predict disease or its progression, as well as the development of technologies or resources to promote early detection. For example, the NIH-supported [Drug-Induced Liver Injury Network](#) (DILIN) performs research on liver toxicity caused by prescription drugs or CAM. Among many research projects, DILIN researchers are developing better diagnostic tools and studying the mechanisms of liver injury. Related clinical research on acute liver failure from drug-induced liver injury conducted by the [Acute Liver Failure Study Group](#) has identified a potential biomarker for liver injury caused by excessive amounts of the over-the-counter pain reliever acetaminophen, which could be used clinically to aid diagnosis. In another example, the



Alcohol Biosensors Program is engineering devices for the continuous measurement of alcohol concentrations that will provide new tools for clinical and basic research on alcohol use disorders.

In addition to advanced technology, the dissemination of knowledge to health care providers is one of the most important tools for disease detection and diagnosis. NIH has updated the booklet [Helping Patients Who Drink Too Much: A Clinician's Guide](#) to educate primary care and mental health clinicians on evidence-based methods to screen, diagnose, and manage patients who may have alcohol use disorders. In addition to traditional printed handouts and fact sheets, NIH also offers information for doctors and other health professionals in electronic formats. Two CD-ROMs, *Bone Health Information for You and Your Patients* and *Lupus and Other Related Information for You and Your Patients*, provide print-friendly PDF files of health education brochures and professional educational resources, as well as Web links to current clinical trials and other resources from Federal agencies and nonprofit organizations. Additional efforts to convey information about chronic disease detection and diagnosis to the medical community are described in the section "Health Communication and Information Campaigns and Clearinghouses" in Chapter 3.

## **Identifying Risk and Preventing Chronic Disease**

Many chronic diseases have genetic or hereditary components that increase the risk of disease in certain individuals or population groups. Chronic diseases also may have known, modifiable risks factors such as diet, smoking, chronic stress, exposure to environmental toxins, or a variety of other factors. Often, disease results from complex and poorly understood interactions among multiple genetic, environmental, and behavioral risk factors. NIH supports research to identify all types of risk factors for chronic diseases and to develop new strategies to modify risk to prevent disease.

The completion of the Human Genome Project has opened new avenues of research into the genetic causes of chronic diseases. Diseases and conditions for which NIH-supported investigators have recently identified susceptibility genes include:

- Age-related macular degeneration, a common cause of irreversible vision loss ([Age-Related Eye Disease Study](#))
- Inflammatory bowel disease (Inflammatory Bowel Disease Genetics Consortium)
- Alcoholism and related disorders ([Collaborative Study on the Genetics of Alcoholism](#))
- Diabetic Kidney Disease ([Genetics of Kidneys in Diabetes Study](#))

The datasets collected through many NIH-supported genetics studies are available, with appropriate mechanisms in place to safeguard subjects' privacy, to qualified researchers worldwide.

Ongoing initiatives such as the [ENDGAME \(Enhancing Development of Genome-Wide Association Methods\)](#) consortium are developing new approaches to understanding the role of genetic variation in normal physiology and disease, whereas two major ongoing studies (the [Candidate Gene Association Resource](#) and the [Framingham SHARe Program](#)) are focusing on

the genetics of cardiovascular disease. In addition, a public-private partnership led by NIH—the [Genetic Association Information Network \(GAIN\)](#)—is exploiting the completion of a detailed map of human genetic variation to search for genes involved with specific diseases and to develop tools to understand how environmental factors interact with genetic susceptibilities. (For more on GAIN, see the section “Genomics” in Chapter 3.)

Genetic susceptibility is rarely the only risk factor for developing a chronic disease. NIH also supports research to identify other, nongenetic risk factors that, either alone or in conjunction with genetic factors, influence the development or progression of chronic diseases. Identifying risk factors for a specific disease from the myriad behaviors and environments of individuals requires studying large numbers of people for extended periods of time. Two research studies of osteoporosis and other age-related chronic diseases—the Study of Osteoporotic Fractures and Mr. OS—have uncovered specific risk factors, such as bone mineral density of the hip, that predict the risk of fractures in the elderly. The [Osteoarthritis Initiative](#) is tracking 4,800 individuals who are at high risk for knee osteoarthritis to identify biological markers that predict disease progression. NIH-supported researchers also are investigating the complex biological and behavioral factors underlying childhood and maternal obesity and testing behavioral interventions in schools, homes, and the community in an effort to stem the rising obesity epidemic.

Many population groups, whether stratified by race, ethnicity, sex, age, or other characteristics, seem to be particularly vulnerable to specific chronic diseases. NIH research programs that are exploring genetic and nongenetic disease risk factors in specific populations include:

- Cardiovascular disease among African Americans ([Jackson Heart Study](#))
- Heart disease, COPD, kidney disease, and asthma in Latin Americans ([Hispanic Community Health Study](#))
- Obesity and diabetes in the Pima Indians of Arizona (Gila River Indian Community Longitudinal Study)
- Alcohol consumption, drug use, and related disorders in various racial and ethnic groups ([National Epidemiologic Survey on Alcohol and Related Conditions](#))
- Interdisciplinary centers on the influence of sex and gender as it relates to diseases and conditions such as chronic pain, irritable bowel syndrome, and urologic health ([Specialized Centers of Research on Sex and Gender Factors Affecting Women’s Health](#))
- Type 1 diabetes in children ([The Environmental Determinants of Diabetes in the Young](#))

Knowing the factors that increase or decrease the risk of disease can help researchers design innovative strategies to prevent disease in susceptible individuals. Interventions are being developed and tested to prevent trauma-related mental health disorders, such as posttraumatic stress disorder, in persons engaged in high-risk occupations such as the military or emergency response. The [Diabetes Prevention Program Outcomes Study](#) currently is assessing long-term outcomes in its subjects; the study previously had demonstrated that lifestyle change or treatment with the drug metformin significantly delayed the onset of type 2 diabetes in at-risk individuals. Lifestyle changes (modifications in diet and physical activity) were nearly twice as effective as drug treatment in reducing the risk of developing type 2 diabetes in that study. Furthermore, the physical activity increases in the lifestyle modification group were sustained for 4 years,

indicating that modest changes in behavior can be accomplished and maintained for long periods. A related clinical trial, [Look AHEAD](#) (Action for Health in Diabetes), is testing whether an intensive lifestyle intervention for weight loss can reduce the incidence of cardiovascular events in 5,100 overweight or obese subjects with type 2 diabetes. Testing strategies for prevention and early treatment of type 1 diabetes is the focus of the [TrialNet](#) clinical research network. The network recently began a new clinical study of oral insulin to prevent or delay type 1 diabetes in at-risk individuals.

Prevention of chronic diseases in children is a particularly important focus of NIH research. The onset of a chronic disease in childhood often is associated with serious comorbidities (disorders or diseases in addition to the primary disease); therefore, many of these diseases, if left unchecked, have negative implications for the health of the future adult population. HEALTHY is a multicenter clinical trial testing behavioral interventions aimed at decreasing the risk of obesity and type 2 diabetes in middle school children. Likewise, the goal of the national public education outreach program [Ways to Enhance Children's Activity and Nutrition \(WeCan!\)](#) is to reduce childhood obesity by helping children age 8-13 achieve and maintain a healthy weight. Asthma, another serious disease of childhood, is strongly related to environmental exposures such as indoor allergens. Researchers in North Carolina are conducting a dust mite reduction study in the homes of study subjects between ages 5 and 15 to determine whether this strategy can reduce or prevent asthma and other adverse outcomes related to dust mite exposure. The [Underage Drinking Research Initiative](#) supports multiple efforts to understand and prevent alcohol use by children and adolescents and its progression to abuse and dependence, and the Rapid Response Program supports the implementation and evaluation of programs to reduce underage alcohol use on college campuses.

NIH also sponsors awareness campaigns and other educational efforts to disseminate the results of its prevention research to the general public (see the section "Health Communications and Information Campaigns and Clearinghouses" in Chapter 3). One such campaign, [The Heart Truth](#), takes a multifaceted approach to educate women on the risk factors for heart disease, the leading cause of death in American women.

## **Treating Chronic Disease and Comorbidities**

Despite the remarkable advances of modern medicine, chronic diseases, by definition, require long-term medical or behavioral intervention or a combination of multiple treatment modalities. For some diseases, no effective therapies or cures are currently available, and the diseases can only be managed to control symptoms. Daily management of chronic diseases to prevent or slow the progression or development of comorbidities often imposes a significant burden on patients and their families. For example, type 1 and type 2 diabetes can be managed by injections of insulin or by taking insulin-sensitizing drugs; however, optimal control of diabetes to reduce the risk of complications also requires careful and continuous monitoring of blood glucose levels, diet, and physical activity throughout the day. A major focus of NIH research is the development and testing of new therapies for chronic disease that will cure disease, ease the process of disease management, treat patients who are not helped by current therapies, or otherwise reduce the burden of chronic illness. (For a general discussion of treatment and other clinical research, see the section "Clinical and Translational Research" in Chapter 3.)

To facilitate clinical trials for many diseases, NIH supports multiple networks of investigators at medical centers across the country who can conduct studies more efficiently by working together. In addition, NIH is investing in the development of a [Patient-Reported Outcomes Measurement Information System](#) that will devise standardized measurements of symptoms that affect quality of life. Validated measures of patient-reported symptoms such as pain, fatigue, emotional distress, and others will revolutionize clinical research across a spectrum of chronic diseases and conditions.

The NIH clinical research portfolio comprises numerous trials to evaluate the safety and efficacy of therapies for many chronic diseases. The examples described here illustrate the diversity of diseases and potential therapies being studied with NIH support. Information about these and other NIH-supported clinical trials is available at <http://clinicaltrials.gov>.

- **Diabetes:** The long-running Diabetes Control and Complications Trial and its follow up, the [Epidemiology of Diabetes Interventions and Complications](#) study, have demonstrated that intensive insulin therapy, although not a cure for diabetes, can dramatically reduce the risk of diabetic complications of the eyes, nerves, kidneys, and heart.
- **Chronic Obstructive Pulmonary Disease (COPD):** The [Long-Term Oxygen Treatment Trial](#) is assessing the role of home oxygen therapy for patients with COPD and moderate hypoxemia (low blood oxygen level).
- **Idiopathic Pulmonary Fibrosis:** A clinical research network has been established to treat patients with newly diagnosed idiopathic pulmonary fibrosis, using combinations of drugs that might attack the fibrotic process at multiple points and thereby stabilize or improve the disease.
- **Nonalcoholic Steatohepatitis (NASH):** The [NASH Clinical Research Network](#) is investigating whether vitamin E or the drug pioglitazone is an effective treatment for nondiabetic adults with NASH, a liver disease associated with obesity and diabetes.
- **Hepatitis C:** The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis ([HALT-C](#)) Trial is studying whether long-term antiviral therapy can prevent the progression of liver disease in patients who have hepatitis C infection and who were not helped by short-term therapy.
- **Polycystic Kidney Disease (PKD):** The [HALT-PKD](#) trial is evaluating the use of blood pressure management in combination with medication as a means to slow progression of PKD in patients with either early or advanced disease.
- **Age-Related Macular Degeneration (AMD):** An NIH-supported trial reported in 2005 that certain vitamin and mineral supplements reduce progression of AMD, a leading cause of blindness in the elderly; the [Age-Related Eye Disease Study](#), Part 2, is extending that result by testing additional supplements that might also slow down AMD.
- **Uveitis:** Localized steroid treatment is being testing in the [Multicenter Uveitis Steroid Treatment](#) (MUST) trial as a therapy for this major cause of blindness. If successful, this trial would improve on current treatments for uveitis that expose the entire body to corticosteroids and immune suppression drugs.
- **Ulcerative Colitis:** Many patients with ulcerative colitis do not respond to currently available treatments. A clinical trial is under way to determine whether a drug used to treat type 2 diabetes (rosiglitazone) can also control the symptoms of ulcerative colitis.

- **Drug Abuse and Addiction:** NIDA's National Drug Abuse Clinical Trials Network is a multisite research project that tests the effectiveness of new and improved behavioral, pharmacological, and integrated treatment interventions in real-life community settings with diverse populations.

Children do not always respond to treatments in the same way as adults. For this reason, NIH is committed to conducting clinical intervention trials to identify therapies that are safe and effective for use in children with chronic diseases. For example, the NASH Network (see above) is testing the use of the drug metformin or vitamin E as a treatment for fatty liver disease in children. Type 2 diabetes—a disease that was previously seen primarily in adults—is becoming more prevalent in children, and the safety of long-term use of adult diabetes drugs in children is not known. The Treatment Options for Type 2 Diabetes in Youth ([TODAY](#)) study is evaluating three strategies for treating children and adolescents with type 2 diabetes. NIH supports a multipronged approach to developing and testing therapies for asthma. The Inner-City Asthma Consortium (ICAC) evaluates immune-based therapies for asthma in inner-city children, who are disproportionately affected by the disease. At the same time, the Asthma Exacerbations: Biology and Disease Progression program is conducting basic and clinical research to facilitate development of new treatments to control asthma symptoms in children and adults.

In addition to drug development and evaluation, NIH supports research on nonmedicinal interventions for chronic diseases, including behavioral and surgical approaches. For example, researchers have developed two effective behavioral therapies—the Matrix Model and Motivational Incentives for Enhanced Drug Abuse Recovery—that help people overcome methamphetamine addiction. A clinical trial infrastructure also has been set up to facilitate testing of innovative treatments for mental disorders such as schizophrenia, bipolar disorder, and depression that include medical and/or behavioral therapies. The Health Maintenance Consortium is fostering collaboration among independent research projects aimed at promoting behavior change in areas such as diet, exercise, HIV prevention, smoking cessation, and others. Many diverse strategies are being tested for treatment of obesity, including the use of bariatric surgery. The [Longitudinal Assessment of Bariatric Surgery](#) (LABS) is evaluating the risks and benefits of bariatric surgery in obese adults, and a related observational study, Teen-LABS, is collecting data on the use of this procedure in obese adolescents.

Organ transplantation is a surgical option for some chronic diseases. Transplantation can alleviate disease, prolong survival, and improve quality of life, but the procedure carries its own risk of complications, including those caused by drugs that prevent organ rejection. Researchers are investigating the use of MRI to noninvasively monitor transplant rejection. If successful, this technology could be used by physicians to modulate drug regimens to precise levels that prevent rejection while allowing the patient's body to maintain enough immune activity to ward off infections. NIH established the Clinical Trials in Organ Transplantation program to further improve the outcome of organ transplantation. Researchers also are studying transplantation of specific organ tissues to treat disease, such as transplanting the insulin-producing islet cells of the pancreas to treat type 1 diabetes. The international Clinical Islet Transplantation Consortium is developing and conducting clinical studies that could improve this treatment approach for people with type 1 diabetes.



An important aspect of the NIH mission is to communicate the results of its research so that patients and the public can benefit from up-to-date information on treatment options (see the section “Health Communication and Information Campaigns and Clearinghouses” in Chapter 3). Sometimes this goal is accomplished through public awareness campaigns, such as one for COPD called “[COPD: Learn More, Breathe Better](#),” which distributes materials on COPD to patients, persons at risk, health care professionals, and community-level organizations to raise awareness of COPD. COPD is a disease that often goes undiagnosed, and therefore untreated, in an estimated 12 million Americans. For other diseases, translational researchers are exploring the best ways to transfer knowledge from controlled research settings into standard medical practice and the community to achieve maximum benefits for public health. Research is ongoing to find sustainable and cost-effective means to translate the successes of clinical trials for the treatment of diabetes and obesity into the real world. NIH-supported scientists also are identifying ways to promote the use of evidence-based interventions for treatment of mental illnesses.

A 2002 survey conducted by NIH and CDC found that one-third of American adults use some form of complementary and alternative medicine (CAM) to prevent or treat disease, including diverse modalities such as acupuncture, meditation, megavitamin therapy, herbs, special diets, chiropractic care, prayer, and other methods. The goal of NIH research on CAM is to provide an evidence-based assessment of the safety and effectiveness of CAM practices in order to guide and protect patients and consumers who are making treatment choices. NIH has developed a 5-year strategic plan to define priorities for CAM research, much of which pertains to a variety of organ systems and chronic diseases.

NIH-supported studies of popular dietary supplements have reported mixed results. One study showed that high doses of a form of vitamin E did not lower cholesterol in the blood, whereas in another study, glucosamine and chondroitin sulfate supplements did not relieve osteoarthritis pain in the general study population, although patients with moderate-to-severe pain did benefit. In other ongoing research, multidisciplinary teams are uncovering scientific explanations for some of the effects of acupuncture in relieving pain and are evaluating the use of this technique in patients with coronary artery disease, spinal cord injury, post-thoracotomy pain syndrome, and a number of other chronic conditions.

## **Addressing Pain and Palliative Care in Chronic Diseases**

Pain and palliation—care to alleviate the symptoms of disease and improve quality of life—are issues associated with many chronic diseases, regardless of the organ system affected. NIH supports research to understand the origins of pain, develop therapies to manage pain effectively, and design palliative therapies to reduce suffering and improve disease outcomes. NIH is pursuing multidisciplinary approaches to the discovery of non-opioid pain medications that can selectively and safely treat chronic pain without creating drug dependence. For example, basic pharmacological research has uncovered previously unknown receptor combinations in the body that represent new targets for pain control. Nonpharmacological strategies for pain management also are being closely studied. For example, researchers have confirmed that acupuncture is an effective add-on to conventional treatment for osteoarthritis, a common cause of pain and reduced quality of life in elderly patients. The Spine Patient Outcomes Research Trial has determined which patients with back pain are most likely to benefit from surgical intervention.

The Orofacial Pain: Prospective Evaluation and Risk Assessment study is seeking better ways to manage the chronic pain of temporomandibular muscle and joint disorders.

Because of the broad diversity of chronic diseases associated with pain, NIH established the [NIH Pain Consortium](#) to enhance research and promote collaboration among the many ICs that have an interest in pain and pain management research. Since its establishment, the consortium has sponsored two symposia featuring new and exciting advances in pain research and pain management. Consortium ICs also have issued an NIH-wide research initiative to encourage pain research and delineate cross-cutting NIH interests in pain.

NIH research addresses the application of palliative care at all stages of a disease process, including at the end of life, and encompasses the needs of patients and their caregivers. Behavioral strategies have been shown to improve patient outcomes for several chronic diseases, including diabetes, irritable bowel syndrome, and asthma. Researchers also have developed a support intervention that significantly improves the quality of life for caregivers of patients with Alzheimer's disease; further research is needed to determine how best to implement this intervention through community health service networks so that more caregivers can benefit. In FY 2006, the proceedings of an NIH-sponsored State-of-the-Science Conference on Improving End-of-Life Care were published as a supplement to the *Journal of Palliative Medicine*. This special supplement reported on the state of the science in end-of-life care and proposed new research directions to improve care for all patients and their families in the final stages of disease.

### **Notable Examples of NIH Activity**

**Key for Bulleted Items:**

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

### **Understanding Fundamental Mechanisms of Organ Health and Disease**

**Innovative Technologies for Engineering Small Blood Vessels:** NIH has initiated a program of basic research studies for the future development of replacements for damaged or diseased small blood vessels. Thousands of patients each year could benefit from small blood vessel substitutes (e.g., to bypass coronary artery or peripheral vascular occlusions or to establish arteriovenous shunts for hemodialysis), but currently available replacement grafts have a high failure rate. Recent advances in materials science, bioengineering, and tissue engineering, as well as the availability of better computational tools, are providing opportunities for the development of replacement blood vessels with properties that closely match those of natural blood vessels.

- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NHLBI)



**Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS):** In a joint effort, NHLBI, the Center for Medicare and Medicaid Services, and FDA created INTERMACS, a national registry for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure. Data from INTERMACS are expected to improve patient evaluation and management; aid in the development of safer, more effective devices; and enhance research.

- For more information, see <http://www.uab.edu/ctsresearch/mcsd>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NHLBI)

**Women's Health Initiative:** In January 2007, NIH awarded support for a dozen 2-year research projects to apply genomics, proteomics, and other innovative technologies to improve understanding of several major diseases that commonly affect postmenopausal women. The new endeavor builds on the long-running Women's Health Initiative, which conducted several clinical trials and an observational study to examine strategies for preventing heart disease, breast and colorectal cancers, and osteoporosis in a cohort of more than 160,000 subjects. Investigators will use stored blood, DNA, and other biological samples and associated clinical data to analyze genetic factors and biological markers that may be useful in predicting disease outcomes or the effects of therapeutic and preventive regimens in postmenopausal women.

- For more information, see <http://www.whisience.org/baa/2006.php>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*.
- (E) (NHLBI)

**Inflammation in the Elderly:** Inflammatory processes, particularly those mediating chronic inflammation, have been implicated as predictors or initiators of or contributors to a number of chronic diseases and conditions of aging. NIH currently supports research to determine relationships of age-related changes in inflammation and inflammatory mediators to physiologic and pathophysiologic aging changes, risks and progression of age-related morbidity and disability, and changes in tissue and organ function. Funded projects include studies of vascular inflammation and neurotoxicity in the aging brain and inflammatory responses to sleep loss.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-05-011.html>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIA)

**Neurobiology of Appetite Control:** NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. Examples include research on how serotonin reduces appetite; the actions of the protein mTOR in sensing nutrients in the body so as to modulate food intake; and a strategy to block ghrelin, a stomach-secreted hormone that signals the brain to increase food intake. This research has implications for new therapies for obesity.

- [Cota D, et al. \*Science\* 2006;312:927-30](#), PMID: 16690869
- [Heisler LK, et al. \*Neuron\*. 2006;51:239-49](#), PMID: 16846858
- [Zorrilla EP, et al. \*Proc Natl Acad Sci U S A\* 2006;103:13226-31](#), PMID: 16891413

- For more information, see <http://tinyurl.com/22o9my> (Obesity chapter)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDDK)

**Lymphatic System in Health and Disease:** NIH recently announced two funding opportunities for research to increase understanding about the lymphatic system and its function in health and disease. The lymphatic system plays a critical role in the well-being of many other systems in the body. When it is not working properly, a broad array of diseases and disorders can result, including lymphedema (characterized by accumulation of lymph fluid that often results in swelling of the arms or legs), inflammation and infections, cancer, and metabolic disorders. In July 2007, NIH issued the Program Announcement “Lymphatic Biology in Health and Disease” to encourage research on the biology of the lymphatic system and potential new therapeutic approaches. In addition, in December 2006, NIH re-issued the Program Announcement “Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases” to stimulate research on the lymphatic system and lymphatic dysfunction and related diseases, as well as to develop new diagnostic methods and treatment interventions.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-420.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-165.html>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHLBI, NCCAM, NCI, NIAMS, NIBIB, NICHD, NIDDK, NINR)

**Understanding the Mechanisms of Alcohol-Induced Tissue Injury:** Virtually every organ system of the body is impacted by heavy alcohol use (the most vulnerable being the brain and liver), and the resulting pathological conditions contribute to increased mortality and morbidity among all age and racial/ethnic groups and genders. NIH is especially interested in elucidating mechanisms of injury common to multiple body and organ systems. A number of Program Announcements and RFAs have been issued to support research to increase our understanding of the underlying cellular and molecular mechanisms of tissue injury caused by alcohol consumption, including alcohol’s genetic, epigenetic, and metabolic effects. The long-term goals of these initiatives are to identify biomarkers for alcohol exposure and for the early detection of alcohol-induced tissue injury, and to develop new therapeutics that control or modify outcomes of chronic alcohol use.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-065.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-360.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-361.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-004.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-005.html>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 2: *Neuroscience and Disorders of the Nervous System*, and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E/I) (NIAAA)

**Jackson Heart Study Advanced Imaging Component:** The Jackson Heart Study is a longitudinal study of heart disease and cardiovascular disease in about 5,000 African Americans in the Jackson Mississippi area. Data collection for this study began in 2000. New imaging techniques that include dynamic MR imaging of the heart to assess cardiac function and CT

imaging to assess visceral abdominal fat and calcification of the aorta and coronary vessels can provide significant additional understanding of heart disease in this minority population. NIH is in the process of adding these valuable components to the study of heart disease. The CT studies began in spring of 2007 and the MR studies are being set up now and will begin in early 2008.

- For more information, see <http://www.nhlbi.nih.gov/about/jackson/index.htm>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NIBIB, NCMHD, NHLBI)

**Systems Biology Approach to Salivary Gland Physiology:** Previous research has catalogued the genes and proteins expressed in the salivary glands. This initiative puts those catalogues into context by defining when and where genes and proteins are expressed and how they function as parts of a fully integrated biological system. The initiative combines the power of mathematics, biology, genomics, computer science, and other disciplines to translate this highly detailed information into more precise and practical leads to treat Sjögren's syndrome, a debilitating autoimmune disorder that affects millions of Americans. The initiative also will help in learning to use saliva as a diagnostic fluid for a variety of conditions, from AIDS to cancer to diabetes.

- For more information, see <http://grants2.nih.gov/grants/guide/rfa-files/RFA-DE-08-001.html>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Genomics*.
- (E) (NIDCR)

**Beta Cell Biology Consortium (BCBC):** The BCBC is collaboratively pursuing key challenges relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development to understand how insulin-producing beta cells are made, exploring the potential of stem cells as a source for making islets, and determining the mechanisms underlying beta cell regeneration. The BCBC has generated key research resources, such as animal models, microarrays, and antibodies, which are available to the scientific community.

- For more information, see <http://www.betacell.org>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Molecular Biology and Basic Sciences*
- (E) (NIDDK)

**Urinary Tract Infections:** NIH supports a Specialized Center of Research on Sex and Gender Factors Affecting Women's Health. This program advances new understanding of host-pathogen interactions that occur throughout the infectious cycle, including host defense response in the bladder and the virulence mechanisms by which bacterial pathogens subvert the defenses.

- [Justice SS, et al. Proc Natl Acad Sci U S A 2006;103:19884-9, PMID: 17172451](#)
- For more information, see <http://clinicaltrials.gov/ct/show/NCT00068120>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIDDK)

**Systems Science and Health:** Solutions to complex problems like chronic disease require approaches that can address a broad range of factors within a single framework—from genetic to environmental, cellular to behavioral, and biological to social. A 2007 Symposium Series on Systems Science and Health focuses on approaches that consider how numerous factors interact nonlinearly over time in multiple feedback loops to influence health. These approaches show promise for unlocking the secrets of complex, multidimensional health problems and for transforming this knowledge into effective interventions that can fundamentally change population health.

- For more information, see [http://obssr.od.nih.gov/Content/Lectures+and+Seminars/Systems\\_Symposia\\_Series/SEMINARS.htm](http://obssr.od.nih.gov/Content/Lectures+and+Seminars/Systems_Symposia_Series/SEMINARS.htm)
- (OBSSR, CDC, FIC, NCI, NICHD, NIGMS)

**Mechanisms of Action of CAM:** Important and potentially promising findings from recently reported research aimed at elucidating the fundamental mechanisms of various CAM interventions include the following:

- ▷ Extracts of turmeric (a common component of Ayurvedic traditional Indian medicines and ingredient in Indian cuisine) containing compounds known as curcuminoids prevent experimental rheumatoid arthritis in an animal model.
  - ▷ Green tea is widely promoted for a variety of health-related benefits. It contains a group of chemicals called catechins, one of which is known as epigallocatechin gallate (EGCG). Investigators recently reported that an EGCG-enriched extract of green tea significantly improves glucose and lipid metabolism in an animal model of obesity/insulin resistance/metabolic syndrome.
- [Funk JL, et al., \*J Nat Prod.\* 2006;69:351-5](#), PMID: 16562833
  - [Li RW, et al., \*J Ethnopharmacol.\* 2006;104:24-31](#), PMID: 16202550
  - This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
  - (E) (NCCAM)

**Inflammatory Factor Mediates Nerve Degeneration in Glaucoma Model:** In glaucoma, elevated eye pressure plays a role in damaging fibers in the optic nerve, which relays visual signals to the brain. However, the link between pressure and nerve damage is not well understood. Recent research in mice suggests a critical role for the protein TNF- $\alpha$  in developing glaucoma. A molecular target in the glaucoma disease pathway opens up doors for drug therapy.

- [Nakazawa T, et al. \*J Neurosci\* 2006;26:12633-41](#), PMID: 17151265
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NEI)

**Wound Healing and Skin Biology:** Recent advances in wound healing research have brought greater understanding to skin biology, with implications for hair growth and skin diseases, as well as treatment of chronic wounds. When skin is wounded, a protein, S100A7, is released and

attaches to and reduces survival of potentially disease-causing bacteria on the skin, preventing the development of wound-related infections.

- [Lee KC, Eckert RL. \*J Invest Dermatol.\* 2007;127:945-57](#), PMID: 17159909
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2007/wound\\_bacteria.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/wound_bacteria.asp)
- (E) (NIAMS)

**Leiomyomata Uteri (Uterine Fibroids):** Some estimates suggest that uterine fibroids could affect as many as 77 percent of women nationwide and that more than 25 percent have active symptoms. NIH researchers recently found that, unlike normal uterine tissue, abnormal fibroid tissue is not affected by reproductive hormones. This suggests that the conventional hormone therapies used to treat fibroid tumors are unlikely to yield lasting improvements. Based on the findings, NIH researchers are planning studies to test two new drug treatments. One would block collagen from forming to help keep existing fibroids from growing larger; the second would help to break apart collagen fibrils in an attempt to shrink existing tumors.

- [Leppert PC, et al. \*Fertil Steril.\* 2004;82:1182-7](#), PMID: 15474093
- (E/I) (NICHD)

**Anti-inflammation/Resolution Regulator May Be Involved in a Wide Range of Human Diseases:** Resolvin E1 (RvE1) is a new family of bioactive products of omega-3 fatty acid. Using periodontitis as a model disease, a team of NIH-funded researchers recently reported that RvE1 can dramatically alter the progression of microbe-initiated local inflammatory disease. RvE1 therapy demonstrates greater efficacy without the side effects of chronic antibiotic usage. The results of their study provide new directions for treatment of localized aggressive periodontitis and other inflammation-related bone disorders. In many chronic disorders similar to periodontitis, prolonged and unresolved inflammation contributes to pathogenesis. It is now clear that several endogenous biochemical pathways activated in the host during defense reactions can counter-regulate inflammation. This study provides evidence for the role of resolvin E1 as an endogenous anti-inflammation/resolution regulator that may be involved in the pathogenesis of a wide range of human diseases.

- [Hasturk H, et al. \*FASEB J\* 2006;20:401-3](#), PMID: 16373400
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)

**New Molecular Targets to Halt Periodontal Bone Loss:** Approximately 80 percent of American adults have some form of periodontal disease. Chronic periodontitis erodes supporting structures of the tooth, leading to tooth loss. The risk of periodontal diseases is higher in smokers and individuals with diabetes; 18 million Americans suffer from diabetes and related complications, including increased incidence and severity of periodontitis. This higher incidence and severity is associated with increased cell death in bone and tissue-forming cells called osteoblasts and fibroblasts. The loss of these cells results in decreased capacity to repair tissue and bone. NIH-supported investigators published two separate papers describing the mechanisms by which the diabetic state enhances cell death. The papers suggest that diabetes-induced cell death and compromised tissue repair are mediated by the TNF- $\alpha$  pro-apoptotic pathway, the major effector being caspase-3. Inhibition of TNF- $\alpha$  or caspase-3 activity rescues cell death and

restores repair capacity. Discrimination between harmful microbes and commensal species is a critical property of the mucosal immune system, which is essential for maintaining health. Host immune cells have surface receptors that recognize bacterial species such as those known to be associated with periodontitis. Host immune cells can selectively learn to respond strongly or to tolerate endotoxin produced by recognized bacteria. NIH-supported scientists found that patients with chronic periodontitis overproduce a molecule known as SHIP, which plays an important regulatory role in signaling immune cells to tolerate endotoxin. Data from these studies suggest possible targets for developing new ways to treat or prevent chronic periodontitis.

- [Al-Mashat HA, et al. \*Diabetes\* 2006;55:487-95](#), PMID: 16443785
- [Liu R, et al. \*Am J Pathol\* 2006;168:757-64](#), PMID: 16507891
- [Muthukuru M, Cutler CW. \*Infect Immun\* 2006;74:1431-5](#), PMID: 16428799
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)

**Advances in Treatment Development for Mental Disorders:** NIH continues to fund research into the development of new, targeted medications and treatments for mental disorders:

- ▷ *Drug Development for Cognitive Impairments in Schizophrenia:* The Treatment Unit for Research on Neurocognition in Schizophrenia program is a network that is testing the safety and efficacy of new therapeutic compounds for treating the cognitive deficits of schizophrenia.
  - (E) (NIMH)
- ▷ *Studies of Fragile X Syndrome:* NIH has entered into a public-private partnership to study and test possible medications for treating fragile X syndrome, the most common cause of inherited mental impairment. Fragile X syndrome is caused by a single gene mutation that ultimately results in exaggerated activity of a brain protein called mGluR5. Researchers will study, in animals, the safety of chemical compounds known to block this mGluR5 activity. If this phase goes well, researchers will move forward with clinical studies.
  - (E) (NIMH, NINDS, NICHD)
- ▷ *Faster-Acting Depression Treatments:* A recent NIH-funded study found that people with treatment-resistant depression experienced relief in as little as 2 hours after a single intravenous dose of ketamine, a medication usually used in higher doses as an anesthetic. Used in very low doses, ketamine is important for depression research but at higher doses could have side effects that may limit its clinical use. Nevertheless, this research could inform the development of faster- and longer-acting medications for treating depression.
  - For more information, see <http://www.nimh.nih.gov/press/ketamine.cfm>
  - This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
  - (I) (NIMH)



## Detecting and Diagnosing Chronic Disease

**Helping Patients Who Drink Too Much: A Clinician's Guide:** In January 2007, NIH issued an update to its 2005 edition of this clinician's guide. Targeted to primary care and mental health clinicians, the guide presents a user-friendly, research-based approach to screening, diagnosing, and managing patients with heavy drinking and alcohol use disorders. The updated guide offers the following new resources: CME/CE credits for physicians and nurses available through Medscape; support for medication-based therapy in non-specialty settings; a new handout with strategies to help patients reduce or quit drinking; a new dedicated Web page devoted to the guide and supporting resources for clinicians and patients; and an updated PowerPoint presentation for educators and instructors. NIH has worked closely with several organizations to disseminate the guide to their memberships.

- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (NIAAA)

**Alcohol Biosensors Program:** This Advanced Research Program, modeled on DoD's DARPA (Defense Advanced Research Projects Agency) program, was developed by NIH to generate a technical solution to address the need for continuous measurement of alcohol concentrations over time in clinical and basic research on alcohol use disorders. NIH awarded five research and development contracts for alcohol biosensor development. Each research group employed a different technological approach for alcohol measurement, and all have made substantial progress in engineering commercially viable alcohol biosensors, some of which are likely to make their way to market in the next few years.

- This example also appears in Chapter 3: *Technology Development*.
- (E) (NIAAA)

**Drug-Induced Liver Injury Network (DILIN):** DILIN is addressing the problem of drug-induced liver toxicity, which is increasing in the United States and has serious consequences for individuals and society. This Network enables research on liver toxicity due to prescription drugs or complementary and alternative medicines. Current studies are developing better tools for diagnosing, and ultimately preventing, drug-induced liver injury, as well as enhancing knowledge of disease processes. The Network has evolved into a resource on drug-induced liver toxicity for the national clinical community and the public.

- For more information, see <http://diln.dcri.duke.edu>
- (E) (NIDDK)

## Identifying Risk and Preventing Chronic Disease

**Genome-Wide Association (GWA) Studies and Database of Genotype and Phenotype (dbGaP):** In December 2006, NIH released the initial dbGaP dataset, using GWA data from the Age-Related Eye Diseases Study (AREDS), a landmark study of the clinical course of age-related macular degeneration (AMD) and cataracts. AREDS documents, protocols, and aggregated data are made available with no restrictions. To protect patient confidentiality,

de-identified, individual-level patient characteristics and family data are accessible only by authorized investigators. Correlating phenotype and genotype data provides information about the genetic and environmental interactions involved in a disease process or condition, which is critical for better understanding complex diseases and developing new diagnostic methods and treatments. Using these data, recent studies have linked two genes with progression to advanced AMD. After other factors were controlled for, certain forms of the genes increased the risk of AMD progression by 2.6- to 4.1-fold; smoking and body weight further increased risk with these gene variants.

- [Seddon JM, et al. \*JAMA\* 2007;297:1793-800](#), PMID: 17456821
- For more information, see <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gap>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Genomics*.
- (E) (NEI, NIA, NLM)

**Diabetes Prevention Program Outcomes Study (DPPOS):** The landmark NIH Diabetes Prevention Program (DPP) clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed the development of type 2 diabetes in people at high risk. The DPPOS is a long-term follow-up study of DPP subjects that is determining the durability of the interventions in preventing disease. DPP researchers recently confirmed that a variant in a gene predisposes people to type 2 diabetes. DPP subjects at highest genetic risk benefited from healthy lifestyle changes as much or more than those who did not inherit the variant. Participants over 60 years of age responded especially well to the lifestyle intervention, showing a 71 percent risk reduction in the incidence of diabetes, compared to groups treated with metformin or standard medical advice. The lifestyle intervention had greater impact with increasing age (from age 25 to over 60); the metformin treatment had progressively less impact with increasing age.

- [Florez JC, et al. \*N Engl J Med.\* 2006;355:241-50](#), PMID: 16855264
- For more information, see <http://tinyurl.com/24okog>
- For more information, see <http://tinyurl.com/295h4l>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK, CDC, IHS, NCMHD, NEI, NHLBI, NIA, NICHD, ORWH)

**The Heart Truth:** The Heart Truth, NIH's national awareness campaign for women about heart disease, continues to extend the reach of campaign messages and promotion of the Red Dress as the national symbol for women and heart disease. Hundreds of locally sponsored Heart Truth events have taken place, and more than a billion media impressions have been achieved. The Heart Truth Road Show helps subjects learn about heart disease risk factors, provides free health screenings, and disseminates educational materials. In April 2006, the campaign launched the Heart Truth Champions program to recruit health advocates and educators in local communities to increase awareness about women and heart disease. National Wear Red Day—the first Friday in February—has become an annual event when Americans wear red clothing and accessories in recognition of the importance of heart disease in women.

- For more information, see <http://www.nhlbi.nih.gov/health/hearttruth>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NHLBI)

**Ways to Enhance Children’s Activity & Nutrition (WeCan!):** This national public education outreach program, focusing on parents and families in home and community settings, is designed to help children 8-13 years old achieve and maintain a healthy weight. *WeCan!* program materials offer tips and activities to encourage healthy eating, increase physical activity, and reduce sedentary or computer and television screen time. Many national partners and supporting organizations are promoting the *WeCan!* messages and materials, and the program is being implemented in a variety of settings. In 2007, NIH began the *WeCan!* city program to assist towns and cities in mobilizing their communities to prevent childhood obesity. The first three cities that will participate in the new effort have pledged to offer *WeCan!* evidence-based obesity prevention programs to parents and youth in collaboration with community-based partners. In addition, each city will distribute *WeCan!* tips and information to city employees.

- For more information, see <http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/>
- For more information, see <http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=268>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (NHLBI, NCI, NICHD, NIDDK)

**National Epidemiologic Survey on Alcohol and Related Conditions (NESARC):** This nationally representative survey collected comprehensive, detailed data from approximately 40,000 individuals on alcohol consumption, use of 10 categories of drugs, and symptoms of alcohol and specific drug use disorders, as well as mood, anxiety, and personality disorders. In addition to diagnostic criteria, NESARC assessed indicators of impairment and distress due to each disorder, as well as disorder-specific treatment and help seeking. Analysis of these data is ongoing and continues to provide valuable information such as prevalence and comorbidity of mental health and substance use disorders. In addition, because NESARC data include a representative sample of ethnic and racial minority populations in the United States, a better assessment of the needs of specific populations can be made. One recent study using these data examined differences in the use of alcohol treatment services across the three largest ethnic groups in America. It showed that Hispanics and African Americans with higher levels of problem severity were less likely to have used treatment services than were Whites with problems of comparable severity, providing useful information about disparities in treatment utilization.

- [Schmidt LA, et al. \*Alcohol Clin Exp Res\* 2007;31:48-56](#), PMID: 17207101
- For more information, see <http://pubs.niaaa.nih.gov/publications/arh29-2/152-156.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, and Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (NIAAA)

**Osteoporosis:** NIH supports several longstanding prospective cohort studies, including the Study of Osteoporotic Fractures (SOF) in women and Mr. OS, a study of osteoporosis and other age-related diseases in men. Major contributions from the SOF, which began in 1986, include findings that bone mineral density of the hip is one of the best predictors of fracture for women. Recently, Mr. OS researchers identified specific lifestyle, medical, and demographic characteristics associated with low bone mass and fracture risk in older men.

- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Advisory\\_Council\\_Minutes/2006/sum01\\_06.asp](http://www.niams.nih.gov/News_and_Events/Advisory_Council_Minutes/2006/sum01_06.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2007/bonemass\\_men.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/bonemass_men.asp)
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIAMS, NIA)

**Childhood and Maternal Obesity:** As the maternal and childhood obesity epidemic grows, researchers are trying to understand the interaction among the many complex biological and behavioral factors that contribute to this rise, identify the long-term impact on mother and child, and develop effective interventions to reverse these trends. NIH obesity research, which includes a range of racial and ethnic groups, is examining topics such as:

- ▷ Basic research on the physiology, psychology, and genetics of obesity in children
  - ▷ Developing working definitions of the metabolic syndrome in children and adolescents
  - ▷ Linking maternal obesity, reproductive health, and pregnancy to adverse health outcomes
  - ▷ Behavioral intervention trials in schools, the home, and the community
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
  - (E/I) (NICHD, NCCAM, NCI, NCMHD, NHLBI, NIDCR, NIDDK, NINR, OBSSR, ODP/ORD)

**Trial to Reduce the Incidence of Type 1 Diabetes for those Genetically at Risk (TRIGR):** Researchers are conducting a study to determine whether the onset of type 1 diabetes can be delayed or prevented by weaning genetically susceptible infants to Nutramigen<sup>®</sup>, a hydrolysate of cow milk protein, instead of to a standard cow milk-based infant formula. Earlier studies in animal models have shown that hydrolyzed protein diets prevented the onset of type 1 diabetes. TRIGR is the first large effort designed to ascertain whether a simple nutritional intervention during infancy can delay or prevent the onset of type 1 diabetes in children who are at high genetic risk for the disease. Enrollment for the study was recently completed, totaling more than 2,000 children from 15 countries.

- For more information, see <http://www.nichd.nih.gov/research/supported/TRIGR.cfm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NICHD, NIDDK)

**HEALTHY:** The HEALTHY multicenter clinical trial aims to prevent risk factors for type 2 diabetes in middle-school children. A pilot study for HEALTHY found that an alarmingly high 15 percent of students in middle schools enrolling mainly minority youth had three major risk factors for diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease the risks for obesity and diabetes. In the full-scale HEALTHY trial, 42 enrolled middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. Over 80 percent of the enrolled students are from minority populations.

- For more information, see <http://www.nih.gov/news/pr/aug2006/niddk-28.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIDDK)

**Inflammatory Bowel Disease Genetics Consortium:** This consortium of researchers in the United States and Canada applies knowledge from the Human Genome Project to the identification of genetic factors influencing the development of inflammatory bowel diseases. A genome-wide screen of samples collected recently identified three new inflammatory bowel disease susceptibility genes. The identification of such genetic factors can provide key insights into disease development and targets for designing more effective therapies for inflammatory bowel disease.

- [Rioux JD, et al. \*Nat Genet.\* 2007;39:596-604](#), PMID: 17435756
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-011.html>
- This example also appears in Chapter 3: *Genomics*.
- (E) (NIDDK)

**Irritable Bowel Syndrome: Center for Neurovisceral Sciences and Women’s Health:**

Irritable bowel syndrome is a common disorder that occurs much more frequently in females than in males. The Women’s Health and Functional Visceral Disorders Center at the University of California-Los Angeles studies the role of sex-related factors in the development of irritable bowel syndrome and its response to treatment. Basic and clinical research involving patients, animal models, and functional brain imaging techniques are exploring sex differences in stress responses within the central nervous system, colon, and hormonal and immune systems. Researchers hope to identify factors that can form the basis of more effective treatment options for irritable bowel syndrome.

- For more information, see <http://www.cns.med.ucla.edu>
- (E) (NIDDK, ORWH)

**Environmental Intervention in the Prevention of Asthma:** Asthma is strongly related to environmental exposures. Exposure to indoor cat, dog, house dust mite, cockroach, and mold allergens is of particular concern because about 75-80 percent of children with asthma have significant allergies, which can trigger asthma, and thus these allergens have considerable medical and economic impact. Recent data have documented the ubiquity and specific levels of critical indoor allergens. In addition, a number of studies have shown that sensitization to indoor allergens (including those that derive from house dust mites, cats, dogs, rodents, cockroaches, and fungi) is a risk factor for the subsequent development of asthma. These studies include case-control studies, prospective studies, and allergen avoidance trials. Because house dust mites have been shown to be one of the strongest risk factors for persistence of asthma, an environmental intervention dust mite reduction study is under way in North Carolina. Volunteers between the ages of 5 and 15 years who are allergic or sensitive to dust mites are being recruited for the study. A study team will visit the homes of subjects four times over a 12-month period to measure indoor dust mite levels and collect information about the home. The results of the study will provide information that will help reduce or prevent adverse health outcomes from exposure to house dust mites and other allergens.

- For more information, see <http://www.niehs.nih.gov/health/topics/conditions/asthma>
- (NIEHS)

**Head Off Environmental Asthma in Louisiana:** Nearly 20 million people, 6.5 million of them children, suffer from asthma in the United States, and minorities are disproportionately represented. NIEHS, with the National Center on Minority Health and Health Disparities (NCMHD) and others, co-funds the Head Off Environmental Asthma in Louisiana (HEAL) project to assess the impact on asthma of environmental health conditions that were caused and exacerbated by Hurricane Katrina in New Orleans children, as well as implement an intervention program to address these problems. The Project's three main goals are (1) to conduct an extensive epidemiology study to assess the nature of the environmental and psychological impacts on children in New Orleans of Hurricane Katrina and subsequent flooding; (2) to examine the genetic and environmental risk factors for asthma, including genetic susceptibility to mold toxins, and gene interactions; and (3) to design, implement, and evaluate a case management program to meet the health care needs of children with asthma in a disrupted and highly challenging environment. The project has a clear plan for informing the community of the goals, implementation, and outcomes, as well as for receiving input from the community.

- For more information, see <http://heal.niehs.nih.gov>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*.
- (NIEHS, NCMHD)

**The Collaborative Study on the Genetics of Alcoholism (COGA):** In its 18th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) who are densely affected by alcoholism. Several genes have been identified, including *GABRA2*, *ADH4*, *ADH5*, and *CHRM2*, that influence the risk for alcoholism and related behaviors, such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected, and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes that influence vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

- For more information, see <http://zork.wustl.edu/niaaa>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Genomics*, and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAAA) (GPRA Goal)

**Look AHEAD (Action for Health in Diabetes):** This multicenter NIH-led clinical trial is examining the health effects of an intensive lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and increased physical activity. The impact of the intervention on the incidence of major cardiovascular events will be



evaluated in 5,100 overweight or obese subjects with type 2 diabetes. Look AHEAD is one of four trials that collectively address GPRA Goal SRO-6.2.

- [The Look AHEAD Research Group. \*Diabetes Care\* 2007;30:1374-83](#), PMID: 17363746
- For more information, see <http://tinyurl.com/2xaypk>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Minority Health and Health Disparities*
- (E/I) (NIDDK, CDC, NCMHD, NHLBI, NINR, ORWH)(GPRA Goal)

**International Tobacco and Health Research and Capacity Building Program:** Without a significant shift in worldwide smoking patterns, tobacco is projected to cause approximately 10 million deaths each year by 2025; 70 percent of this increase will occur in developing countries. To address this rising epidemic, NIH reissued the International Tobacco and Health Research and Capacity Building Program for funding in 2007. Grantees are generating a solid evidence base that can inform effective tobacco control strategies and policies. The program focuses on five critical areas: (1) epidemiology and surveillance, (2) susceptibility and risk for smoking uptake, (3) behavioral and social sciences, (4) effective interventions, and (5) policy-related research. The program also emphasizes research on determinants of youth smoking in diverse cultural and economic settings. A central goal of this program is to strengthen capacity in tobacco research in low- and middle-income nations, which advances the science and permits greater international collaboration.

- For more information, see [http://www.fic.nih.gov/programs/research\\_grants/tobacco/index.htm](http://www.fic.nih.gov/programs/research_grants/tobacco/index.htm).
- This example also appears in Chapter 2: *Cancer*.
- (E) (FIC, NCI, NIDA, NIDCR, ORWH)

**Jackson Heart Study:** The Jackson Heart Study, a large epidemiological study of cardiovascular disease among more than 5,300 African American residents of Mississippi, has been renewed through FY 2013. The project is exploring genetic, biological, and environmental factors that influence the development and course of cardiovascular disease in African Americans. It is also seeking to expand minority participation in public health and epidemiological research by providing classes and hands-on training to interested undergraduate students. Moreover, a community health education component is using data derived from the study cohort to develop and disseminate up-to-date information on reduction of risk factors, practice of healthy lifestyles, and adherence to proven risk-reducing therapies.

- For more information, see <http://jhs.jsums.edu/jhsinfo>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NHLBI, NCMHD)

**Osteoarthritis Initiative (OAI):** The OAI is a long-term effort, developed with support from private sector sponsors and with the participation of the Food and Drug Administration, to create a resource to identify and evaluate biomarkers of osteoarthritis to be used in clinical research.

The OAI, which began in FY 2002, has recruited 4,800 subjects who are at high risk for knee osteoarthritis.

- For more information, see [http://www.niams.nih.gov/Funding/Funded\\_Research/Osteoarthritis\\_Initiative/default.asp](http://www.niams.nih.gov/Funding/Funded_Research/Osteoarthritis_Initiative/default.asp)
- (E) (NIAMS, NCCAM, NCMHD, NIA, NIBIB, NIDCR, ORWH)

**Genetics of Kidneys in Diabetes (GoKinD):** This program facilitates investigator-driven research into the genetic basis of diabetic kidney disease through a biospecimen repository. Individuals with type 1 diabetes were screened to identify two subsets, one with clear-cut kidney disease and another with normal kidney function despite long-term diabetes. Nearly 10,000 DNA, serum, plasma, and urine samples—plus genetic and clinical data—from more than 1,700 adults with diabetes have been collected. The entire GoKinD collection is being genotyped for whole-genome association studies as part of the previously described Genetic Association Information Network (GAIN).

- [Mueller PW et al. \*J Am Soc Nephrol.\* 2006;17:1782-90, PMID: 16775037](#)
- For more information, see [http://www.jdrf.org/index.cfm?fuseaction=home.viewPage&page\\_id=B9C33021-1321-C834-0382E079E7865807](http://www.jdrf.org/index.cfm?fuseaction=home.viewPage&page_id=B9C33021-1321-C834-0382E079E7865807)
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Genomics*.
- (E) (NIDDK)

**The Environmental Determinants of Diabetes in the Young:** Pinpointing the environmental factors, such as infectious agents or diet, that can trigger type 1 diabetes in genetically susceptible individuals is crucial to developing prevention strategies. To address this knowledge gap, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. This international consortium is enrolling newborns at high genetic risk and following them until age 15 to identify environmental triggers for type 1 diabetes. The study is amassing the largest set of data and samples in the world for newborns at risk for type 1 diabetes.

- For more information, see <http://teddy.epi.usf.edu>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK, CDC, NIAID, NIEHS)

**The Gila River Indian Community Longitudinal Study:** NIH's Phoenix Epidemiology and Clinical Research Branch studies type 2 diabetes as it occurs among Pima Indians of Arizona, who have the highest prevalence of diabetes in the world. Working closely with Pima volunteers, the Branch has made substantial progress in identifying genetic, physiologic, and behavioral factors that lead to obesity and diabetes. The Branch also has facilitated improved treatment and prevention services in this community, leading to improved blood glucose control and blood pressure in Pima with diabetes. One important result is that the rate of kidney failure due to diabetes in Pima age 45 and older has declined since 1990.

- For more information, see [http://intramural.niddk.nih.gov/research/labbranch.asp?Org\\_ID=503](http://intramural.niddk.nih.gov/research/labbranch.asp?Org_ID=503)
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIDDK)

**Type 1 Diabetes TrialNet:** NIH is supporting this international network of investigators, clinical centers, and core support facilities that conducts research to advance knowledge about type 1 diabetes and tests strategies for its prevention and early treatment. TrialNet recently launched a clinical trial to test whether oral insulin could prevent or delay type 1 diabetes in people with a certain disease marker. The network also completed enrollment of two trials to determine whether medicines to slow the immune response could prevent further insulin-producing beta cell destruction in people newly diagnosed with type 1 diabetes. The TrialNet infrastructure is critically important for testing emerging therapies for prevention and early treatment.

- For more information, see <http://www.diabetestrialnet.org/>
- For more information, see [www.nih.gov/news/pr/jan2007/niddk-31.htm](http://www.nih.gov/news/pr/jan2007/niddk-31.htm)
- (E) (NIDDK, American Diabetes Association, Juvenile Diabetes Research Foundation, NCRR, NIAID, NICHD)

**Prevention of Trauma-Related Mental Disorders in High-Risk Occupations:** NIH is supporting a research initiative to develop and test preemptive interventions to prevent trauma-related disorders, such as posttraumatic stress disorder, among occupational groups at high risk for trauma exposure, such as the military, fire fighters, police, and rescue workers.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-010.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIMH)

**The U.S. Surgeon General's Family History Initiative:** Many people see most diseases as the result of interactions of multiple genes and environmental factors. Health care professionals have known for a long time that common diseases, such as heart disease, cancer, and diabetes, and rare diseases, such as hemophilia, cystic fibrosis, and sickle cell anemia, can run in families. The U.S. Surgeon General's Family History tool was created in a collaborative effort among the Office of the Surgeon General, NIH, CDC, AHRQ, and the Health Resources and Services Administration (HRSA). The U.S. Surgeon General's Family History tool (available in both English and Spanish) is free and has proven to be an effective personalized tool for individualizing preventive care and disease prevention—in other words, maintaining good health. Recently updated, this tool allows an individual to record health conditions that have affected his or her relatives. It utilizes a three-generation pedigree to gather information on health conditions in one's family to help doctors take action to keep individuals and families healthy.

- [Guttmacher AE, et al. \*N Engl J Med.\* 2004;351:2333-6](#), PMID: 15564550
- For more information, see <http://www.hhs.gov/familyhistory>
- For more information, see <https://familyhistory.hhs.gov>
- This example also appears in Chapter 3: *Genomics*.
- (OD, NHGRI)

**Transdisciplinary Tobacco Use Research Centers:** Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging

techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships.

- For more information, see <http://dceps.nci.nih.gov/tcrb/ttunc>
- This example also appears in Chapter 2: *Cancer* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NCI, NIAAA, NIDA)

**Retinopathy Occurs in Middle-aged Adults Even Without Diabetes:** Signs of retinopathy are common in the eyes of the elderly, particularly in those with diabetes. In the Atherosclerosis Risk in Communities (ARIC) study, African American subjects were significantly more likely to have signs of retinopathy (13 percent) compared with White subjects (5.5 percent). Among people with diabetes, 27 percent had signs of retinopathy. Unexpectedly, retinopathy signs were also observed in 4.3 percent of people who did not have frank diabetes but tended to have elevated blood pressure. Future studies will examine whether these signs of retinopathy result from high blood pressure and whether they indicate an increased risk of systemic cardiovascular disease or predict a subsequent diagnosis of diabetes.

- [Wong TY et al. \*Am J Ophthalmol\* 2007;143:970-6](#), PMID: 17399675
- For more information, see <http://www.csc.unc.edu/aric>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E/I) (NHLBI, NEI)

**Environmental Triggers and Skin Diseases:** CDC has excluded patients with eczema (also known as atopic dermatitis) from smallpox vaccination programs (in response to bioterrorism threats). There is concern of the risk of spreading vaccinia virus from the vaccine to the skin, which can cause eczema vaccinatum, an overwhelming and potentially lethal systemic infection. Researchers have learned that vaccinia virus grows much more in atopic dermatitis skin samples than in normal skin. Also, atopic dermatitis skin samples have lower levels of naturally occurring antimicrobial peptides, which could contribute to atopic dermatitis patients' susceptibility to eczema vaccinatum.

- [Howell MD et al. \*Immunity\*. 2006;24:341-8](#), PMID: 16546102
- (E) (NIAMS, NIAID)

**Osteoarthritis:** African Americans have a higher risk of bilateral radiographic (x ray-defined) osteoarthritis of the knee and hip than Whites. Two NIH-funded studies have revealed that mechanical stress can increase the production and release of osteoarthritis-related biomarkers. The research highlights the importance, when analyzing biomarkers, of considering the type and degree of physical activity in which patients with osteoarthritis participate.

- [O'Kane JW et al. \*Osteoarthritis Cartilage\* 2006;14:71-6](#), PMID: 16188465
- [Piscocya JL et al. \*Osteoarthritis Cartilage\* 2005;13:1092-9](#), PMID: 16168680
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/stress\\_oa\\_biomarker.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/stress_oa_biomarker.asp)
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (COE) (NIAMS, NIA)

**Bone Health:** NIH researchers have established reference curves for bone mineral content and density in children. The early findings are now available according to age, sex, and race and can be used to help identify children with bone deficits and to monitor changes in bone in response to chronic diseases or therapies. Early study findings showed that bone minerals continue to accrue beyond the teenage years, so the study will continue as the adolescent subjects approach young adulthood. In another study, NIH scientists discovered two genes for osteogenesis imperfecta, or brittle bone disease. The genes affect how collagen, an important building block for bone, is formed. Although there is no treatment for the disorder, the findings allow researchers to test families who have lost a child to osteogenesis imperfecta for the presence of the defective genes.

- [Kalkwarf HJ et al. \*J Clin Endocrinol Metab.\* 2007;92:2087-99](#), PMID: 17311856
- [Barnes AM et al. \*N Engl J Med.\* 2006;355:2757-64](#), PMID: 17192541
- [Cabral WA et al. \*Nat Genet.\* 2007;39:359-65](#), PMID: 17277775
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E/I) (NICHD, NIAMS, NIDCR, NCRR)

**The Rapid Response Program:** In April 2002, the Task Force on College Drinking released its seminal report *A Call to Action: Changing the Culture of Drinking at U.S. Colleges*. As part of its college focus, NIH initiated support of collaborations between university personnel who have responsibility for alcohol programs on various campuses and established researchers in college drinking to implement and evaluate programs to reduce underage alcohol use and its consequences. These programs include:

- ▷ RFA AA-03-008: “Research Partnership Awards for Rapid Response to College Drinking Problems.” Five U01 (cooperative agreement) 5-year grants were awarded in December 2002.
- ▷ PAR-03-133: “Rapid Response to College Drinking Problems.” Fifteen 3-year grants were awarded in June 2003.

This rapid funding mechanism (U18, cooperative agreement) supports timely research on interventions to prevent or reduce alcohol-related problems among college students. It was intended to support studies of services or interventions that could capitalize on “natural experiments” (e.g., unanticipated adverse events, policy changes, new media campaigns, campus-community coalitions, etc.). Each U18 grantee was required to partner with a U01 grantee. Together, these pairs, working with NIH Scientific Staff Collaborators, jointly design, develop, implement, and evaluate college drinking projects on their campuses.

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NIAAA)

**Underage Drinking Research Initiative:** In 2004, NIH launched this ongoing initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence, all framed within the context of overall development. Activities and accomplishments in 2007 include:

- ▷ Provided the scientific foundation for *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking* (released March 6, 2007) and for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking
- ▷ Convened scientific meetings of experts, including the Underage Steering Committee, which met four times over a 2-year period; a Meeting on Diagnosis of Alcohol Use Disorders among Youth (April 2006); and a Meeting on Screening for Child and Adolescent Drinking and Alcohol Use Disorders Among Youth (June 2007)
- ▷ Issued three RFAs, including “Underage Drinking: Building Health Care System Responses” (four projects awarded in FY 2006), “Impact of Adolescent Drinking on the Developing Brain” (five projects awarded in FY 2007),” and “Alcohol, Puberty and Adolescent Brain Development” (three projects awarded in FY 2007)
- ▷ Published *Alcohol Research & Health* Volume 28, Number 3, “Alcohol and Development in Youth: A Multidisciplinary Overview”
- ▷ Published a supplement of seven developmentally focused papers covering a broad range of underage drinking topics (accepted for the journal *Pediatrics*).
  - For more information, see <http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm>
  - This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 2: *Neuroscience and Disorders of the Nervous System*, and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
  - (E) (NIAAA)

**Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs):** ORWH led the development and implementation of a second round of SCORs with co-funding from five NIH institutes and FDA. The interdisciplinary nature of these research centers provides innovative approaches to advancing research on the influence of sex and gender as it relates to health and disease. Primary research areas funded include chronic pain, pregnancy, substance abuse, irritable bowel syndrome and interstitial cystitis, mental health, polycystic ovarian syndrome, and urologic health.

- For more information, see <http://orwh.od.nih.gov/interdisciplinary/SCORs.html>
- (E) (ORWH, NICHD, NIDA, NIDDK, NIMH, and NIAMS)

**Gene Influences Antidepressant Response:** Whether depressed patients will respond to an antidepressant depends in part on which version of a gene they inherit. Having two copies of one version of a gene that codes for a component of the brain's mood-regulating system increased the odds of a favorable response to an antidepressant by up to 18 percent, compared to having two copies of the other, more common version.

- For more information, see <http://www.nimh.nih.gov/science-news/2006/gene-influences-antidepressant-response.shtml>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Genomics*
- (E) (NIMH)



## **Genetic Resources/Tools**

**Medical Sequencing:** The completion of the human genome sequence, as well as genomic sequences of numerous other organisms, has already made a substantial impact on both biological and medical research. Public access to the raw data produced from these large-scale sequencing efforts has empowered many additional studies about the genomic contributions to disease. To expedite the transition from research data to medical practice, NIH supports initiatives that both drive technology that will make whole-genome sequencing affordable and produce data useful to biomedical research. Making affordable the sequencing of any individual's complete genome will allow personalized estimates of future disease risk and improve prevention, diagnosis, and treatment of disease. NIH's medical sequencing program is utilizing DNA sequencing to identify the genes responsible for rare, single-gene diseases; sequence all of the genes on the X chromosome to identify the genes involved in sex-linked diseases; and survey the range of variants in genes known to contribute to common diseases.

- For more information, see <http://www.genome.gov/15014882>
- This example also appears in Chapter 3: *Genomics*.
- (E/I) (NHGRI)

**Population Genomics, GAIN, and GEI:** In February 2006, DHHS announced the creation of two related groundbreaking initiatives in which NIH is playing a leading role. The Genetic Association Information Network (GAIN) and the Genes, Environment, and Health Initiative (GEI) will accelerate research on the causes of common diseases. GAIN is a public-private partnership among NIH, the Foundation for NIH, Pfizer, Affymetrix, Perlegen, the Broad Institute, and Abbott. GEI is a trans-NIH effort combining comprehensive genetic analysis and environmental technology development to understand the causes of common diseases. Both GAIN and GEI are powered by completion of the "HapMap," a detailed map of the 0.1 percent variation in the spelling of our DNA that is responsible for individual predispositions for health and disease. Data from GAIN will help to narrow the hunt for genes involved in six common diseases. In June 2007, the first GAIN dataset, on attention deficit hyperactivity disorder, was released. GEI will provide data for approximately another 15 disorders and will develop enhanced technologies and tools to measure environmental toxins, dietary intake, and physical activity, as well as an individual's biological response to those influences.

- For more information, see <http://www.genome.gov/19518664>
- For more information, see <http://www.genome.gov/19518663>
- For more information, see <http://genesandenvironment.nih.gov>
- For more information, see <http://www.genome.gov/11511175>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E/I) (NHGRI)

**Multiplex Initiative:** With the completion of the sequence of the human genome, genetic susceptibility tests that give personalized information about risk for a variety of common health conditions are now being developed and marketed. This genetic information ultimately will improve primary care by enabling more personalized treatment decisions for common diseases like diabetes and heart disease. This information also might motivate patients to change unhealthy behaviors. NIH investigators have teamed with the Group Health Cooperative in Seattle and the Henry Ford Health System in Detroit to launch a study to investigate the interest

level of healthy young adults in receiving genetic testing for eight common conditions. Called the Multiplex Initiative, the study will also look at how people who decide to have the tests interpret and use the results in making health care decisions. One thousand subjects who meet the study's eligibility requirements will be offered free multiplex genetic testing. The testing is designed to yield information about 15 different genes that play roles in common diseases such as type 2 diabetes and coronary heart disease. Trained research educators will make follow-up telephone calls to help subjects interpret and understand test results, and subjects will receive newsletters to update them on new developments about the tested genes. This research should provide insights into how best to utilize the powerful tools of genomic medicine to improve health.

- For more information, see <http://www.genome.gov/25521052>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Genomics*.
- (E/I) (NHGRI)

**Candidate Gene Association Resource:** Over the years, NHLBI has supported a number of major population studies that have collected extensive data on cardiovascular disease and its risk factors and manifestations. To increase the utility of the data for conducting genetic association studies, NIH initiated the Candidate Gene Association Resource program in FY 2006. This new resource will have the capacity to perform high-throughput genotyping for up to 50,000 subjects in cohort studies that have stored samples and data available on a wide array of characteristics (phenotypes) associated with heart, lung, blood, and sleep disorders. The linked genotype-phenotype data will form an invaluable resource for investigators seeking to identify genetic variants related to those disorders.

- For more information, see <http://public.nhlbi.nih.gov/GeneticsGenomics/home/care.aspx>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Genomics*.
- (E) (NHLBI)

**Enhancing Development of Genome-wide Association Methods (ENDGAME):** The ENDGAME consortium, which comprises 11 interactive teams of investigators, has been initiated to explore new approaches for designing and conducting genome-wide association studies (GWAS) of complex diseases. ENDGAME investigators are developing and testing innovative, informative, and cost-effective study designs as well as analytical strategies and tools for performing the studies. All strategies and tools developed will be made available to the scientific community. Results from ENDGAME are expected to greatly enhance the utility of GWAS for increasing understanding about genetic variations and their role in health and disease.

- This example also appears in Chapter 3: *Genomics*
- (E) (NHLBI, NCI, NHGRI, NIEHS, NIGMS)

**Framingham SNP-Health Association Resource (SHARe):** The Framingham SHARe is a comprehensive new effort by NIH and the Boston University School of Medicine to pinpoint genes underlying cardiovascular and other chronic diseases. The program builds on the Framingham Heart Study, which was begun in 1948 to identify factors that contribute to cardiovascular disease, and on other NIH-funded research demonstrating that common but minute variations in human DNA, called single nucleotide polymorphisms (SNPs), can be used

to identify genetic contributors to common diseases. The initiative will examine more than 500,000 genetic variants in 9,000 study subjects across three generations. NIH will develop a database to make the data available to researchers around the world. The database will help researchers integrate the wealth of information collected over the years in the Framingham study with the new genetic data, resulting in an increased understanding of genetic influences on disease risk, manifestation, and progression. Because of its uniqueness in including three generations of subjects with comparable data obtained from each generation at the same age, the Framingham Heart Study is the first study to be included in the SHARe initiative. NIH is currently considering expansion of SHARe to include other large longitudinal studies, such as the Jackson Heart Study and the new Hispanic Community Health Study.

- For more information, see <http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2460>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*.
- (E) (NHLBI, NLM)

**Hispanic Community Health Study:** In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Latin American heritage living in the United States. The project, which will include about 16,000 subjects, is designed to identify factors that predispose individuals to develop heart disease, stroke, asthma, COPD, sleep disorders, dental disease, hearing loss, diabetes, kidney disease, liver disease, cognitive impairment, and other chronic conditions. Characteristics such as diet, physical activity, obesity, smoking, blood pressure, blood lipids, acculturation, socioeconomic status, psychosocial factors, occupation, health care access, environment, and use of medications and dietary supplements will be assessed.

- For more information, see <http://www.nhlbi.nih.gov/new/press/06-10-12.htm>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NHLBI, NCMHD, NIDCD, NIDCR, NIDDK, NINDS, ODS)

## Treating Chronic Disease and Comorbidities

**HBO “Addiction” Documentary:** NIH collaborated with Home Box Office (HBO) to create a 90-minute documentary, “Addiction,” which aired on March 15, 2007. An NIH expert in the treatment of alcoholism was one of several principal spokespersons for the documentary and was featured in a supplementary broadcast on treatment advances. Several NIH grantees appeared in the documentary. A general-audience HBO book was produced to accompany the film.

- For more information, see <http://www.hbo.com/addiction>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NIAAA, NIDA)

**Success in Treating Drug Addiction Internationally:** International efforts to disseminate effective drug abuse treatments have seen success in countries with epidemic opiate addiction and/or HIV problems. Because of NIH research demonstrating that addiction is a chronic, relapsing disease that can be effectively treated, a culture change is starting to occur in these countries. For example, despite experiencing severe drug problems, Malaysia lagged behind in

the treatment of drug addiction and related disorders, even as it coped with having the second-highest HIV prevalence rate among adult populations and the highest proportion of HIV cases from injection drug use. Historically, drug abusers were “rehabilitated” involuntarily in correctional facilities, and although 60 percent of prisoners had drug-related offenses, no or minimal treatment was available in prison and no medications were permitted. This primarily criminal treatment approach had limited effectiveness, which led to widespread public dissatisfaction and the recent introduction of medications for addiction. These include naltrexone (1999), buprenorphine (2001), and methadone (2003). These drug treatment programs, which were rapidly embraced by the country’s medical community, have resulted in tens of thousands of opiate-dependent patients receiving medical treatment. Now the Ministry of Health, rather than the Ministry of Security, has authority for providing medical treatment for heroin addiction. This shift signals a remarkable change in Malaysian policies and approaches to addiction and an important opportunity to develop, implement, and disseminate effective treatments. A similar success story is starting to unfold in China as well.

- [Mazlan M, et al. \*Drug Alcohol Rev.\* 2006;25:473-8, PMID: 16939945](#)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDA, NIAID)

**Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC):** The DCCT demonstrated that intensive control of blood glucose levels reduced complications of the eyes, nerves, and kidneys in patients with type 1 diabetes. Long-term findings from the follow-on EDIC study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients should begin intensive therapy as early as possible. EDIC recently found that recurrent hypoglycemia associated with intensive control does not affect patients’ long-term cognitive function. After more than 20 years of studying this patient cohort, crucial insights continue to emerge.

- For more information, see <http://www.bsc.gwu.edu/bsc/studies/edic.html>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK)

**Practical Clinical Trials:** NIH has completed primary and secondary phases of several practical clinical trials that have examined treatment effectiveness for mental disorders such as schizophrenia, bipolar disorder, and depression. The infrastructure developed for each of these large multisite trials—involving more than 10,000 subjects at more than 200 sites—has forged efficient, effective, and collaborative relationships between scientists and clinicians throughout the country. To capitalize on the national networks established for the trials, NIH will fund infrastructure-only support for the platform of clinical sites and an administrative core. It is anticipated that the platform will serve as a critical foundation for supporting subject enrollment, facilitating communication among trial sites, maintaining up-to-date training in diagnosis and treatment, and providing needed administrative organization.

- For more information, see <http://www.nimh.nih.gov/healthinformation/catie.cfm>
- For more information, see <http://www.nimh.nih.gov/healthinformation/stard.cfm>

- For more information, see <http://www.nimh.nih.gov/healthinformation/stepbd.cfm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIMH)

**Scientific Basis of the Placebo Effect:** The placebo effect can be defined as the measurable, observable, or felt changes that occur during, but are not directly attributable to, a specific health intervention. It is a ubiquitous and frequently powerful phenomenon that operates in all forms of medicine, so good clinical research is designed to account for its effects as well as those of the intervention under study. Because of the power of the placebo effect, it is equally important to understand the mechanisms by which it operates and to explore how its benefits might be maximized to enhance the quality and effectiveness of all forms of health care. An ongoing NIH initiative is examining multiple aspects of the placebo effect through interdisciplinary investigations employing molecular, physiological, biochemical, immunological, genetic, behavioral, and social science approaches. This work is beginning to shed light on many facets of the placebo effect. For example, one recently published study showed that placebo-associated pain relief was correlated with activation of areas of the brain that are associated with pain relief that occurs through both innate mechanisms and with use of opioid narcotics. Other ongoing studies are examining the role and importance of the placebo effect in the relationship between patient and health care provider.

- [Zubieta JK, et al. \*J Neurosci\* 2005;25:7754-62](#), PMID: 16120776
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**The Scientific Basis of Acupuncture:** Ongoing research on acupuncture includes a substantial portfolio of basic and translational studies employing state-of-the-art neuroimaging technology. This work is beginning to provide powerful scientific insight into the potential neurobiological mechanisms of action by which acupuncture might work. Clinical trials of acupuncture for a number of medical conditions are also under way, including studies examining (1) the potential role of traditional acupuncture as an additive/alternative treatment for the prevention of acute cardiac events in patients with coronary artery disease, (2) whether manual or electro-acupuncture contributes to neurological recovery after spinal cord injury, and 3) the efficacy of acupuncture in relieving post-thoracotomy pain syndrome (severe and persistent aching or burning pain along surgical scars in the chest).

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**Gene Therapy for Leber's Congenital Amaurosis (LCA):** LCA is a rare, inherited retinal degenerative disease that causes severe vision loss in infancy. Although the disease is currently untreatable, NIH-funded investigators have restored vision in dogs with LCA by using gene therapy to replace defective copies of the retinal gene *RPE65*. Furthermore, new evidence

suggests retinal activity also restores function to the brain's visual center. Investigators have recently begun to translate this promising therapy to patients with LCA.

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NEI)

**Multicenter Uveitis Steroid Treatment (MUST) Trial:** Uveitis, a disease that causes inflammation in middle layers of the eye, is a major cause of blindness in the United States and often requires systemic, long-term treatment with oral corticosteroids and immunosuppressants. Ideally, a local therapy impacting only the eye is preferable to systemic therapy. This comparative effectiveness trial tests a new intraocular implant therapy in patients with severe uveitis.

- For more information, see <http://www.mustrial.org>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NEI)

**COPD: Learn More, Breathe Better:** Through its new education campaign, “COPD: Learn More, Breathe Better,” NIH is raising public and professional awareness about chronic obstructive pulmonary disease (COPD). Launched in January 2007, the campaign is a cooperative effort, engaging the public, health care providers, health insurers, and researchers in improving COPD diagnosis and treatment. The campaign relies on print and radio public service announcements and printed informational materials intended for distribution to patients with COPD, persons at risk for the disease, health care professionals, and community organizations. Joining NIH in implementing this new campaign by promoting it among their constituencies are more than 20 partners, including the American Academy of Family Physicians, the American Lung Association, the American Thoracic Society, the American College of Chest Physicians, and the U.S. COPD Coalition.

- For more information, see <http://www.nhlbi.nih.gov/health/public/lung/copd>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NHLBI)

**Pediatric Circulatory Support:** Options for the circulatory support of pediatric patients younger than age 5 are currently limited to short-term extracorporeal devices, the use of which is often complicated by infection, bleeding, and blood clots. Recognizing the need for additional options, NIH established a program to facilitate the development of new circulatory support systems for infants and children with congenital or acquired cardiovascular diseases. The program supports five research groups developing a variety of devices for different pediatric applications. The common objective for the devices is to provide reliable circulatory support for infants and children while minimizing adverse effects.

- For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-HL-03-004.html>
- This example also appears in Chapter 3: *Technology Development*.
- (E) (NHLBI)



**Sildenafil for Pulmonary Hypertension in Adult Patients with Sickle Cell Disease:** In 2006, NIH began a new study to evaluate a course of treatment with sildenafil in patients with sickle cell disease who have pulmonary hypertension. A randomized, double-blind, placebo-controlled, Phase II clinical trial is testing the drug's safety and efficacy in improving exercise capacity, symptoms, and measures of circulatory function. The trial involves approximately 180 patients at extramural sites and at the NIH Clinical Center. Because pulmonary hypertension occurs frequently in persons with sickle cell disease and confers a high risk of death, a positive outcome of this trial would represent an important step toward improved patient care.

- For more information, see <http://www.clinicaltrials.gov/ct2/show/NCT00492531?term=sildenafil&rank=7>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NHLBI)

**Monitoring Organ Rejection Using MRI:** Organ transplants give patients a new lease on life. However, preventing their immune systems from rejecting the transplanted organ sometimes presents a challenge. Physicians must strike a balance between suppressing the immune system so that it does not reject the organ and maintaining enough immune activity to ward off infections. Tracking how the body accepts the new organ is critical to this process. The current “gold standard” for monitoring organ rejection is tissue biopsy, an invasive procedure in which a physician removes a small sample of the transplanted organ for testing. Biopsy has two drawbacks: patient discomfort (the physician must perform the procedure multiple times) and poor selectivity (biopsy removes tissue from only a limited number of sites and can miss rejection starting elsewhere in the organ). To overcome these limitations, NIH-supported researchers are developing a new method to monitor organ rejection with MRI. They label macrophages (immune cells) with polymer-coated, micron-sized iron oxide particles. These magnetic particles allow the migration of the macrophages to rejection sites in the transplanted organ to be clearly tracked by MRI. At present, this work is being performed on rats, but the investigators are extending it to large animals and humans. If successful, the approach could be used to optimize the administration of immunosuppressant drugs in clinical situations.

- [Wu YL, et al. \*Proc Natl Acad Sci U S A\*. 2006;103:1852-7, PMID: 16443687](#)
- For more information, see <http://www.nibib.nih.gov/HealthEdu/PubsFeatures/eAdvances/25Sep06>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIBIB)

**Asthma Exacerbations—Biology and Disease Progression:** In FY 2005, NIH began a basic and clinical research initiative to improve understanding of the causes of asthma exacerbations and to facilitate the development of more effective treatments to control symptoms. Twelve projects have been funded under this initiative. As part of NIH GPRA reporting activity, NIH is assessing the progress of the initiative through an ongoing GPRA goal, “to identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating exacerbations, by 2014.”

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-029.html>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHLBI, NIAID) (GPRA Goal)

**Long-Term Oxygen Treatment Trial (LOTT):** Although oxygen therapy is known to benefit patients with COPD who experience severe hypoxemia (low blood oxygen level) when resting, the value of this treatment in patients with less serious disease is not known. In November 2006, NIH and the Centers for Medicare and Medicaid Services launched the LOTT, the largest-ever randomized clinical trial of the effectiveness and safety of long-term, home oxygen therapy for patients with COPD and moderately severe hypoxemia. Results are expected to shed light on the role of oxygen therapy in the management of these patients and to provide a basis for Medicare coverage decisions. The LOTT trial is the focus of a new NIH GPRA goal to be included in GPRA reporting in 2007: “by 2012, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia.”

- For more information, see <http://www.jhucct.com/lott/>
- For more information, see <http://www.nhlbi.nih.gov/new/press/06-11-20.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NHLBI) (GPRA Goal)

**Programs to Accelerate Medication Development for Alcoholism Treatment:** Alcoholism is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ from one drinker to another. Therefore, a diverse repertoire of medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure their interest in taking promising compounds through the final phase of clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- ▷ Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies have already produced several targets for human studies that are now under way, such as rimonabant, a cannabinoid CB1 receptor blocker, and antalarmin, a corticotropin-releasing factor receptor blocker.
  - ▷ A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early human trials network.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
  - (E/I) (NIAAA) (GPRA Goal)

**Improving Transplantation Outcomes:** Organ transplantation prolongs survival and improves quality of life for children and adults with a wide range of diseases. Yet despite advances in organ transplantation, organ recipients rarely achieve normal life expectancy and health-related quality of life. To improve the outcome of organ transplantation, NIH supports the Clinical Trials in Organ Transplantation (CTOT) initiative, a cooperative, multisite consortium that conducts interventional and observational clinical studies, as well as studies of the mechanisms of graft rejection. The consortium includes 34 clinical sites and 30 immunology laboratories at 13

universities. Five clinical trials are currently enrolling individuals undergoing kidney, heart, liver, or lung transplantation.

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIAID, NHLBI, NIDDK) (GPRA Goal)

**Blending Initiative: Bench to Bedside to Community:** Efforts to systematically move science-based interventions and practices into community settings are exemplified in the testing of drug abuse treatment approaches directly in the community settings where they will be used by drug treatment professionals who are trained to implement them. This work is occurring through the National Drug Abuse Treatment Clinical Trials Network at NIH, which involves practitioners from community treatment programs not only in formulating research protocols, but also in providing real-world feedback on their success and feasibility. The adoption of the addiction medication buprenorphine by a growing number of community treatment programs treating patients with opioid addiction is an example of real culture change issuing from NIH clinical research. A similar approach is under way to enhance treatment for drug-addicted individuals involved with the criminal justice system through research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) initiative. It seeks to achieve better integration of drug abuse treatment for criminal offenders with other public health and public safety forums and is a collaborative effort by NIH and multiple Federal agencies and health and social service professionals. These initiatives are helping to change the culture of how drug abuse treatment is delivered in this country.

- For more information, see <http://www.drugabuse.gov/CTN>
- For more information, see <http://www.cjdats.org>
- For more information, see <http://www.drugabuse.gov/Blending>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Clinical and Translational Research*, and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NIDA) (GPRA Goal)

**Treatments to Fight Methamphetamine Addiction:** The abuse of methamphetamine—a potent and highly addictive psychostimulant—is a serious problem in the United States. Methamphetamine abuse can have devastating medical, psychological, and social consequences. Adverse health effects include memory loss, aggression, psychotic behavior, heart damage, and abnormal brain function. Methamphetamine abuse also contributes to increased transmission of hepatitis and HIV/AIDS and can spawn increased crime, unemployment, and other social ills. The good news is that methamphetamine abuse and addiction are treatable, and people do recover. As methamphetamine abuse has increased, so has NIH’s support of research to combat it, including research on genetics, brain development, and translation of findings. This research has led to the development of two effective behavioral therapies for methamphetamine addiction: (1) the Matrix Model, consisting of a 16-week program that includes group and individual therapy and addresses relapse prevention, behavioral changes, establishment of new drug-free environments, and other issues; and (2) Motivational Incentives for Enhanced Drug Abuse Recovery, a cost-effective incentive method for cocaine and methamphetamine addiction that has been shown to sustain abstinence in twice the number of subjects engaged in treatment as usual.

Increasingly, community treatment providers nationwide are implementing motivational incentives as part of drug addiction treatment.

- For more information, see <http://www.drugabuse.gov/ResearchReports/Methamph/Methamph.html>
- For more information, see <http://www.drugabuse.gov/Testimony/6-28-06Testimony.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDA)

**Nonalcoholic Steatohepatitis (NASH) Clinical Research Network:** NASH is strongly associated with obesity and type 2 diabetes, conditions that have increased dramatically in recent decades. Network research addresses GPRA Goal SRO-4.3. The Network is conducting a randomized clinical trial to evaluate the safety and efficacy of the insulin-sensitizing drug pioglitazone or vitamin E compared to placebo for the treatment of non-diabetic adults with NASH. Also, in a separate trial in children, the Network is comparing the insulin-sensitizing drug metformin, vitamin E, and placebo in treating nonalcoholic fatty liver disease.

- For more information, see <http://www.jhucct.com/nash>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDDK, NCI, NICHD) (GPRA Goal)

**Age-Related Eye Disease Study, Part 2 (AREDS2):** Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly in the United States and will be an increasing burden in future years, based on demographics. The original AREDS study, completed in 2005, demonstrated that antioxidant vitamin and mineral supplements reduced the progression to advanced AMD by 25 percent. Building on these landmark findings, AREDS2 is assessing additional supplements (lutein, zeaxanthin, and long-chain omega-3 fatty acids) as a treatment for AMD and cataracts. AREDS2 is also evaluating the effects of eliminating beta-carotene and/or reducing zinc in the original AREDS formulation on AMD progression. AREDS2 investigators will also explore gene-environment interactions in the development of these conditions, cognitive function, and cardiovascular health.

- For more information, see <http://www.areds2.org>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
- (E) (NEI, NIA)

**Diabetic Retinopathy Clinical Research Network (DRCR.net):** Diabetes, a leading cause of blindness in working-age adults, causes blood vessels in the retina to leak and can lead to retinal detachment. Laser treatment is effective but is not optimal. DRCR.net is a collaborative, nationwide, public-private network of eye doctors and investigators in 165 clinical sites conducting clinical research of diabetes-induced retinal disorders (diabetic retinopathy and diabetic macular edema) with the aim of evaluating promising new therapies. DRCR.net serves as a model network to provide the infrastructure to facilitate multiple concurrent and consecutive clinical trials of innovative therapies, to rapidly develop and initiate new protocols, and to interact with industry partners while ensuring scientific rigor and high ethical standards.

- For more information, see <http://public.drcr.net>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NEI)

**Comprehensive Sickle Cell Centers (CSCCs):** The CSCCs were established in 1972 in response to a Presidential initiative and a Congressional mandate to support multidisciplinary research to expedite the development and application of new knowledge for improved diagnosis and treatment of sickle cell disease. In addition to basic research, training, and patient services activities, the CSCCs currently support multicenter Phase II trials, neurocognitive and neuroimaging studies, development of a collaborative database, and a study on the epidemiology of priapism (painful, prolonged erection) among patients with sickle cell disease. Ten centers are funded through FY 2007, and the program will be renewed in FY 2008.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-008.html>
- For more information, see <http://www.sicklecell-info.org>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*.
- (E) (NHLBI)

**Improving the Lives of Asthmatic Children in the Inner City:** The NIH Inner-City Asthma Consortium (ICAC) evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children, who are disproportionately affected by asthma. An ICAC longitudinal birth cohort study involving 500 inner-city children is investigating the immunologic causes of the development of recurrent wheezing, a surrogate marker for asthma in children younger than age 3. The ICAC is also conducting a multicenter trial to evaluate the safety and efficacy of Xolair (omalizumab) in children with moderate to severe allergic asthma whose symptoms are inadequately controlled with inhaled steroids. Finally, researchers are conducting a clinical trial to determine the safety and dosing levels of a potential new allergy immunotherapy for cockroach allergen, which previous ICAC findings showed are a major determinant of asthma severity among inner-city children.

- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIAID)

**Dialysis Access Consortium:** Arteriovenous fistulas and grafts are the two most common methods of gaining repeated access to the circulation of patients on hemodialysis. The Dialysis Access Consortium (DAC) is conducting two trials to assess the impact of anticlotting reagents in preventing early failure in arteriovenous fistulas and grafts. The Arteriovenous Fistula Trial is evaluating the ability of clopidogrel to maintain access patency, while the Arteriovenous Graft Trial is evaluating the ability of aspirin combined with extended-release dipyridamole to maintain access patency.

- [Dember LM et al. \*Clin Trials\*. 2005;2:413-22](#), PMID: 16317810
- [Dixon BS et al. \*Clin Trials\*. 2005;2:400-12](#), PMID: 16317809
- For more information, see <http://www.niddk.nih.gov/patient/dac/DAC.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK)

**Inflammatory Bowel Disease: Randomized Trial of Rosiglitazone for Ulcerative Colitis:** Current treatments for ulcerative colitis, a form of inflammatory bowel disease, are not effective for all patients. NIH-supported scientists demonstrated that rosiglitazone, a medication used to



treat type 2 diabetes, reduced inflammation in an animal model of ulcerative colitis. Subsequently, a small clinical study showed that rosiglitazone was effective in controlling ulcerative colitis symptoms. NIH is now supporting a full-scale clinical trial of this potential new therapy for ulcerative colitis.

- For more information, see <http://clinicaltrials.gov/show/NCT00065065>
- (E) (NIDDK)

**Longitudinal Assessment of Bariatric Surgery (LABS):** The multicenter, NIH-funded LABS consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Because bariatric surgery is also sometimes used in clinical practice as a treatment for severely obese adolescents, NIH is also supporting an observational study of teens already scheduled for surgery, Teen-LABS, to collect data to help determine whether it is an appropriate treatment option for extremely obese adolescents.

- For more information, see <http://tinyurl.com/399zmt>
- For more information, see <http://tinyurl.com/yoer3l>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK, ORWH)

**Polycystic Kidney Disease (PKD):** The Consortium for Radiologic Imaging Studies of PKD (CRISP) showed that MRI could accurately track structural changes in the kidneys of people with the more common form of PKD. An extension, CRISP II, will continue to monitor these patients to determine whether these changes in kidney volume predict changes in kidney function. NIH is also conducting two clinical trials of people with the most common form of PKD; one is in patients with early kidney disease and another is in patients with more advanced disease. These two trials are the largest multicenter studies of PKD conducted to date and are collectively termed HALT-PKD. They are testing whether optimum blood pressure management, in combination with medication, will slow the progression of PKD.

- [Grantham JJ, et al. \*N Engl J Med\*. 2006;354:2122-30, PMID: 16707749](#)
- For more information, see <http://tinyurl.com/2qu94j>
- For more information, see <http://www.pkd.wustl.edu/pkd-tn/>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK)

**Stress Incontinence Surgical Treatment Efficacy (SISTER) Trial:** The first of several studies to be conducted by the NIDDK-funded Urinary Incontinence Treatment Network, the SISTER trial recently showed that the sling surgical procedure helps more women achieve dryness than the Burch surgical technique. Two years after surgery, 66 percent of women who had the sling procedure and 49 percent who had the Burch were continent.

- [Albo ME et al. \*N Engl J Med\*. 2007;356:2143-55, PMID: 17517855.](#)
- For more information, see <http://www.nih.gov/news/pr/may2007/niddk-21.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK)



**Studies of Diabetes in Youth:** Previously known as a disease of adults, type 2 diabetes is increasingly being observed in youth. The Treatment Options for Type 2 Diabetes in Youth study is comparing three different treatment strategies for children with the disease. The SEARCH for Diabetes in Youth Study is providing key data on childhood diabetes incidence and prevalence. SEARCH estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. While type 2 diabetes is increasing in children over age 10, particularly minorities, type 1 diabetes accounts for most new cases, with an estimated 15,000 youths diagnosed annually.

- For more information, see <http://www.todaystudy.org/index.cgi>
- For more information, see <http://www.searchfordiabetes.org>
- This example also appears in Chapter 3: *Clinical and Translational Research*, Chapter 3: *Epidemiological and Longitudinal Studies*, and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDDK, CDC)

**The Clinical Islet Transplantation Consortium:** The purpose of this international consortium is to develop and implement a program of single- and/or multicenter clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. Research pursued through this consortium aims to make improvements in the field of islet transplantation and to share the data and results with the broad scientific community.

- For more information, see [www.isletstudy.org](http://www.isletstudy.org)
- (E) (NIDDK, NIAID)

**Translational Research for the Prevention and Control of Diabetes and Obesity:** NIH is supporting research projects to explore ways to bring knowledge from successful clinical research into medical practice and community settings. Studies are seeking to develop effective, sustainable, and cost-effective methods to prevent and treat type 1 and type 2 diabetes and obesity in clinical health care practice and other real-world settings. Many of these studies focus on minority populations disproportionately burdened by type 2 diabetes and obesity.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK)

**Maintenance of Long-Term Behavioral Change:** Behavioral factors contribute to the development and outcomes of many chronic diseases. Successful prevention of and treatment for chronic diseases depend, in part, upon the sustained maintenance of behavior change over time. This initiative supports research projects that examine biopsychosocial processes and test interventions designed to achieve long-term health behavior change. Funded projects focus on diet, physical activity, HIV prevention, smoking cessation, drug abstinence, suicide prevention and mammography screening. In addition, A Health Maintenance Consortium (HMC) comprising NIH program staff, research investigators at the individual sites, and representatives from cosponsoring private foundations has been established to explore the opportunities for further collaboration across the studies.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-OB-03-003.html>
- For more information, see [http://obssr.od.nih.gov/Content/Research/Request\\_for\\_Applications\\_%28RFAs%29/Behavioral+Change+RFA+Outcome.htm](http://obssr.od.nih.gov/Content/Research/Request_for_Applications_%28RFAs%29/Behavioral+Change+RFA+Outcome.htm)
- For more information, see <http://hmcrc.srph.tamhsc.edu/default.aspx>
- (E) (OBSSR, NCI, NEI, NIA, NIAAA, NICHD, NIDA, NIDDK, NIMH, NINR, ODP/ORD)

**Patient-Reported Outcomes Measurement Information System (PROMIS):** This NIH Roadmap initiative is developing ways to measure symptoms—such as pain, fatigue, physical functioning, social-role participation, and emotional distress—that influence quality of life across numerous chronic diseases.

- For more information, see <http://www.nihpromis.org/default.aspx>
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Announcements/2007/PROMIS\\_supp.asp](http://www.niams.nih.gov/News_and_Events/Announcements/2007/PROMIS_supp.asp)
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (Roadmap—all ICs participate) (GPRA Goal)

**Comprehensive Review of Meditation Research:** A recent comprehensive literature review on meditation research included more than 800 studies of a variety of forms of meditation for a number of chronic conditions, including hypertension, coronary artery disease, and substance abuse. The review concludes that there are promising indications that meditation may have beneficial effects on a variety of outcomes, including blood pressure, perceived stress, anxiety, and behavioral modification, but additional and higher-quality research is needed.

- For more information, see <http://www.ahrq.gov/clinic/tp/medittp.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**Mind-Body Medicine:** NIH supports a substantial portfolio of multidisciplinary clinical, translational, and basic research on mind-body interventions, such as meditation and Tai Chi Chuan. This effort is based on (1) promising findings from preliminary controlled clinical investigations and (2) laboratory evidence suggesting that these interventions often involve or invoke well-known biological mechanisms that are known to play key roles in the cause of and recovery from illness and in the preservation of health and wellness. For example:

- ▷ Investigators recently demonstrated that patients who practiced Tai Chi Chuan, a form of moving meditation based on traditional Chinese medicine, experienced significant augmentation in levels of immunity to the virus that causes shingles after vaccination against the virus.
  - ▷ Other investigators have demonstrated that patients with chronic heart failure show improvements in quality of life, exercise ability, and biomarkers of cardiac health when Tai Chi Chuan is added to conventional medical care.
- [Irwin MR, et al. \*J Am Geriatr Soc.\* 2007;55:511-7](#), PMID: 17397428
  - [Yeh GY, et al. \*Am J Med.\* 2004;117:541-8](#), PMID: 15465501
  - This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
  - (E) (NCCAM)

**Research on Popular Dietary Supplements:** A significant body of research on CAM practices focuses on documenting the safety and efficacy of various widely used dietary supplements. Important recently reported findings include the following:

- ▷ The combination of glucosamine plus chondroitin sulfate did not provide significant relief of pain from osteoarthritis of the knee in the overall study population, although a subset of the study subjects with moderate-to-severe pain showed significant relief with the combined supplements.
- ▷ The dietary supplement alpha-tocopherol (a form of vitamin E), administered at a high dosage of 1,200 IU/day for 2 years, had no effect on serum concentrations of total, low-density lipoprotein, or high-density lipoprotein cholesterol.
  - [Clegg DO, et al. \*N Engl J Med.\* 2006;354:795-808](#), PMID: 16495392
  - [Singh U, et al. \*Clin Chem.\* 2007;53:525-8](#), PMID: 17234730
  - This example also appears in Chapter 3: *Clinical and Translational Research*.
  - (E) (NCCAM, NIAMS, ODS)

**Losartan Offers Promise for the Treatment of Marfan Syndrome:** New research offers hope that losartan, a drug commonly prescribed to treat hypertension, might also be used to treat Marfan syndrome, a genetic disorder that often causes life-threatening aortic aneurysms. After discovering that Marfan syndrome is associated with a mutation in the gene encoding fibrillin-1, researchers tried for many years, without success, to develop treatment strategies that involved repair or replacement of fibrillin-1. A major breakthrough occurred when NIH-funded researchers discovered that one of the functions of fibrillin-1 is to bind to another protein, TGF-beta, and regulate its effects. After careful analyses revealed aberrant TGF-beta activity in patients with Marfan syndrome, researchers began to concentrate on treating the disease by normalizing the activity of TGF-beta. Losartan, which is known to affect TGF-beta activity, was tested in a mouse model of Marfan syndrome. The results showed that the drug blocked the development of aortic aneurysms as well as lung defects associated with the disease. Based on the promising results, the NHLBI Pediatric Heart Network, in partnership with the National Marfan Foundation, began a clinical trial in 2007 to assess losartan therapy in patients with Marfan syndrome.

- [Habashi JP, et al. \*Science.\* 2006;312:117-21](#), PMID: 16601194
- For more information, see <http://clinicaltrials.gov/show/NCT00429364>
- For more information, see <http://www.pediatricheartnetwork.org>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHLBI)

**Acute Liver Failure Study Groups:** The adult and pediatric Acute Liver Failure Study Groups address the problem of acute liver failure due to drugs or other factors. The groups' research has provided knowledge and tools for managing the clinical and public health burden of acute liver failure. In 2002, the adult Study Group highlighted a dramatic increase in liver injury due to the over-the-counter pain reliever acetaminophen. The groups then developed a serum-based assay

to detect acetaminophen-induced acute liver failure in adults and children. Current studies are testing potential therapies to improve survival in patients with acute liver failure.

- [Ostapowicz G et al. \*Ann Intern Med.\* 2002;137:947-54](#), PMID: 16950959
- For more information, see <http://tinyurl.com/2qu94j>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDDK, FDA)

**Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial:** The HALT-C trial studies whether long-term antiviral therapy can prevent the progression of liver disease in people with hepatitis C who do not respond to standard, short-term therapy. The trial has advanced understanding of the impact of disease severity and antiviral drug dose on response to long-term therapy and yielded a new tool to monitor treatment response. These advances can help health care providers to determine which patients are unlikely to respond to long-term antiviral therapy, so that those patients can be spared from ineffective treatment and its side effects.

- [Morishima C et al. \*Hepatology.\* 2006;44:360-7](#), PMID: 17241864
- For more information, see <http://www.haltctrial.org>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK, NCI, NIAID)

**Multidisciplinary CAM Research:** Investigators are utilizing increasingly sophisticated, multidisciplinary, bedside-to-bench and bench-to-bedside approaches to elucidate the efficacy, safety, and mechanisms of action of a wide variety of CAM practices. Ongoing research encompasses virtually all organ systems and medical and scientific disciplines, as well as numerous CAM modalities and practices spanning the four major CAM domains (biologically based practices, manipulative and body-based practices, energy medicine, and mind-body medicine), as well as the alternative whole medical systems of which they are a part. Guided by its 5-Year Strategic Plan, recommendations of the National Advisory Council for Complementary and Alternative Medicine, the plans of other ICs, and input from expert panels and various stakeholders, NCCAM establishes priorities to fill gaps in the CAM research portfolio, capitalize on emerging opportunities, and leverage resources.

- For more information, see <http://nccam.nih.gov/about/plans/2005/strategicplan.pdf>
- For more information, see <http://nccam.nih.gov/research/priorities/index.htm#5>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**Advancing Novel Science in Women's Health Research (ANSWHR):** In FY 2007, NIH published two Program Announcements for a new grants program called Advancing Novel Science in Women's Health Research (ANSWHR). Both announcements are intended to

promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex and gender differences.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAS-07-381.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAS-07-382.html>
- (E) (ORWH, NCI, NEI, NHLBI, NHGRI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDCD, NIDCR, NIDA, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, FIC, NCCAM, OBSSR, and ODS)

**Research Enhancement Awards Program (REAP):** NIH successfully implemented a trans-NIH Research Enhancement Awards Program (REAP) in both FY 2006 and FY 2007 by awarding a total of more than \$6.8 million dollars. Sixteen grants were awarded in each fiscal year. This program is directed at meritorious grants that have just missed the IC pay line that will advance research on women's health and/or the study of sex and gender factors. Scientific areas covered by these grants include diabetes, fibromyalgia, genetic studies of ovarian failure, health disparities, heart failure evaluation in postmenopausal women, HIV/AIDS, interstitial cystitis, lupus, neuroendocrine development, pain control, rheumatoid arthritis, smoking in pregnancy, substance abuse, and breast cancer and CAM.

- (E) (ORWH)

**Trans-NIH Chronic Fatigue Syndrome Research:** NIH coordinates chronic fatigue syndrome research through the trans-NIH Working Group on Research on Chronic Fatigue. This working group developed an action plan to enhance the status of chronic fatigue syndrome research at NIH and among the external and intramural scientific communities. The working group held a workshop on grantsmanship in FY 2007 to provide researchers with an overview of funding opportunities, an understanding of the NIH funding process, and an opportunity to meet with program officials. In addition, the Office of Research on Women's Health and a subset of the working group ICs issued an RFA in FY 2006 to explicate how the brain, as the mediator of the various body systems involved, fits into the schema for understanding chronic fatigue syndrome. This RFA solicited proposals from multidisciplinary teams of scientists to develop an interdisciplinary approach to the study of chronic fatigue syndrome in men and women across the lifespan and resulted in seven new research projects on chronic fatigue syndrome.

- For more information, see <http://orwh.od.nih.gov/cfs.html>, <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html>
- For more information, see <http://orwh.od.nih.gov/cfs/2006NIHfundedCFSstudies.html>
- For more information, see <http://orwh.od.nih.gov/cfs/cfsFundingGMWs.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (ORWH, NIAID, NIAMS, NIAAA, NIA, NICHD, NIDA, NIDDK, NINDS, NCRR, CSR, NIEHS, NIDCR, NINR, NHLBI, NIMH, NCCAM, FIC, ODS, OBSSR)

**Research to Strengthen the Dissemination and Implementation of Evidence-Based Mental Health Interventions:** NIH continues to support research designed to strengthen the dissemination and implementation of evidence-based mental health practices. NIH released a Program Announcement to encourage transdisciplinary teams of scientists and practice stakeholders to work together to develop innovative approaches for identifying and overcoming barriers to the adoption of evidence-based interventions. This Program Announcement also

serves as the basis for a GPRA Goal. NIH also supports research designed to enhance implementation by providing evidence of intervention benefits not just to the individual, but to a broader system as well. For example, a recent study reported that providing a minimal level of enhanced care for employees' depression would result in significant savings to employers.

- [Wang PS et al., \*Arch Gen Psychiatry\* 2006;63:1345-53](#), PMID: 17146009
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-086.html>
- For more information, see <http://www.nimh.nih.gov/press/cost-benefitsimulation.cfm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I/E) (NIMH, NCI, NIDA, NIDCD, NINR, NIAAA, NIDCR, NIDDK, NICHD) (GPRA)

## Addressing Pain and Palliative Care in Chronic Diseases

**Improving End-of-Life Care: Special Supplement to the *Journal of Palliative Medicine*:** In FY 2005, NIH sponsored the State-of-the-Science Conference on Improving End-of-Life Care. This conference addressed the current state of end-of-life care and proposed important new directions for end-of-life research. Key conclusions to emerge from the conference included: the rapid increase in older adults facing the need for end-of-life care requires the development of research infrastructure to better examine end-of-life issues; enhanced communication between patients, families, and providers is crucial to end-of-life care; and improved outcome measures are needed to better conduct end-of-life research. In FY 2006, a special issue of the *Journal of Palliative Medicine* presented a series of papers developed from this workshop on a wide variety of topics. The supplement includes articles on measuring end-of-life care outcomes; analyzing racial, cultural, and ethnic factors that influence end-of-life care; improving care for dying children and their families; and examining factors in the health care system that influence end-of-life care.

- [Grady PA. \*J Palliat Med.\* 2005;8:S1-3](#), PMID: 16499457
- For more information, see <http://www.liebertonline.com/toc/jpm/8/supplement+1>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NINR)

**Promising Approaches to Treating Chronic Pain:** Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can produce drug dependence. Thus, an area of enormous need is the development of potent non-opioid analgesics, for which NIH has implemented an aggressive and multidisciplinary research program. Many of these initiatives are yielding tangible results that stand to revolutionize the field of pain management. At the molecular level, cannabinoid research has shown that it is possible to selectively activate the cannabinoid system to provide analgesia with minimal or no psychotropic side effects or abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different receptors, the targeting of which could provide a vastly expanded range of pharmacotherapeutic effects. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on a non-neuronal brain cell type, glia, has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their pro-inflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of analgesic drugs. At the brain circuit level, a new



approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects "learn" how to regulate pain by viewing and then controlling images of their own brains in real time.

- For more information, see <http://www.nida.nih.gov/whatsnew/meetings/painopioides>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDA, NINDS)

**Resources for Enhancing Alzheimer's Caregiver Health II (REACH II):** Family members and friends who care for people with dementia face a variety of challenges that can seriously compromise their own well-being. Investigators have found that a personalized intervention consisting of home visits, structured telephone support sessions, and telephone "check-ins" can significantly improve the quality of life for caregivers of Alzheimer's disease patients. The study is the first randomized, controlled trial to look at the effectiveness of an Alzheimer's disease caregiver support intervention for ethnically diverse populations. Follow-up studies are needed to examine how this intervention might be used through existing community health service networks.

- For more information, see <http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20061120caregiverQOL.htm>
- (E) (NIA, NINR)

**NIH Pain Consortium:** The aims of the NIH Pain Consortium are to enhance pain research and promote collaboration among researchers across the many NIH Institutes and Centers that have programs and activities addressing pain. The consortium held its second annual symposium, *Advances in Pain Research*, on May 1, 2007, to feature new and exciting advances in pain research and pain management. Topics included neuropathic pain, visceral pain, inflammatory pain, and treatment-induced pain. Topics included NIH and extramural scientific communities, health care providers, and the public. Consortium ICs also issued an NIH-wide Funding Opportunity Announcement, "Mechanisms, Models, Measurement, and Management in Pain Research," to encourage pain research and delineate cross-cutting NIH interests in pain.

- For more information, see <http://videocast.nih.gov/PastEvents.asp>
- For more information, see <http://painconsortium.nih.gov/index.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NIDCR, CC, FIC, NCCAM, NCI, NCCR, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIGMS, NIMH, NINDS, NINR, OBSSR, OD, ODP/ORD, ORWH, OTT)

**Behavioral Strategies to Improve Quality of Life and Chronic Disease Outcomes:** As health care advances continue to transform previously acute conditions into chronic conditions and individual life expectancy is increasing, issues of quality of life have become ever more important. Studies focusing on the management of disease- and treatment-related symptoms have demonstrated the capacity for behavioral strategies to mitigate the effects of symptoms and contribute to improving short- and long-term patient outcomes. For example, behavioral strategies have been shown to improve patient outcomes across various diseases, including diabetes, irritable bowel syndrome, and asthma. In recognition of the need for new behavioral

strategies to manage chronic illness, NIH has established a goal to develop and test, by 2012, at least two behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes. Beginning in FY 2008, progress toward achieving this goal will be updated annually in the NIH section of the President's budget submission in a report on NIH GPRA responsibilities.

- For more information, see <http://officeofbudget.od.nih.gov/ui/HomePage.htm>
- (E) (NINR, NCI) (GPRA Goal)

**Acupuncture for Osteoarthritis of the Knee:** Clinical trials supported by NIH and others suggest that acupuncture may have a useful role in treating a variety of chronic painful conditions, hypertension, and obesity. For example, in 2006 NIH-funded investigators reported findings from the longest, largest, randomized, controlled clinical trial of acupuncture ever conducted. The results demonstrated that acupuncture is an effective adjunct to conventional treatment for osteoarthritis, the most common form of arthritis and a major cause of pain, limitation of activity, and health care utilization among the elderly. Study subjects receiving acupuncture had significantly reduced disability and improved quality of life. The innovative trial design resulted from an interdisciplinary collaboration of rheumatologists, licensed acupuncturists, and biostatisticians, ensuring that the research methodology was scientifically sound and accurately reflected acupuncture as traditionally practiced.

- [Manheimer E. et al. \*Acupunct Med\* 2006;24:S7-14](#), PMID: 17308513
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA):** This 5-year clinical study's longitudinal design will greatly accelerate the identification of better treatments to control the pain of temporomandibular muscle and joint disorders. The OPPERA study marks one of the first prospective clinical studies of a chronic pain disorder. A prospective study is the "gold standard" of medical research: it looks forward in time, monitoring the health of those in the study over several years to track the onset or progression of a disease. With the study's 5-year vantage point, investigators will begin identifying individual genetic, physiologic, and psychological factors that cause or contribute to temporomandibular muscle and joint disorders and advance virtually all aspects of understanding and caring for these disorders.

- For more information, see [http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/Archived/News\\_Releases/NRY2005/PR12052005.htm](http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/Archived/News_Releases/NRY2005/PR12052005.htm)
- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/InterviewsOHR/TIS012006.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDCR)

**Spine Patient Outcomes Research Trial (SPORT):** Before SPORT, many patients with back pain were conflicted about whether to undergo surgery. Now, people who have back pain due to a herniated disc can be assured that a surgical procedure called lumbar discectomy is generally effective in relieving pain from herniated discs, but, if their pain is tolerable, their symptoms will probably subside, even without surgery, over time. On the other hand, if a patient has

spondylolisthesis with stenosis, they are likely to benefit more from decompression and fusion surgery than from nonoperative treatments.

- [Weinstein JN, et al. JAMA. 2006;296:2441-50](#), PMID: 17119140
- [Weinstein JN, et al. JAMA. 2006;296:2451-9](#), PMID: 17119141
- [Weinstein JN, et al. N Engl J Med. 2007;356:2257-70](#), PMID: 17538085
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/backpain\\_surgery.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/backpain_surgery.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Press\\_Releases/2007/06\\_28.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/06_28.asp)
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIAMS, NIOSH, ORWH)

## NIH Strategic Plans Pertaining to Chronic Diseases and Organ Systems

### National Heart Lung and Blood Institute (NHLBI)

- [NHLBI Strategic Plan: Shaping the Future of Research](#)

### National Cancer Institute (NCI)

- [NCI Strategic Plan for Leading the Nation](#)

### National Institute of Dental and Craniofacial Research (NIDCR)

- [NIDCR Strategic Plan](#)
- [NIDCR Implementation Plan](#)

### National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

#### *Strategic Plans:*

- [National Diabetes Education Program \(NDEP\) Strategic Plan](#)
- [Overcoming Bladder Disease—A Strategic Plan for Research](#)
- [Renal Disease Research Plan](#)
- [Strategic Plan for Polycystic Kidney Disease](#)
- [Strategic Plan of the National Kidney Disease Education Program \(NKDEP\)](#)
- [Strategic Plan for Pediatric Urology: The Strategic Plan for Pediatric Urology, NIDDK—Research Progress Report](#)

#### *Reports from Planning Activities:*

- [Clinical Research on Kidney Disease](#)
- [NIDDK Annual Compendium of Recent Advances and Emerging Opportunities](#)
- [Progress Report on NIDDK Efforts to Promote Translational Research](#)
- [Research Needs in Pediatric Kidney Disease—2000 and Beyond](#)
- [Strategic Planning for Polycystic Kidney Disease](#)
- [Urolithiasis Research Symposium](#)
- [Long-Range Research Plan for Digestive Diseases](#) (expected to be completed in 2008)

**National Institute of Allergy and Infectious Diseases (NIAID)**

- [\*NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis \(2001\)\*](#)
- [\*Vaccine Research Center Strategic Plan: Research Toward Development of an Effective AIDS Vaccine \(2001\)\*](#)
- [\*NIAID Plan for Research on Immune Tolerance \(1998\)\*](#)
- [\*NIH Action Plan for Transplantation Research \(2007\)\*](#)

**National Eye Institute (NEI)**

- [\*National Plan for Eye and Vision Research \(2004\)\*](#)
- [\*Vision Research—A National Plan 1999-2003: A Report of the National Eye Advisory Council\*](#)
- [\*Progress in Eye and Vision Research 1999-2006\*](#)
- [\*Ocular Epidemiology Strategic Planning Panel Report—Epidemiological Research: From Populations Through Interventions to Translation \(2007\)\*](#)
- [\*Age-Related Macular Degeneration Phenotype Consensus Meeting Report\*](#)
- [\*Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration Workshop Report\*](#)

**National Institute on Aging (NIA)**

- [\*Living Long and Well in the 21st Century: Strategic Directions for Research on Aging\*](#)

**National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**

- [\*NIAMS Long-Range Plan: Fiscal Years 2006-2009\*](#)

**National Institute of Mental Health (NIMH)**

- [\*NIMH Strategic Plans and Priorities\*](#)
- [\*Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research\*](#)
- [\*Pathways to Health: Charting the Science of Brain, Mind, and Behavior\*](#)

**National Institute on Drug Abuse (NIDA)**

- [\*NIDA Draft Strategic Plan\*](#)

**National Institute on Alcohol Abuse and Alcoholism (NIAAA)**

- [\*National Institute on Alcohol Abuse and Alcoholism Five Year Strategic Plan FY08-13\*](#)

**Recommendations of the NIAAA Extramural Advisory Board (EAB):**

- [\*Developing an NIAAA Plan for HIV-Related Biomedical Research\*](#)
- [\*Fetal Alcohol Spectrum Disorders Research\*](#)
- [\*Mechanisms of Alcohol Addiction\*](#)
- [\*Mechanisms of Behavioral Change\*](#)

**National Institute of Nursing Research (NINR)**

- [\*NINR Strategic Plan: Changing Practice, Changing Lives\*](#)

**National Center for Complementary and Alternative Medicine (NCCAM)**

- [Expanding Horizons of Health Care: Strategic Plan 2005-2009](#)

**John E. Fogarty International Center (FIC)**

- [Pathways to Global Health Research](#) (Draft)

**Office of AIDS Research (OAR)**

- [FY 2008 Trans-NIH Plan for HIV-Related Research](#)

**Office of Dietary Supplements (ODS)**

- [Promoting Quality Science in Dietary Supplement Research, Education, and Communication: A Strategic Plan for the Office of Dietary Supplements, 2004-2009](#)

**Trans-NIH Strategic Plans**

- [Strategic Plan for NIH Obesity Research](#)  
(CSR, DNRC, FIC, NCCAM, NCI, NCMHD, NCRR, NHGRI, NHLBI, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDA, NIDCR, NIDDK, NIEHS, NIMH, NINDS, NINR, OBSSR, ODP, ODS, ORWH, OSP)
- [Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan](#)  
(CSR, NCCAM, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)
- [Action Plan for Liver Disease Research](#)  
(CSR, FIC, NCCAM, NCI, NCRR, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCR, NIDDK, NIEHS, NIGMS, NINDS, NINR, NLM)
- [NIH Action Plan for Transplantation Research \(2007\)](#)  
(NCI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NIDA, NIDCR, NIDDK, NIMH, NINDS)

## Detailed Burden of Illness and Related Health Statistics

The following summary illustrates the depth and breadth of chronic disease burden (all statistics refer to the U.S. population unless otherwise specified):

### Cardiovascular Diseases<sup>63</sup>

#### *Coronary heart disease*

Mortality: 452,000 (2004)

Prevalence: 15.8 million (2004)

#### *Heart failure*

Mortality: 58,000 (2004)

Prevalence: 5.2 million (2004)

#### *Arrhythmias*

Prevalence: >2 million with atrial fibrillation

#### *Congenital heart defects*

Incidence: 8 of every 1,000 newborns (35,000 per year)

Prevalence: 1 million adults

#### *Peripheral arterial disease*

Prevalence: 8-12 million

### Lung Diseases<sup>64</sup>

#### *Chronic obstructive pulmonary disease*

Mortality: 120,000 (2004)

Prevalence: 12 million people diagnosed; additional 12 million undiagnosed (2004)

#### *Asthma*

Mortality: 4,000 (2004)

Prevalence: 22 million (2004)

Total costs (direct and indirect): \$12.7 billion (1998)

#### *Cystic Fibrosis*

Prevalence: 30,000

Incidence: 1 in every 3,000 newborns

### Diabetes Mellitus<sup>65</sup>

Mortality: 224,092 (2002); 6th leading cause of death

Prevalence: 20.8 million (diagnosed and undiagnosed); type 1 diabetes accounts for 5-10% of diagnosed cases (2005)

Total costs (direct and indirect): \$132 billion (2002)

### Obesity<sup>66</sup>

Prevalence: 34.1 percent of adults are overweight; 32.2% adults are obese; 18.8% children (aged 6-11) and 17.4% adolescents (aged 12-19) are overweight (2004)

Total health care costs (direct and indirect): \$117 billion (2000)

### Chronic Kidney Disease<sup>67</sup>

Prevalence: 3.83% adults (7.7 million people) (1999-2000)

Costs: \$32.5 billion for treating end-stage renal disease (ESRD) (2004)

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<sup>63</sup> For more information, see <http://www.nhlbi.nih.gov/about/factbook/toc.htm> (chapter 4. Disease Statistics); <http://www.nhlbi.nih.gov/health/dci/index.html>

<sup>64</sup> For more information, see <http://www.nhlbi.nih.gov/about/factbook/toc.htm> (Chapter 4, Disease Statistics); <http://www.nhlbi.nih.gov/health/dci/index.html>; Weiss KB. *J Allergy Clin Immunol.* 2001;107:3-8, PMID: 11149982

<sup>65</sup> For more information, see [http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2005.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf)

<sup>66</sup> For more information, see <http://win.niddk.nih.gov/statistics/index.htm>; Ogden CL et al. *JAMA* 2006;295:1549-55, PMID: 16595758

<sup>67</sup> For more information, see <http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/index.htm>



**Urologic Diseases<sup>68</sup>*****Benign prostatic hyperplasia***

Prevalence: 6.5 million Caucasian men aged 50-79 (2000)

Cost (direct): \$1.1 billion (2000)

***Painful bladder syndrome/interstitial cystitis***

Prevalence: 0.8% of women (1.2 million) and 0.1% of men (0.08 million) (1988-1994)

Cost (direct): \$65.9 million (2000)

***Kidney stones***

Prevalence: 5% of adults (1988-1994)

Cost: \$2.07 billion (2000)

***Urinary incontinence***

Prevalence: 38% of women and 17% of men, aged 60 and older (1999-2000)

Cost (direct): \$463.1 million

***Urinary tract infection***

Prevalence: 34% of adults (62.7 million) self-reported at least one occurrence (1988-1994)

Cost (direct): \$3.5 billion (2000)

**Digestive Diseases<sup>69</sup>**

Mortality: 234,000 (2002)

Prevalence: 60-70 million people (1996)

Disability: 1.9 million people unable to perform daily activities (1990-1992)

Costs: \$85.5 billion (direct); \$20 billion (indirect) (1998)

**Chronic Liver Disease<sup>70</sup>*****Chronic liver disease or cirrhosis***Mortality: 27,013; 12<sup>th</sup> leading cause of death (2004)

Prevalence: 5.5 million people (2-3% of adults) (1998)

Cost (direct and indirect): \$1.6 billion (1998)

***Gallbladder disease***

Mortality: 3,086 (2004)

Prevalence: 12% of adults (20 million) (1998)

Cost: \$6 billion (1998)

***Viral hepatitis***

Mortality: 5,000 (Hepatitis B); 8,000-10,000 (Hepatitis C)

Prevalence: 1.25 million (Hepatitis B); 3.2 million (Hepatitis C) with chronic infection (1999-2002)

***Alcoholic liver diseases***

Mortality: 12,201 (2001)

Years of potential life lost (YPLL): 316,321 (2001)

**Blood Diseases<sup>71</sup>*****Sickle cell disease***

Prevalence: 70,000; 1 in 500 African American births; 1 in 1,000-1,400 Hispanic-American births

***Thalassemia (includes Cooley's anemia)***

Prevalence: 1,000

***Hemophilia***

Prevalence: 18,000

Incidence: 400 newborns each year<sup>1</sup>**Musculoskeletal Diseases<sup>72</sup>*****Osteoarthritis***<sup>68</sup> For more information, see <http://kidney.niddk.nih.gov/statistics/uda/index.htm>;<http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/index.htm><sup>69</sup> For more information, see <http://digestive.niddk.nih.gov/statistics/statistics.htm><sup>70</sup> For more information, see [http://www.cdc.gov/nchs/data/nvsr/nvsr55/nvsr55\\_19.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr55/nvsr55_19.pdf);[http://www.cdc.gov/ncidod/diseases/hepatitis/resource/dz\\_burden.htm](http://www.cdc.gov/ncidod/diseases/hepatitis/resource/dz_burden.htm);<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm>; Minino AM, et al. *National Vital Statistics Report 2007*;55:1-119, PMID: 17867520; Sandler RS, et al. *Gastroenterology* 2002;122:1500-1511, PMID: 11984534<sup>71</sup> For more information, see <http://www.nhlbi.nih.gov/health/dci/index.html>; <http://www.cdc.gov/ncbddd/hbd/thalassemia.htm><sup>72</sup> For more information, see [http://www.niams.nih.gov/Health\\_Info/Osteoarthritis/default.asp](http://www.niams.nih.gov/Health_Info/Osteoarthritis/default.asp);[http://www.niams.nih.gov/Health\\_info/Bone/default.asp](http://www.niams.nih.gov/Health_info/Bone/default.asp); <http://nihseniorhealth.gov/osteoporosis/toe.html>

	<p>Prevalence: 12.1% of adults (21 million)</p> <p><b>Osteoporosis</b> Prevalence; 10 million adults, 80% of whom are women; 34 million have low bone mass Disability: &gt;1.5 million fractures Costs (direct): \$14 billion</p> <p><b>Osteogenesis Imperfecta</b> Prevalence: 20,000-50,000</p> <p><b>Paget's disease of bone</b> Prevalence: 1 million</p>
<b>Skin Diseases and Conditions</b> <sup>73</sup>	<p>Prevalence: At any given time, 1 in 3 people has a skin disease. Total health care costs: &gt;\$34.3 billion (2003)</p> <p><b>Atopic dermatitis</b> Prevalence: &gt;15 million Costs (to health insurance companies): &gt;\$1 billion</p>
<b>Eye Diseases</b> <sup>74</sup>	<p><b>Age-related macular degeneration</b> Prevalence: 1.75 million; leading cause of vision loss in persons age 65 or older (2004)</p> <p><b>Uveitis</b> Prevalence: 115.3 cases per 100,000 persons (2004) Disability: 30,000 new cases of blindness (1990)</p> <p><b>Diabetic retinopathy</b> Prevalence: 4.1 million adults aged 40 or older (2004)</p> <p><b>Glaucoma</b> Prevalence: 2.2 million</p>
<b>Deafness</b> <sup>75</sup>	<p><b>Hearing loss</b> Prevalence: 2-3 of 1,000 newborns; 15% (32.5 million) adults; 10% (22 million) adults aged 20-69 suffer hearing damage due to noise exposure</p> <p><b>Otitis media (middle ear infection)</b> Cost: \$5 billion</p> <p><b>Balance and dizziness</b> Prevalence (balance): 4% (8 million) Prevalence (dizziness): 1.1% (2.4 million) Cost: \$8 billion for falls by older adults</p>
<b>Dental and Craniofacial Disorders</b> <sup>76</sup>	<p><b>TMJ disorder</b> Prevalence: 5-12% of the population; twice as prevalent in women as men</p> <p><b>Chronic periodontitis</b> Prevalence: 80% of adults with 1 in 5 having severe periodontitis</p>
<b>Mental Illness</b> <sup>77</sup>	<p><b>Mental disorders</b> Prevalence: 6% of adults (approximately 12.5 million) have a serious mental disorder Disability: No. 1 leading cause; accounts for 29.6% of all disability adjusted life years (DALYs) (U.S. and Canada) Cost: \$63 billion lost to decreased productivity</p> <p><b>Depression</b> Prevalence: 2% of adults (approximately 4.4 million) have a serious depressive disorder Disability: leading cause among mental health disorders; accounts for 11.2% of all DALYs (U.S. and Canada) Cost: \$36.2 billion due to lost work; \$51.5 billion including lost productivity while at work</p>

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<sup>73</sup> For more information, see [http://www.niams.nih.gov/Health\\_Info/Atopic\\_Dermatitis/default.asp](http://www.niams.nih.gov/Health_Info/Atopic_Dermatitis/default.asp)

<sup>74</sup> Friedman DS, et al. *Arch Ophthalmol* 2004;122:564-72, PMID: 15078675; Gritz DC, Wong IG. *Ophthalmol* 2004;111:491-500, PMID: 15019324; Nussenblatt RB. *Int Ophthalmol* 1990;14:303-8, PMID: 2249907; Kempen JH et al. *Ophthalmol* 2004;122:552-63, PMID: 15078674; Friedman DS, et al. *Arch Ophthalmol* 2004;122:532-8, PMID: 15078671

<sup>75</sup> For more information, see <http://www.nidcd.nih.gov/health/hearing/>; <http://www.nidcd.nih.gov/health/balance/>

<sup>76</sup> For more information, see <http://www.nidcr.nih.gov/HealthInformation/StatisticsandData.htm>

<sup>77</sup> For more information, see [http://www.who.int/whr/2004/annex/topic/en/annex\\_3\\_en.pdf](http://www.who.int/whr/2004/annex/topic/en/annex_3_en.pdf); <http://www.mentalhealthcommission.gov/reports/FinalReport/toc.html>; Kessler RC, et al. *Arch Gen Psych* 2005;62:617-27, PMID: 15939839; Greenberg PE, et al. *J Clin Psychiatry* 2003;64:1465-75, PMID: 14728109

**Alcohol Use Disorders**<sup>78</sup>

*Alcohol use disorders*

Prevalence: 18 million (8.5% of the population aged 18 or older)

*Alcohol-attributable chronic disease*

Total costs: \$122 billion (est.)

Disability: Alcohol use is the 7th leading cause of DALYs

**Addiction**<sup>79</sup>

Total cost: >\$500 billion (est.; includes health- and crime-related costs as well as losses in productivity)—approximately \$181 billion for illicit drugs, \$168 billion for tobacco, and \$185 billion for alcohol.

*Abuse or dependence on alcohol and illicit drugs*

Prevalence: 22.2 million people or 9.1% of the population aged 12 or older (est.) (2005)

*Cigarette smoking*

Mortality: 440,000 (2002)

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<sup>78</sup> For more information, see <http://pubs.niaaa.nih.gov/publications/economic-2000/alcoholcost.PDF>; <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm>; Grant BF, et al. *Arch Gen Psychiatry* 2004;61:807-16, PMID: 15289279; Michaud et al. *Population Health Metrics* 2006;4:11, PMID: 17049081

<sup>79</sup> For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm>; <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5425a1.htm>; Office of National Drug Policy. The Economic Costs of Drug Abuse in the United States: 1992-2002. Washington, DC: Executive Office of the President (Publication No. 207303); <http://www.oas.samhsa.gov/NSDUH/2k5NSDUH/2k5results.htm>; <http://www.cdc.gov/MMWR/preview/mmwrhtml/mm5114a2.htm>



## LIFE STAGES, HUMAN DEVELOPMENT, AND REHABILITATION

*In 1961, Dr. Robert Guthrie, a pediatrician and microbiologist, developed a simple test, using a “heel-stick” drop of blood, to detect phenylketonuria (PKU) in newborn infants. This rare, inherited disease interferes with the body’s capacity to metabolize protein. Unless treated almost immediately with a special diet, PKU progressively derails a child’s intellectual development. Children with untreated PKU may appear healthy as newborns, but by age 3 to 6 months, they begin to lose interest in their surroundings, and by 1 year of age, their intellectual function is irreversibly impaired. Dr. Guthrie’s discovery has allowed for rapid, inexpensive screening of all infants at birth. Those identified with PKU can be started on the preventive diet and escape the disorder’s permanent damaging effects. Building on Dr. Guthrie’s discovery, NIH-supported scientists developed an additional newborn screening test, this time for congenital hypothyroidism. Like PKU, this condition may not be apparent at birth, but unless simple preventive treatment begins almost immediately in affected infants, irreversible damage to the developing brain occurs within months. All states now mandate newborn PKU and hypothyroidism screening, and the developmental disability associated with these two disorders has all but disappeared in the United States.*

### Introduction

From before conception through old age, complex biological processes interacting with physical and psychosocial factors in an environment determine health and functioning at any given life stage and provide the foundation of the next stage. NIH research in this area encompasses the formation and development of cells, tissues, organs and organ systems, as well as the physical, cognitive, and behavioral characteristics of the child, adolescent, and adult in his or her environment. Although developmental processes proceed most rapidly in gestation and the early years of childhood, they continue throughout the course of life.

This area of research includes studies of normative processes of growth, maturation, and aging. Understanding “what goes right” developmentally at each life stage is critical to discovering how to protect and enhance human health and functioning. Knowledge from such normative research also is essential to understanding the role of developmental vulnerabilities in the origins, expression, prevention, and treatment of illness and injury. For example, understanding the normal brain immaturity of adolescents is essential to understanding aberrant behaviors of youth and developing interventions that will work for them. Similarly, understanding normal, progressive maturation and functional decline in relation to disease processes is key to discovering better interventions to extend healthy active years of life. At all life stages, normative data on physical and psychosocial development are critical to designing effective rehabilitative interventions.

Individuals may experience underdeveloped, lost, damaged, or deteriorated function during any of the life stages. Medical rehabilitation research is the study of physiologic mechanisms, methods of treatment, and devices that serve to improve, restore, or replace these functions. This research includes translating new knowledge into medical, behavioral, psychological, social,

and technological interventions to optimize impaired functioning. A key aspect of medical rehabilitation research is its focus on the effects of functional impairment on the whole person, rather than on a single organ system. Thus, it views the person in the context of a system of interacting variables, including psychosocial, organic, and environmental.

By necessity, the scope of NIH research on life stages, human development, and rehabilitation is broad. Dynamic, ongoing interactions among developmental processes and physical and psychosocial environmental factors are implicated in a wide range of disorders and disabilities. Research in this area includes basic, clinical, epidemiological, and translational studies of normative processes and of many chronic diseases such as cancer, obesity, osteoporosis, and cardiovascular and metabolic disorders. Also included is research on mental illness, including addiction, and cognitive disabilities such as intellectual disability, autism, and Alzheimer's disease. Whereas the section "Chronic Diseases and Organ Systems" in this report addresses these conditions generally, this section focuses on life stage and developmental dimensions of chronic and other conditions and on rehabilitative interventions.

NIH Institutes dedicated to specific disorders and organ systems incorporate life stages and developmental perspectives into their research initiatives and projects. For example, NCI supports research on how cancer risk and therapies may differ in children, adults, and the elderly. Among NIDCR's research priorities are studies of genetic and environmental interactions that may explain disfiguring birth defects of the head, face, and mouth. NINR and NIAAA strategic plans incorporate a life-course approach.

As the Institute with statutory responsibility for child health and human development research, NICHD conducts and supports research programs in reproductive health and the developmental processes that begin before conception and continue through gestation, birth, infancy, childhood, and adolescence. As the Institute charged with research on aging, NIA conducts and supports research on both the maintenance and loss of functions during the aging process, diseases associated with aging, and the problems and needs of older individuals and their caregivers. NINR conducts research focused on establishing a scientific basis for patient care across all life stages and is designated the lead NIH Institute for end-of-life research. NIEHS focuses on the influences of environmental agents on the development and progression of human disease.

Mission-specific rehabilitation research is supported by 18 Institutes, including NIA, NIBIB, NICHD, NIDCR, and NINDS. A focal point for this area is the National Center on Medical Rehabilitation Research, within NICHD, which emphasizes the rehabilitation and lifelong care of people with physical disabilities resulting from injury, stroke, and other disorders.

## **Burden of Illness and Related Health Statistics**

Because of the wide range of disorders studied in NIH life stages, human development, and rehabilitation research, data on the health and economic costs of specific conditions are presented throughout this report. This section presents selected examples of general data on lifetime burdens of illness and on burdens at the beginning and later stages of life.



### ***Lifetime Burden***

From birth to death, per-person health care costs in the United States have been estimated to average \$316,579 in 2000 dollars. Of this total, an estimated 7.8 percent of health care costs accrue from birth to age 20, 12.5 percent between ages 20 and 39, 31.0 percent between ages 40 and 64, and 48.6 percent, or almost half of all lifetime health care expenditures, after age 65.<sup>80</sup> Between 1992 and 1996, 22 percent of all medical expenditures for the period after age 65 occurred in the last year of life.<sup>81</sup> Although rates of self-reported disability in people age 65 and older have been declining in recent years, any cost savings from this trend may be offset by the burgeoning growth of this population as a proportion of U.S. residents.<sup>82</sup> Between 2000 and 2050, the proportion of this older population is expected to increase from 5.9 percent to 11.6 percent of U.S. residents.

### ***Early Origins of Disease and Disability***

Preterm birth and the associated problem of low birth weight signal the potential for significant developmental problems that may originate in the prenatal period, or even before, as a result of a family's genetic makeup and its environmental exposures.<sup>83</sup> Preliminary data indicate that in 2004-2005, 12.7 percent of U.S. births were preterm, a rate that has risen 20 percent since 1990. Infants born with low birth weight in 2005 comprised 8.2 percent of births, an increase of more than 20 percent since the mid-1980s.<sup>84</sup>

Although medical advances and supportive environments enable increasing numbers of preterm infants to survive and to "catch up" developmentally in childhood, the health and economic burdens associated with these births begin immediately and may last a lifetime. In 2001, costs for preterm, low-birth-weight hospital admissions were \$5.8 billion in the United States, or 47 percent of the costs of all hospital stays of infants.<sup>85</sup> Preterm birth accounts for one of five children with intellectual disability, one of three children with vision impairment, and almost half of children with cerebral palsy. For an individual with intellectual disability, lifetime costs of medical care, special education, residential care, lost wages, and other associated expenditures are estimated to be \$1,014,000 in 2003 dollars.<sup>86</sup>

### ***Later Emergence of Disease and Disability***

Aging comprises a set of dynamic biological, physiological, and psychosocial processes and systems that are interactive and independent and that result in wide variations in health outcomes and functioning. For some individuals, sensory, cognitive, and physical capacities continue at remarkably high levels for decades. For others, increasing age is accompanied by a significant, progressive decline in almost all physiological functions and a significantly increased risk of

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<sup>80</sup> [Alemayehu B, Warner KE. \*Health Serv Res.\* 2004;39:627-42](#), PMID: 15149482

<sup>81</sup> [Hoover DR et al. \*Health Serv Res.\* 2002;37:1625-42](#), PMID: 12546289

<sup>82</sup> [Freedman VA et al. \*JAMA.\* 2002;288:3137-46](#), PMID: 12495394

<sup>83</sup> [Drake, AJ, Walker BR. \*J Endocrinol.\* 2004;180:1-16](#), PMID: 14709139

<sup>84</sup> For more information, see <http://www.cdc.gov/nchs/products/pubs/pubd/hestats/prelimbirths05/prelimbirths05.htm>

<sup>85</sup> [Russell, RB et al. \*Pediatrics\* 2007;120:e1-e9](#), PMID: 17606536

<sup>86</sup> For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5303a4.htm>

age-related chronic diseases and disability. Recent estimates indicate that approximately 80 percent of all individuals in the United States who are 65 years or older have at least one chronic condition, and 50 percent have at least two.<sup>87</sup>

The marked variability among older adults in aging processes and disease burden may be explained in part by risks incurred in earlier decades. For example, periods of rapid tissue growth in gestation, early childhood, adolescence, and during pregnancy may be periods of heightened risk to later-emerging cancers.<sup>88</sup> Low birth weight is related to increased risk in adults for cardiovascular disease, such as myocardial infarction, stroke, and hypertension.<sup>89</sup> Maternal diabetes during pregnancy may increase the risk of diabetes and obesity in offspring.<sup>90</sup> Prenatal influences also may increase risks of osteoporosis<sup>91</sup> and Alzheimer's disease.<sup>92</sup> In each case, discovering effective interventions at early stages in life could contribute to lower burdens of disease and disability associated with aging.

## **NIH Funding for Life Stages, Human Development, and Rehabilitation Research**

In FYs 2006 and 2007, NIH funding for rehabilitation research was \$324 million and \$344 million respectively. Currently, NIH does not collect trans-NIH funding data on the category of life stages and human development research. The table at the end of this chapter indicates some of the research areas involved in this investment (see “Estimates of Funding for Various Diseases, Conditions, and Research Areas”).

### **Summary of NIH Activities**

The goal of life stages, human development, and rehabilitation research is to enable people to achieve a full lifespan with the best health and function at every life stage. Understanding complex developmental pathways to health or illness throughout life is critical to creating new ways to prevent disease and disability before they become symptomatic—or even preempting the disease process before it starts. Developmental stages also are an important consideration in rehabilitation research. For example, differences between age groups such as physical size, physiological processes, psychosocial trajectories, and expected lifespan must be taken into account in planning rehabilitation for an individual. A central goal of research is to provide the scientific evidence needed to support developmentally appropriate rehabilitation plans.

The fundamental concepts of developmental science, such as “developmental windows,” can be brought to bear whether a research project focuses primarily on normative development, multiple life stages, a specific life stage, or rehabilitation. These “windows” are periods in the

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<sup>87</sup> For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a2.htm>

<sup>88</sup> Potischman N, et al. The life course approach to cancer epidemiology. In: A life course approach to chronic disease epidemiology, Second Edition. Kuh D, Ben-Shlomo Y (eds). Oxford University Press, New York, 2004, p. 260-80.

<sup>89</sup> Rich-Edwards JW, et al. *BMJ* 1997;315:396-400, PMID: 9277603

<sup>90</sup> Dabelea D, Pettitt DJ. *J Pediatr Endocrinol Metab* 2001;14:1085-91, PMID: 11592564

<sup>91</sup> Javaid MK, Cooper C. *Best Pract Res Clin Endocrinol Metab* 2002;16:349-67, PMID: 12064897

<sup>92</sup> Basha MR et al. *J Neurosci*. 2005;25:823-9, PMID: 15673661

life of a cell, a fetus, a child, or an adult when the normal processes of growth and maturation may be more sensitive to the effects of external factors, often referred to as “environmental influences.” Because human development progresses in a multifaceted environment, scientists study a wide range of external factors that could have adverse or protective effects on human health and functioning. This research might examine the effects of physical agents such as, for example, diet, exercise, pesticides, industrial chemicals, or mold. But it also might investigate the influences on health and development of factors such as parenting styles, family structure, education, community social norms and economic status, and/or intergenerational influences.

## **Normative Research**

Scientists’ efforts to identify and understand interactions among developmental processes and external factors are being accelerated by powerful new technologies. For example, advanced imaging technologies are being used to create a robust database of normal brain development during childhood and adolescence. The resulting data will enable scientists to better understand the atypical developmental processes associated with autism, intellectual disability, and other developmental disorders. Novel analytic techniques developed in genomics research have created new research opportunities in the emerging field of epigenetics. This new field builds on discoveries that the timing of gene functions—the “on” and “off” switches that control myriad biological processes—can be altered without changing the structural DNA “coding” of a gene. The health effects of these subtle and potentially reversible alterations may be transient or may persist and even be passed down from parent to child. One new NIH initiative in developmental epigenetics focuses on alterations in gene expression that may occur spontaneously or in response to environmental exposures well before birth. Multiple initiatives, comprising a [Roadmap Epigenomics Initiative](#), are intended to develop comprehensive reference maps of the epigenome and to develop new analytic technologies.

In other normative research, a long-term study of women before, during, and after menopause is designed to improve understanding of the health effects, psychosocial influences, and subsequent health consequences of this major life stage for women. Extended studies of older populations are enabling scientists to disentangle the effects of disease from the normal aging process.

Discoveries by NIH-supported scientists conducting normative research have enabled them to preempt the development of cleft palates in experimental mice that were bred to manifest this disabling defect. Having identified a protein that influences the development of certain undifferentiated cells in the embryo, scientists then identified the critical point in normal embryonic development of the palate, or roof of the mouth. They subsequently manipulated the protein at that point in development to reverse the initiation of the clefting process in the mice.

## **Multistage Research**

NIH research encompassing multiple developmental or life stages seeks to understand what factors early in life may contribute to health or to health risks in later life (see also the section “Epidemiological and Longitudinal Studies” in Chapter 3). This conceptual model builds on seminal “life course” studies that found clues to the origins of adult chronic diseases in the

earliest period of human life—gestation. The first life course studies linked the risk of heart disease, stroke, hypertension, and diabetes in adults to adaptation of the fetus to inadequate nutrient supply in utero.<sup>93</sup>

NIH research examples in this section illustrate how the life-course research model has expanded to include a greater number of developmental stages and a wider array of potentially influential environmental factors. For example, the [National Children's Study](#) (NCS) is designed to enroll women who intend to become pregnant and to follow their pregnancies and then their children from birth to age 21. Investigators will use multiple techniques to examine many aspects of the children's lives over time—from family genetics, to the constructed environment of neighborhoods and schools, to chemical exposures linked to the atmosphere, food, and water supplies. The overall NCS goal is to understand the relationships among multiple exposures and multiple health outcomes. NIH also is collaborating with the Norwegian National Public Health Institute in a long-term prospective cohort study of pregnant women and their children, in which a variety of exposure and health variables will be investigated.

Other studies encompassing more than one life or developmental stage investigate specific factors and/or specific health outcomes. For example, investigators within a consortium of NIH-supported research centers study a range of prenatal to adult environmental exposures that may predispose a woman to breast cancer. NIH-supported scientists use longitudinal studies, imaging and genetics tools, and animal studies to examine the contribution of in utero drug exposure to emotional and cognitive development and to vulnerability to later substance abuse and other mental disorders. Research on the long-term safety of fetal and infant exposure to anti-HIV (antiretroviral) drugs, administered to prevent HIV transmission from an infected woman to her child, is one of numerous NIH research efforts in HIV/AIDS. Cohorts of long-term cancer survivors, including those treated in childhood and at other life stages, are being followed to identify the health and developmental effects of cancer drugs and radiation treatments. Known adverse effects include damage to heart muscles; neurocognitive problems; reproductive health problems, including infertility; pain; and second malignancies, as well as anxiety and depression, discrimination in employment and insurance, and general quality of life. This “survivorship” research ultimately seeks to optimize physiological, psychosocial, and functional outcomes for cancer survivors and their families.

## **Stage-Specific Research**

NIH research that focuses on a single life stage seeks to understand the developmental vulnerabilities of that stage and their implications for risk of disease or disability and for effective interventions. For example, sensitivity of the rapidly developing fetus and the newborn to a variety of inborn and external risk factors is the subject of extensive NIH-supported research efforts. Included in this research are ongoing research programs on stillbirth, preterm birth, SIDS, fetal alcohol syndrome, and birth defects. In one study, scientists found that preterm infants could go home earlier from neonatal intensive care units if their parents received an educational and behavioral intervention that began shortly after their child's

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<sup>93</sup> [Barker DJP. \*Clin Sci \(Lond\)\*.1998;95:115-28](#), PMID: 9680492

admission to the unit and continued after the child went home. During the intervention, fathers as well as mothers learned about the appearance and characteristics of preterm infants and how best to parent their child. This research also found that the intervention lessened mothers' anxiety, depression, and overall parenting stress and increased fathers' involvement in infant care.

School-age children are an important research population because habits that can protect an individual's health, or increase his or her risk of later disease or disability, may be established in this developmental period. Examples of this research include testing a middle-school intervention to lower the risk of developing type 2 diabetes in children as they approach adolescence. Once considered an "adult" disease, type 2 diabetes increasingly is seen in children as rates of pediatric obesity continue to rise. To investigate the potential of the school environment to promote the adoption of long-term healthy behaviors, the experimental program is testing the effects of offering healthier food choices in school cafeterias and vending machines, lengthening and intensifying periods of physical activity, and deploying communication campaigns. In another example, scientists have developed a large body of evidence about how children learn to read and are now investigating differences in how children learn math and science. Research into learning processes for children both with and without learning disabilities permits the development of evidence-based teaching methods so that children with a range of abilities can learn these critical subjects. Major developmental disabilities in children, including intellectual disability and autism, also are the subject of ongoing research.

Adolescence, the developmental period in which the immature brain and teenage social contexts may explain risk-taking behaviors, is another focal point of life stages and human development research. Carefully designed studies on teen and college-age substance-abusing behaviors and teen driving are providing the scientific basis for new interventions. Studies of the unique challenges in clinical management of youth with HIV or at risk of infection, and of pharmacological therapies for young people with depression and suicide risk, are yielding important guidance for clinicians. Models for delivering needed services to youth with mental illness as they transition to adulthood are being tested.

Another significant area of stage-specific research encompasses the period in which couples start families. Reproductive health research includes expanding fundamental knowledge of processes that underlie human reproduction, investigating ways to alleviate human infertility, and developing and testing new contraceptive options for men and women. Basic, clinical, and translational studies aim to increase understanding of normal reproduction and reproductive pathophysiology and to develop more effective strategies for diagnosing, treating, and preventing conditions that compromise reproductive health. To advance research in this area, the NIH sponsors [training programs for reproductive health researchers, including obstetricians and gynecologists](#).

As individuals age, interactions among normal aging processes and risks acquired early in life and/or cumulatively over the course of life may heighten their vulnerability to disease and disability. For example, many conditions that emerge or worsen in aging individuals are characterized by inflammation, which leads over time to changes in cell tissue and organ structure and function. These changes may contribute to frailty, independent of overt disease,

and also may increase susceptibility to, and rate of progression in, chronic diseases. NIH-supported projects include studies of vascular inflammation and neurotoxicity in the aging brain and inflammatory response to loss of sleep. The breadth of NIH research in aging processes is illustrated by an initiative on the psychological mechanisms that guide economic decisions of older people and the underlying neurobiological pathways of their economic behaviors. End-of-life studies focusing on enhancing communications among individuals, families, and clinicians and on measuring care outcomes are intended to enable those involved to better manage this experience. An NIH [state-of-the-science conference on end-of-life care](#) and publication of conference proceedings were designed to survey and assess recent advances and to chart additional new directions for this area of research.

## **Rehabilitation Research**

Rehabilitative interventions to enable individuals to gain or recover functions lost to illness or injury may be needed at any life stage. Research in this area recognizes the need for specialized approaches for infants and children at the beginning of the developmental span, for mature adults, and for older people experiencing cumulative effects of normal aging processes and chronic disease. For example, the decline in disability among older people raises questions of whether and how this trend can be maintained or even accelerated. Enabling older people to maintain their health and independence for as long as possible is a major goal of NIH-supported rehabilitation research. Among efforts to reach that goal are projects that are developing and testing exercise and motor-learning interventions for adults who have experienced stroke, hip fracture, and other chronic debilitating diseases and conditions. An important priority in this research is translating findings from the clinical research setting into effective and accessible rehabilitative programs based in communities.

In other rehabilitation research, NIH-supported scientists are applying the newest technology to hasten recovery from and lessen disabling effects of disease and injury. Multiple research projects are focused on novel technologies to supplement or restore lost nervous system functions. Examples include studies to develop devices designed to restore the capacity of people with spinal cord injuries to stand and to control bowel and bladder function. Scientists also are investigating technologies to control seizures as well as brain-machine interfaces to allow persons with paralysis to control devices directly with their brains. To improve rehabilitation for upper-limb paralysis, NIH is supporting the development of robotic exoskeletons that could ultimately provide therapies for stroke patients in their homes and elsewhere. To expand the mobility of soldiers and others who have lost limbs to injury, NIH-funded research includes studies of a new “intelligent” artificial knee joint. Investigators also are developing ways to implant an artificial limb directly onto the bone of a residual limb, eliminating the need for irritation- and infection-prone socket devices. Even more technologically advanced options for replacing irretrievably injured body parts may one day result from pioneering research in tissue regeneration.



## Notable Examples of NIH Activity

### Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

### Normative Research

**Developmental Epigenetics:** This rapidly evolving area of research examines how nonstructural changes in gene expression during normal developmental processes can influence health outcomes across the generations. NIH is expanding its research in this area to help scientists learn how typical epigenetic changes and variations occur at the molecular level, starting well before birth. Understanding these epigenetic changes—how they are inherited and passed on to subsequent generations and what factors influence them—could hold the scientific key to understanding and modifying certain factors that lead to a number of diseases or conditions, from obesity to heart disease.

- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (I) (NICHD)

**Researchers Report Chemical Rescue of Cleft Palate in Mice:** A growing understanding of the multiple roles played by the enzyme GSK3 has enabled scientists to realize that this protein molecule has a role in determining the developmental fates of certain undifferentiated cells in the embryo. A few years ago, this realization led a team of scientists to develop a technique that prompts small molecules directly to turn GSK3 on and/or off with a high degree of precision at different stages of fetal development. In the March 1 issue of the journal *Nature*, NIH-supported scientists and their colleagues reported using this on-off technique to determine the critical developmental period of the palate, or roof of the mouth, in mice. Remarkably, the researchers showed that, by turning GSK3 back on in pregnant mice during this key developmental window, their embryos in most cases corrected their developing cleft palates. As they reported, five out of nine mouse pups had complete reversal of the developing cleft, and another newborn had a partial rescue of the cleft. As the authors noted, “New approaches to rescuing selected developmental defects require detailed knowledge of timing and levels of protein expression; our studies provide an improved method for defining these experimental conditions in vivo.”

- [Liu KJ, et al. \*Nature\* 2007;446:79-82](#), PMID: 17293880
- This example also appears in Chapter 3: *Molecular Biology and Basic Science*.
- (E) (NIDCR)

**MRI Study of Normal Brain Development:** Understanding healthy brain development is essential to finding the causes of many childhood disorders, including those related to intellectual and developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases. NIH is creating the Nation’s first database of MRI measurements and analytical tools, as well as clinical and behavioral data, to understand normal brain development in approximately 500 children from across the Nation. This large-scale longitudinal study uses several state-of-the-art

brain imaging technologies. The data will be disseminated as a Web-based, user-friendly resource to the scientific community.

- [Evans AC, et al. \*Neuroimage\*. 2006;30:184-202](#), PMID: 16376577
- For more information, see <http://www.bic.mni.mcgill.ca/nihpd/info/index.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NICHD, NINDS, NIDA, NIMH)

**Study of Normal Brain Development:** The NIH Intramural Research Program is conducting studies to explore brain development with MRI in healthy children and adolescents. Recent studies have addressed differences in brain structure related to risk for Alzheimer's disease and sex differences in brain development trajectories.

- [Shaw P, et al. \*Lancet Neurol\* 2007;6:494-500](#), PMID: 17509484
- [Lenroot RK, et al. \*Neuroimage\* 2007;36:1065-73](#), PMID: 17513132
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (NIMH)

**National Longitudinal Study of Adolescent Health (Add Health):** Several NIH Institutes are supporting this study, which integrates biomedical, behavioral, and social science data to discover the pathways that lead to health and/or disease in adulthood. The NIH initially funded Add Health in 1994 as a social science study of the causes of adolescent health problems and health-related behaviors. As the cohort of adolescents has moved into early adulthood, the study's focus has shifted to the environmental, behavioral, and biological pathways that lead to the development of adult chronic disease. The study initially incorporated measurements of social environments—peer groups, families, schools, and neighborhoods—that could affect health and also incorporated a sibling-pair design that facilitated quantitative genetic studies. Most recently, in collaboration with other Federal offices, NIH funded a new wave of interviews that will include the collection of genetic data and biological markers of disease processes, as well as basic social, individual, and behavioral data. The new design was developed by a collaborative team representing the fields of epidemiology, cardiology, psychology, sociology, behavioral genetics, nutrition, biostatistics, anthropology, medicine, molecular virology, statistics, and survey research.

- For more information, see <http://www.cpc.unc.edu/addhealth>
- (E) (NICHD, NCI, NCMHD, NIA, NIAID, NIDCD, NINR, NIAAA, NIDA, OAR, OBSSR, ORWH)

**Study of Women's Health Across the Nation (SWAN):** The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in ethnically diverse cohorts. Now in its 14th year, SWAN involves seven clinical field sites supported by a central reproductive hormone laboratory, a coordinating center, an advisory panel, and a repository of blood, urine, and DNA specimens. Used in numerous studies, SWAN data have resulted in important findings. For example, changes in bone density occur from premenopause through late perimenopause; premenopausal women have a significantly lower prevalence of forgetfulness than do women at later menopausal stages; and a high body mass index (BMI) is not only associated with insulin resistance, which

dramatically increases the risk of cardiovascular disease, but also with different menopausal hormonal patterns relative to normal BMI.

- (E) (NIA, NINR, NCCAM, NICHD, NIMH, ORWH)

**Baltimore Longitudinal Study of Aging (BLSA):** In 2008, NIA will celebrate the 50th anniversary of the BLSA, America's longest-running scientific study of human aging. More than 1,400 men and women ranging in age from the 20s to the 90s have been study volunteers. The BLSA has generated significant findings to elucidate the normal course of aging and disentangle the effects of disease from the normal aging process.

- For more information, see <http://www.grc.nia.nih.gov/branches/blsa/blsa.htm>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIA)

**Health and Retirement Study (HRS):** The HRS is the leading source of combined data on the health and financial circumstances of Americans over age 50 and is a valuable resource to follow and predict trends and help inform policies for an aging America. Now in its 14th year, the study follows more than 20,000 people at 2-year intervals and provides researchers with an invaluable, growing body of multidisciplinary data on the older Americans' physical and mental health, insurance coverage, finances, family support systems, work status, and retirement planning. Managed under a cooperative agreement between NIH and the University of Michigan, the study was expanded in 2006 to include additional key constructs in cognitive aging. A substudy will provide the first estimates of cognitive impairment and dementia based on nationally representative data and validation of survey measures. HRS staff will also assemble information on sample and questionnaire design, computer-assisted interview programming, interviewer performance, and data dissemination to improve the quality of data collected and provide an incentive for international partners to follow a harmonized design that will maximize the potential for cross-national behavioral and social research on aging.

- For more information, see <http://hrsonline.isr.umich.edu>
- (E) (NIA)

## **Life Stages Research**

**The National Children's Study (NCS):** The NCS promises to be one of the richest information resources available for answering questions related to children's health and development and will form the basis of child health guidance, interventions, and policy for generations to come. The landmark study will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. This extensive research effort will examine factors ranging from those in the natural and manmade environment to basic biological, genetic, social, and cultural influences. By studying children through their different phases of growth and development, researchers will be better able to understand the role of these factors in both health and disease. Specifically, NCS will identify factors underlying conditions ranging from prematurity to developmental disabilities, asthma, autism, obesity, and more. The study is led by a consortium

of Federal agencies, including NICHD and NIEHS, CDC, and the Environmental Protection Agency.

- For more information, see <http://www.nationalchildrensstudy.gov>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NICHD, NIEHS)

**Environmental Health of Mothers and Babies: the Norwegian Mother and Child Cohort Study:**

NIH is participating in the Norwegian Mother and Child Cohort Study, which provides a valuable opportunity to assess the role of environmental exposures in the health of women and their children. The Norwegian Mother and Child Cohort Study, or MoBa, (den norske Mor and barn-undersøkelsen) is an ongoing, long-term, prospective cohort study of 100,000 pregnant Norwegian women and their children. In collaboration with the Norwegian National Public Health Institute (NIPH), NIH is supporting the collection of additional biologic specimens from the pregnant women. These specimens will be used for the measurement of environmental exposures. A variety of exposure and health variables on babies, mothers, and fathers are collected. Records from the cohort study will also be linked to routine national health registries.

- For more information, see <http://www.niehs.nih.gov/research/atniehs/labs/epi/studies>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (NIEHS)

**The Role of Development in Drug Abuse Vulnerability:** NIH supports a number of longitudinal studies at various stages of development, following cohorts over extended time frames. Information is gathered on children's cognitive and emotional development, as well as their vulnerability to addiction later in life. These studies have been critical to estimate, for example, the contribution of in utero drug exposure on emotional and cognitive development, vulnerability to substance abuse, and other mental disorders. This knowledge, together with animal studies that provide complementary and validating information while minimizing the confounding factors that are likely to play a role in prenatal effects of drug exposure in humans, will help us to mitigate the deleterious impact of substance abuse on the developing fetus. With regard to later developmental stages, the application of modern brain imaging technologies has generated unprecedented structural and functional views of the dynamic changes occurring in the developing brain (from childhood to early adulthood). The discovery of these changes has been critical to understanding the role of brain development in decision-making processes and responses to stimuli, including early exposure to drugs. Such studies have suggested, for example, that an unbalanced communication between volitional control and emotional circuits may explain some of the impulsive reactions typical of adolescents, who tend to engage in risky behaviors and are at heightened risk for developing addictions. Collectively, these longitudinal studies, using new imaging and genetics tools, promise a greatly enhanced ability to interpret the effects of myriad environmental variables (e.g., quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics) on brain development and behavior.

- For more information, see [http://www.drugabuse.gov/NIDA\\_notes/NNvol19N3/Conference.html](http://www.drugabuse.gov/NIDA_notes/NNvol19N3/Conference.html)
- For more information, see [http://www.nida.nih.gov/NIDA\\_notes/NNvol19N3/DirRepVol19N3.html](http://www.nida.nih.gov/NIDA_notes/NNvol19N3/DirRepVol19N3.html)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDA, NICHD) (GPRA Goal)

**Transdisciplinary Tobacco Use Research Centers:** Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships.

- For more information, see <http://dcccps.nci.nih.gov/tcrb/tture>
- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI, NIDA, NIAAA)

**The Centers for Transdisciplinary Research on Energetics and Cancer (TREC):** These centers foster collaboration among transdisciplinary teams of scientists to accelerate progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet. The biology and genetics of the many factors that influence diet, physical activity, and obesity across the stages of life are applied to behavioral, sociocultural, and environmental factors, and transdisciplinary training opportunities are provided for scientists. The TREC initiative is interfacing with a number of established NCI initiatives in the area of diet, physical activity, and weight and is integrated with the NIH Obesity Research Task Force Strategic Plan.

- For more information, see <http://cancercontrol.cancer.gov/trec>
- (E) (NCI)

**HIV/AIDS Epidemiological and Long-Term Cohort Studies, Cohorts, and Networks:** NIH supports epidemiological HIV research through a wide range of studies, cohorts, and networks that contributes to our understanding of risk factors that lead to HIV transmission and disease progression. Established in 2005, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) compiles data from NIH-funded international HIV research to answer population-level questions about HIV variants and resistance, HIV pathogenesis in different settings, success of antiretroviral therapy, treatment history of HIV in different populations, success of prevention strategies, and vaccines. The Pediatric HIV/AIDS Cohort Study (PHACS) network, established in 2005, addresses two critical pediatric HIV research questions: (1) the long-term safety of fetal and infant exposure to prophylactic antiretroviral chemotherapy and (2) the effects of perinatally acquired HIV infection in adolescents. The Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) are the two largest observational studies of HIV/AIDS in women and homosexual or bisexual men, respectively, in the United States. These studies exceed the scope of clinical care diagnostics and laboratory analysis on both HIV-infected and, importantly, HIV-negative controls, which allows for novel research on HIV spread, how the disease progresses, and how it can best be treated. The groups focus on contemporary questions such as the interactions among HIV infection, aging, and long-term treatment; cardiovascular disease; and host genetics and its influence on susceptibility to infection, disease progression, and response to therapy.

- For more information, see <http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIAID, NICHD)



**Childhood Cancer Survivors Study (CCSS):** Although survival rates from childhood cancers are encouraging, researchers have found that these young survivors may particularly suffer from the late effects of treatment. In 2006, CCSS researchers documented serious long-term health issues in adults after radiation for childhood cancers. These findings will change treatment regimen guidelines for current childhood cancers and also have implications for individuals from the study who are now adults. The Children’s Oncology Group (COG) has prepared a resource for physicians, “Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.”

- For more information, see <http://www.cancer.gov/cancertopics/coping/childhood-cancer-survivor-study>
- For more information, see <http://www.survivorshipguidelines.org>
- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI)

**Long-Term Cancer Survivors Research Initiatives:** The population of cancer patients surviving more than 5 years continues to grow across life stages, from children through senior adults. These research initiatives focus on the physiological and psychosocial effects of treatment and medical interventions to promote positive outcomes in survivors and their families. Important early findings suggest long latencies for treatment-related effects, highlighting the need for extended follow up, early identification, and intervention before complications become more serious. Implications include the length and quality of survival and the ongoing burden of illness and costs.

- For more information, see [http://cancercontrol.cancer.gov/bb/2006\\_bb.pdf#page=93](http://cancercontrol.cancer.gov/bb/2006_bb.pdf#page=93)
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-04-003.html>
- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI, NIA, CDC)

**Developmental Windows of Vulnerability to Environmental Exposures:** The Breast Cancer and Environment Research Centers supported by NIH function as a consortium to study the impact of prenatal to adult environmental exposures that may predispose a woman to breast cancer. The centers bring together basic scientists, epidemiologists, research translational units, and community advocates within and across the centers to investigate mammary gland development in animals and young girls to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. The overall goals of the BCERC are to develop public health messages to educate young girls and women who are at high risk of breast cancer about the role of specific environmental stressors in breast cancer and how to reduce exposures to those stressors. These public health messages will be based on the integration of basic biological, toxicological, and epidemiological data.

- For more information, see <http://www.bcerc.org>
- This example also appears in Chapter 2: *Cancer*.
- (E) (NIEHS, NCI)

**Population Research:** Given the Nation’s increasing diversity and changing demographics, it is critical to understand how trends in areas such as immigration, fertility, marriage patterns, and family formation affect the well-being of children and families. NIH research in these areas allows policymakers and program planners to better address public health needs. For instance:



- ▷ The Fragile Families and Child Well-Being Study follows children born to unmarried parents to assess how economic resources, father involvement, and parenting practices affect children's development.
  - ▷ The New Immigrant Survey follows the first nationally representative sample of legal immigrants to the United States, providing accurate data on legal immigrants' employment, lifestyles, health, and schooling before and after entering the country.
  - ▷ The National Longitudinal Survey of Youth (1979 cohort) continues to assess the work, educational, and family experiences of a nationally representative cohort of young men and women who were 14–22 years old when they were first studied in 1979. The study also follows children born to female participants up through age 20, creating the opportunity to study intergenerational influences on child development, health behaviors, and educational attainment.
- For more information, see <http://www.fragilefamilies.princeton.edu/index.asp>
  - For more information, see <http://nis.princeton.edu/>
  - For more information, see <http://www.bls.gov/nls/nlsy79ch.htm>
  - This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
  - (E) (NICHD, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

**Brain Disorders in the Developing World: Research Across the Lifespan:** Brain disorders are the leading contributor to years lived with disability in all regions of the world, with the exception of sub-Saharan Africa. This program boosts research in the developing world on childhood disorders such as cerebral palsy and epilepsy, on mental illnesses such as depression and schizophrenia, and on degenerative disorders such as stroke and Alzheimer's disease. Under this program, U.S. investigators and their foreign collaborators are studying the neurocognitive consequences of HIV/AIDS, the relationship between zinc nutrition and brain development, and the neurological disorders stemming from treatable infectious causes, such as cerebral malaria, cisticercosis, TB, and bacterial sepsis.

- For more information, see [http://www.fic.nih.gov/programs/research\\_grants/brain\\_disorder](http://www.fic.nih.gov/programs/research_grants/brain_disorder)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (FIC, NEI, NIA, NIAAA, NICHD, NIDA, NIEHS, NIMH, NINDS, ODS)

**Nonalcoholic Steatohepatitis (NASH) Clinical Research Network:** NASH is strongly associated with obesity and type 2 diabetes, conditions that have increased dramatically in recent decades. Network research addresses GPRA Goal SRO-4.3. The Network is conducting a randomized clinical trial to evaluate the safety and efficacy of the insulin-sensitizing drug pioglitazone or vitamin E compared with placebo for the treatment of nondiabetic adults with NASH. Also, in a separate trial in children, the network is comparing the insulin-sensitizing drug metformin, vitamin E, and placebo in treating nonalcoholic fatty liver disease.

- For more information, see <http://www.jhucct.com/nash>
- (E) (NIDDK, NICHD, NCI, CRADA with industry) (GPRA)

**Acute Liver Failure Study Groups:** The adult and pediatric Acute Liver Failure Study Groups address the problem of acute liver failure due to drugs or other factors. The Groups' research has provided knowledge and tools for managing the clinical and public health burden of acute liver failure. In 2002, the adult study group highlighted a dramatic increase in liver injury due to the

over-the-counter pain reliever acetaminophen. The groups then developed a serum-based assay to detect acetaminophen-induced acute liver failure in adults and children. Current studies are testing potential therapies to improve survival in patients with acute liver failure.

- [Ostapowicz G et al. \*Ann Intern Med.\* 2002;137:947-54](#), PMID: 16950959
- For more information, see <http://tinyurl.com/2qu94j>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK, FDA)

### **Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy**

**(CALERIE):** A large body of research in animals indicates that substantially reducing caloric intake while maintaining optimal nutrition results in significant increase in lifespan. The CALERIE study will help to determine whether these beneficial effects extend to humans. Results from pilot studies demonstrate that overweight people who cut their calories by 25 percent for 6 months have reduced fasting insulin levels and core body temperature, two markers that may be associated with increased longevity in humans. A long-term study began in January 2007.

- For more information, see <http://calerie.dcri.duke.edu>
- (E) (NIA)

## **Stage-Specific Research**

**Fertility and Infertility:** As the CDC has stated, “for many couples who wish to start a family, the dream is not easily realized.” For about 2.1 million married couples who reported not using contraception, the women were still unable to become pregnant after 1 year. NIH supports research to better understand the basic processes underlying human reproduction and to directly alleviate infertility and reproductive disorders. Much of this effort involves translating rapidly emerging laboratory research into clinical applications. Scientists are working to determine how certain gynecological conditions, such as polycystic ovary syndrome and endometriosis, and certain diseases and disorders of the male reproductive system affect fertility. Some evolving and exciting fertility research is applying cryopreservation technology to the freezing of human eggs to preserve fertility in women undergoing cancer treatment. Scientists are also exploring the link between obesity and fertility and assessing the long-term impact of using assistive reproductive technologies.

- (E) (NICHD, ORWH)

**Women’s Reproductive Health Research Career Development Program:** The ORWH cosponsored with NICHD the funding of 20 institutional career development awards designed to increase the number of obstetricians and gynecologists conducting research in women’s health.

- For more information, see <http://www.nichd.nih.gov/research/supported/wrhr.cfm>
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (ORWH, NICHD)

**Pregnancy and Perinatology:** NIH continues to support a portfolio of research on high-risk pregnancies and poor pregnancy outcomes, including preterm labor and birth, fetal disorders, SIDS, poor maternal health, and stillbirth. Much of this research is conducted through centers and networks that bring together researchers from different disciplines and allow them to study larger numbers of patients. For example, NIH recently created two research networks on premature birth and on stillbirth. The Genomic and Proteomic Network for Premature Birth Research aims to accelerate research in the area of premature birth by providing researchers with the latest technology and methods. The Stillbirth Collaborative Research Network aims to identify the causes of stillbirth so that new interventions can be developed to prevent these tragic outcomes.

- (E) (NICHD)

**Prenatal Alcohol, SIDS, and Stillbirth (PASS) Research Network:** After a 3-year feasibility study, NIH established this multidisciplinary consortium to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of SIDS, stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study will follow 12,000 pregnant, high-risk, American Indian and South African women and their infants prospectively until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

- For more information, see <http://www.nichd.nih.gov/research/supported/pass.cfm>
- (E) (NICHD, NIAAA)

**Potential Therapy for Children Afflicted with Progeria Syndrome:** Hutchinson-Gilford Progeria Syndrome (HGPS) is a genetic disorder of accelerated aging. In addition to other symptoms of aging, HGPS patients suffer from accelerated cardiovascular disease and often die in their teen or even preteen years from heart-related illnesses. No treatments are currently available for HGPS; however, recent work led by NHGRI researchers indicates that farnesyltransferase inhibitors (FTIs), a class of drugs originally developed to treat cancer by blocking the growth of tumor cells, are capable of reversing the effects of the defective HGPS protein, lamin A. Ongoing studies in a mouse model have validated the results of preliminary experiments, and a clinical trial of FTIs in children with progeria began in 2007. In FY 2008, researchers plan on expanding the study to investigate whether FTIs are capable of reversing the detrimental effects after progression of the cardiovascular anomalies that are seen in the mouse model. The development of biological assays to assess the effects of FTI treatment on the patients' cells is in progress to monitor the potential beneficial effects of the clinical trial. In addition, it has been demonstrated that the progerin protein is present in small amounts in normal aging tissues. The investigation of this phenomenon is being pursued as a contributory factor to the normal aging process.

- [Cao K, et al. \*Proc Natl Acad Sci U S A.\* 2007;104:4949-54, PMID: 17360355](#)
- [Capell BC, et al., \*Proc Natl Acad Sci U S A.\* 2005;102:12879-84, PMID: 16129833](#)
- For more information see <http://www.genome.gov/10000608>
- For more information, see <http://www.genome.gov/15515061>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Clinical and Translational Research*.
- (I) (NHGRI)

**Newborn Screening:** Screening and treating newborns for phenylketonuria (PKU) and hypothyroidism have virtually eliminated these conditions as a cause of mental retardation in the United States. A new, trans-NIH collaborative effort will build on this success to develop a new generation of microchips and related technologies that should enable screening programs across the Nation to rapidly test newborns for hundreds of genetic conditions in a single test using one drop of an infant's blood. Complementing the technology development is an initiative to stimulate development of new treatments for such conditions as short chain Acyl CoA dehydrogenase deficiency (SCAD), tyrosinemia, and the genetic causes of hearing loss with the promise of significantly reducing the lifelong health burden of these and other conditions.

- This example also appears in Chapter 3: *Technology Development*
- (E) (NICHD, NIDCD, NIDDK)

**Discovering the Causes of Nonsyndromic Cleft Lip and Cleft Palate:** For nearly 60 years, NIH has supported scientific investigation of causes and interventions for cleft lip and cleft palate, which are among the most common birth defects. In recent years, advances in technology made it possible for scientists to directly sequence genes suspected of contributing to cleft lip and/or palate. NIH grantees and their associates have used this approach to identify genetic mutations accounting for up to 13 percent of cases of cleft lip and/or palate. One of the most recent advances occurred in March 2007, when the scientists reported sequencing the coding regions of 12 members of the fibroblast growth factor (FGF) and FGF receptor gene families and finding seven mutations that may contribute to as much as 5 percent of nonsyndromic cleft lip and/or palate. The group followed up by generating three-dimensional computer models of the FGF proteins that predicted how the altered amino acids would affect their normal shape and function. In a separate finding, NIH-supported scientists reported that women who carry a fetus whose DNA lacks both copies of a gene involved in detoxifying cigarette smoke substantially increase their baby's chances of being born with a cleft lip and/or palate if they smoke. About a quarter of babies of European ancestry and up to 60 percent of those of Asian ancestry lack both copies of the gene, called *GSTT1*. The scientists calculated that if a pregnant woman smokes 15 cigarettes or more per day, the chances of her *GSTT1*-lacking fetus developing a cleft increase by nearly 20-fold. Globally, about 12 million women each year smoke through their pregnancies. This finding provides additional motivation for expectant mothers to follow existing advice not to smoke. Other work conducted by NIH scientists looking at occupational exposures of parents suggest that exposures in certain occupations may influence the risk of orofacial clefting in offspring. Specific exposures accompanying these occupations warrant exploration.

- [Riley BM, et al. \*Proc Natl Acad Sci U S A\* 2007;104:4512-7](#), PMID: 17360555
- [Shi M. et al. \*Am J Hum Genet\* 2007;80:76-90](#), PMID: 17160896
- [Nguyen RH, et al. \*Ann Epidemiol\* 2007;17:763-71](#), PMID: 17664071
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E, I) (NIDCR, NIEHS)

**Craniofacial Birth Defects or Syndromes:** Craniofacial defects are among the most common of all birth defects. Birth defects and developmental disorders can be isolated or may be part of complex hereditary diseases or syndromes. Cleft lip and cleft palate are among the more common birth defects in the United States, occurring in about 1 to 2 of 1,000 births. Numerous

other disorders with oral and craniofacial manifestations, such as ectodermal dysplasias, Treacher Collins syndrome, and Apert's syndrome, though considerably more rare than cleft lip and cleft palate, also have serious lifetime functional, esthetic, and social consequences. These disorders are often devastating to parents and children alike. Surgery, dental care, psychological counseling, and rehabilitation may help ameliorate the problems, but often at a great cost and over many years. In fact, the lifetime cost of treating the children born each year with cleft lip or cleft palate is estimated to be \$697 million. NIH is actively pursuing knowledge to prevent future defects as well as treat those who are currently affected. Exciting advances in genetic studies are shedding light on the genes that are important in forming the head and face, how these genes function, and how they interact with environmental, nutritional, and behavioral factors. Such information may ultimately provide the knowledge necessary for prenatal diagnosis, the development of methods to prevent craniofacial birth defects, and the basis for developing better treatments. The development of biocompatible, naturally derived materials and biodegradable scaffolds offers new hope for the treatment of defects resulting from craniofacial birth defects or syndromes.

- For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/00038946.htm>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E, I) (NIDCR, NIEHS)

#### **Understanding the Causes and Conceiving New Treatments for Craniosynostosis:**

Craniosynostosis arises when one or more of the fibrous sutures between the six cranial bones prematurely fuse and lock sections of the skull tightly into place. Because the brain continues to grow during early childhood, craniosynostosis, if left untreated, can distort the shape of the skull and portions of the face, as well as cause hearing loss, blindness, and/or intellectual disability. To better understand the causes of craniosynostosis, a team of NIH-supported researchers study the fusion of cranial sutures in mice. They suspect that the premature fusion involves alterations in the normal biochemical interplay between embryonic tissue, called mesenchyme, from which the cranial sutures form, and a thin fibrous layer of tissue, called the dura mater, that lies beneath it. The scientists also have found that different regions of the dura mater send different developmental signals to the overlying mesenchyme. Defining in fine detail the signals between the mesenchyme and the dura mater could provide the intellectual basis for discovering and developing noninvasive biological approaches to control craniosynostosis. NIH-supported researchers have made an important step in this direction. They isolated mesenchymal cells derived from cranial sutures in two different areas of the skull, cultured each group of cells separately, and later analyzed their gene expression patterns. The scientists found clear differences in the patterns of genes expressed among the two populations of mesenchymal cells. To their knowledge, this marks the first glimpse of the genetic programs that are wired into mesenchymal cells derived from cranial sutures. This line of research potentially opens a new chapter in understanding the causes of and conceiving new treatments for cranial synostosis.

- [Xu Y, et al. \*Plast Reconstr Surg\* 2007;119:819-29](#), PMID: 17312483
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)



**Cesarean Delivery Versus Vaginal Birth:** The rate of cesarean delivery has risen dramatically over the past two decades; in fact, cesarean delivery currently ranks as the most commonly performed surgical procedure in the United States. More research is needed to determine how frequently cesarean deliveries are scheduled for women without medical indications for the procedure, and how these “maternal request” deliveries compare with vaginal delivery in terms of child and maternal health outcomes. Currently, NIH is supporting a Cesarean Registry through the Maternal-Fetal Medicine Units Network. Among other findings, the registry data showed that women who gave birth to a child vaginally, after a previous cesarean delivery of twins or triplets, were not at higher risk for complications during labor and delivery.

- [NIH Consens State Sci Statements. 2006;23:1-29](#), PMID: 17308552
- Varner M for the NICHD MFMU Network, The MFMU Cesarean Registry: VBAC success and complication rates following one previous cesarean for multifetal gestation. Abstract for the Society for Maternal-Fetal Medicine Annual Meeting 2006.
- (E) (NICHD)

**Maternal Oral Health and Obstetric Outcomes:** In recent years, evidence has suggested that a pregnant woman with periodontal (gum) disease might be at increased risk for premature birth. Two similar but not identical NIH-supported trials evaluate this possibility. Conducting more than one large clinical trial on this important public health question will cast a wide enough investigational net to determine which, if any, women are at risk. One study, called the Obstetrics and Periodontal Therapy Trial (OPT), recently concluded that periodontal treatment during pregnancy is safe for mother and baby but does not significantly lower preterm birth risk. The Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR) study is ongoing.

- See <http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2006/PR11012006.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIDCR)

**Study Shows Child’s Weight Can Be Influenced by Mother Before and During Pregnancy:** NIH-supported researchers found that a child’s weight may be influenced by its mother even before the child is born. In a study of more than 3,000 children, scientists found that children of mothers who were obese before pregnancy were more likely to be overweight by 3 years of age. In addition, children born to African American or Hispanic mothers or to mothers who smoked during pregnancy were at greater risk for becoming overweight. These findings indicate the need to develop creative and effective strategies to promote healthy nutritional habits in prospective mothers as a way of reducing later health problems in their children.

- [Reagan PB, Salsberry PJ. Soc Sci Med. 2005;60:2217-28](#), PMID: 16322155
- For more information, see <http://www.nih.gov/news/pr/dec2005/ninr-05.htm>
- (E) (NINR)

**NICU Program Reduces Premature Infants’ Length of Stay and Improves Parents’ Mental Health Outcomes:** In a randomized, controlled clinical trial, NIH-funded investigators tested an educational program, called Creating Opportunities for Parental Empowerment (COPE), among



parents of premature infants. An estimated half a million premature infants are born in the United States each year. Most require hospitalization in a newborn intensive care unit, and their parents often suffer high levels of stress, anxiety, and depression. Compared with controls, parents who participated in the COPE program reported better understanding of the behaviors to expect from their infants and displayed more positive parent-infant interactions. Mothers had lower anxiety, depression, and overall parenting stress, and fathers were more involved in the infants' care. Infants of COPE parents averaged 3.8 fewer days in the neonatal intensive care unit than the control infants, which translated to a savings of roughly \$5,000 per infant.

- [Melnyk BM, et al. \*Pediatrics\*. 2006;118:e1414-27](#), PMID: 17043133
- For more information, see <http://www.nih.gov/news/pr/nov2006/ninr-01.htm>
- (E) (NINR)

**Trial to Reduce the Incidence of Type 1 Diabetes for Those Genetically at Risk (TRIGR):**

Researchers are conducting a study to determine whether the onset of type 1 diabetes mellitus can be delayed or prevented by weaning genetically susceptible infants to Nutramigen<sup>®</sup>, a hydrolysate of cow milk protein, instead of to a standard cow milk-based infant formula. Earlier studies in animal models have shown that hydrolyzed protein diets prevented the onset of type 1 diabetes. TRIGR is the first large effort designed to ascertain whether a simple nutritional intervention during infancy can delay or prevent the onset of type 1 diabetes in children who are at high genetic risk for the disease. Enrollment for the study was recently completed, totaling more than 2,000 children from 15 countries.

- For more information, see <http://www.nichd.nih.gov/research/supported/TRIGR.cfm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NICHD; NIDDK administers the contribution from the special statutory funding program for type 1 diabetes)

**Childhood and Maternal Obesity:** As the maternal and childhood obesity epidemic grows, researchers are trying to understand the interaction among the many complex biological and behavioral factors that contribute to this rise, identify the long-term impact on mother and child, and develop effective interventions to reverse these trends. NIH obesity research, which includes a range of racial and ethnic groups, is examining topics such as:

- ▷ Basic research on the physiology, psychology, and genetics of obesity in children
- ▷ Developing working definitions of the metabolic syndrome in children and adolescents
- ▷ Linking maternal obesity, reproductive health, and pregnancy to adverse health outcomes
- ▷ Behavioral intervention trials in schools, the home, and the community

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E, I) (NICHD, NCCAM, NCI, NCMHD, NHLBI, NIDCR, NIDDK, NINR, OBSSR, ODP)

**Diabetes Research in Children Network (DirecNet):** The risk of hypoglycemia is now the main obstacle to successfully managing type 1 diabetes mellitus in children of all ages. Severe hypoglycemia can lead to seizures or unconsciousness. In 2001, NIH established DirecNet to assess the accuracy and efficacy of continuous glucose monitoring devices, evaluate the effectiveness of the devices as tools to help control blood sugar levels, and determine the incidence of hypoglycemia. DirecNet also focuses on possible changes in neurocognitive

function in children with type 1 diabetes who have frequent bouts of hypoglycemia. The network was recently renewed to use new tools to evaluate factors and mechanisms contributing to hypoglycemia, such as exercise and diet. The goal is to continue to improve management of type 1 diabetes and prevent hypoglycemia by “closing the loop” between measuring glucose levels and delivering insulin.

- For more information, see <http://www.nichd.nih.gov/research/supported/directnet.cfm>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-06-020.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Technology Development*.
- (E) (NICHD, NIDDK, NINDS)

**HEALTHY:** The HEALTHY multicenter clinical trial aims to prevent risk factors for type 2 diabetes in middle-school children. A pilot study for HEALTHY found that an alarmingly high 15 percent of students in middle schools enrolling mainly minority youth had three major risk factors for diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease risk for obesity and diabetes. In the full-scale HEALTHY trial, 42 enrolled middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. More than 80 percent of the enrolled students are from minority populations.

- For more information, see <http://www.nih.gov/news/pr/aug2006/niddk-28.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIDDK)

**Studies of Diabetes in Youth:** Previously known as a disease of adults, type 2 diabetes is increasingly being observed in youth. The Treatment Options for Type 2 Diabetes in Youth study is comparing three different treatment strategies for children with the disease. The SEARCH for Diabetes in Youth Study is providing key data on childhood diabetes incidence and prevalence. SEARCH estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. Although type 2 diabetes is increasing in children over 10, particularly minorities, type 1 diabetes accounts for most new cases, with an estimated 15,000 youths diagnosed annually.

- For more information, see <http://www.todaystudy.org/index.cgi>
- For more information, see <http://www.searchfordiabetes.org>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK, CDC)

**The Environmental Determinants of Diabetes in the Young:** Understanding the environmental factors, such as infectious agents or diet, that can trigger type 1 diabetes in genetically susceptible individuals is crucial to developing prevention strategies. To address this knowledge gap, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. This international consortium is enrolling newborns and following them

until age 15 to identify environmental triggers for type 1 diabetes. The study is amassing the largest set of data and samples in the world for newborns at risk for type 1 diabetes.

- For more information, see <http://teddy.epi.usf.edu>
- This information also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK, NIAID, NIEHS, CDC, and the Juvenile Diabetes Research Foundation)

**Longitudinal Assessment of Bariatric Surgery (LABS):** The multicenter, NIH-funded LABS consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Because bariatric surgery is also sometimes used in clinical practice as a treatment for severely obese adolescents, NIH is also supporting an observational study of teens already scheduled for surgery, Teen-LABS, to collect data to help determine whether it is an appropriate treatment option for extremely obese adolescents.

- For more information, see <http://tinyurl.com/399zmt>
- For more information, see <http://tinyurl.com/yoer3l>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK, ORWH)

**Bone Health:** NIH researchers established reference curves for bone mineral content and density in children. The early findings are now available according to age, sex, and race and can be used to help identify children with bone deficits and to monitor changes in bone in response to chronic diseases or therapies. Early study findings showed that bone minerals continue to accrue beyond the teenage years, so the study will continue as the adolescent participants approach young adulthood. In another study, NIH scientists discovered two genes for osteogenesis imperfecta, or brittle bone disease. The genes affect how collagen, an important building block for bone, is formed. Although there is no treatment for the disorder, the findings allow researchers to test families who have lost a child to osteogenesis imperfecta for the presence of the defective genes.

- [Kalkwarf HJ, et al., \*J Clin Endocrinol Metab.\* 2007;92:2087-99](#), PMID: 17311856
- [Barnes AM, et al. \*N Engl J Med.\* 2006;355:2757-64](#), PMID: 17192541
- [Cabral WA, et al. \*Nat Genet.\* 2007;39:359-65](#), PMID: 17277775
- (E, I) (NICHD)

**Never Too Early—The Milk Matters Campaign:** The risk for osteoporosis actually starts in childhood. Thus, NIH supports a public health campaign to help increase calcium consumption among children and teens, ages 11 to 15, a time of critical bone growth. Milk Matters is designed to educate parents, teachers, and health care providers about how most tweens and teens are not getting enough calcium their diets. The campaign features materials and publications in English and Spanish.

- For more information, see <http://www.nichd.nih.gov/milk/milk.cfm>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NICHD, NIDCR)

**Learning Math and Science:** Educators, university leaders, and scientists have called for evidence-based interventions to improve U.S. students' understanding and achievement in mathematics and science. NIH's long-standing research efforts on individual differences in learning, how children learn to read, and specific learning disabilities enable it to play a leading role in improving understanding and developing these interventions. For example, NIH Mathematics and Science Cognition and Learning program supports both basic and intervention research in all aspects of mathematical thinking and problem solving, as well as in scientific reasoning, learning, and discovery. In partnership with the Department of Education, NIH participates in a national mathematics and science initiative and advises on the best use of scientifically based research on teaching and learning these critical subjects.

- (E) (NICHD)

**Intellectual and Developmental Disabilities:** Intellectual and developmental disabilities have serious, lifelong effects on cognitive and adaptive development. NIH supports research to improve functioning for individuals who have intellectual and development disabilities and to understand the underlying genetic processes to prevent these conditions. For example, NIH supports 14 Mental Retardation/Developmental Disabilities Research Centers to advance diagnosis, prevention, treatment, and amelioration of intellectual and developmental disabilities. Because the centers have developed core research resources in genetics, proteomics, and clinical infrastructure, they also provide support for researchers in the Fragile X Syndrome Research Centers, Rare Disease Cooperative Centers, and Autism Centers. In addition to these centers, NIH supports research to better understand the neurobiology and genetics that underlie the cognitive and behavioral processes in persons with Down's syndrome and other intellectual and developmental disabilities.

- For more information, see <http://www.nichd.nih.gov/about/org/cdbpm/mrdd/supported/index.cfm>
- (E) (NICHD)

**National Database for Autism Research (NDAR):** The NDAR is a collaborative biomedical informatics system being created by NIH to provide a national resource to support and accelerate research in autism.

- For more information, see <http://ndar.nih.gov>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (I, E) (NIMH, NICHD, NINDS, NIEHS, NIDCD, CIT)

**Teen Driving:** Over one-third of teenage deaths are due to motor vehicle accidents. NIH-supported researchers recently completed a study demonstrating that teen drivers' behavior often became more risky in the presence of teen passengers. The researchers found that teenage drivers—both males and females—were more likely to tailgate and exceed the speed limit if there was a teenage male passenger in the front seat. Conversely, male teenagers were less likely to tailgate or exceed the speed limit when a teenage female was in the front passenger seat. To determine why the presence of teen passengers influenced these behaviors, NIH researchers are designing a study that will involve placing electronic monitoring equipment in vehicles with teen

drivers. After learning the specific reasons for the risky behavior, researchers can then work to develop ways to prevent it.

- [Simons-Morton B. et al. \*Accid Anal Prev.\* 2005;37:973-82](#), PMID: 15921652
- (I) (NICHD)

**Underage Drinking Research Initiative:** In 2004, NIH launched this ongoing initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence, all framed within the context of overall development. Activities and achievements in 2007 include:

- ▷ Provided the scientific foundation for *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking* (released March 6, 2007) and for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking
- ▷ Convened scientific meetings of experts, including the Underage Steering Committee, which met four times over a 2-year period; a Meeting on Diagnosis of Alcohol Use Disorders among Youth (April 2006); and a Meeting on Screening for Child and Adolescent Drinking and AUDs among Youth (June 2007)
- ▷ Issued three RFAs, including “Underage Drinking: Building Health Care System Responses” (four projects awarded in FY 2006), “Impact of Adolescent Drinking on the Developing Brain” (five projects awarded in FY 2007), and “Alcohol, Puberty and Adolescent Brain Development” (three projects awarded in FY 2007)
- ▷ Published *Alcohol Research and Health*, Volume 28, Number 3, “Alcohol and Development in Youth: A Multidisciplinary Overview”
- ▷ Published a supplement of seven developmentally focused papers covering a broad range of underage drinking topics (accepted for the journal *Pediatrics*).
  - For more information, see <http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm>
  - (E) (NIAAA)

**The Rapid Response Program:** In April 2002, the Task Force on College Drinking released its seminal report, “A Call to Action: Changing the Culture of Drinking at U.S. Colleges.” As part of its college focus, NIH initiated support of collaborations between university personnel who have responsibility for alcohol programs on various campuses and established college drinking researchers to implement and evaluate programs to reduce underage alcohol use and its consequences. These programs include:

- ▷ RFA AA-03-008: “Research Partnership Awards for Rapid Response to College Drinking Problems.” Five U01 (cooperative agreement) 5-year grants were awarded in December 2002.
- ▷ PAR-03-133: “Rapid Response to College Drinking Problems.” Fifteen 3- year grants were awarded in June 2003. This rapid funding mechanism (U18, cooperative agreement) supports timely research on interventions to prevent or reduce alcohol-related problems among college students. It was intended to support studies of services or interventions that could capitalize

on “natural experiments” (e.g., unanticipated adverse events, policy changes, new media campaigns, campus-community coalitions, etc.). Each U18 grantee was required to partner with a U01 grantee. Together, these pairs, working with NIH Scientific Staff Collaborators, jointly design, develop, implement, and evaluate college drinking projects on their campuses.

- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIAAA)

**Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN):** Although one-third to one-half of new HIV infections occur among adolescents and young adults, researchers know little about how the complex physiological changes associated with adolescence impact the transmission dynamics and course of HIV infection. NIH is supporting a national clinical research network to address the unique challenges and clinical management needs of HIV-positive youth and those at risk of infection. Researchers in this network are building the capacity to develop and conduct selected biomedical, behavioral, and community-based studies, including vaccine and microbicide trials to ensure that the needs of high-risk teens are considered as treatment and prevention interventions are being developed.

- For more information, see <http://www.atnonline.org>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NICHD, NIDA, NIMH)

**Adolescent Depression and Suicide:** NIH continues to support research on the treatment of depression during adolescence, including the concern that certain antidepressant medications, called selective serotonin reuptake inhibitors, can increase the risk of suicide. NIH supported a recent meta-analysis of studies on this subject that found that the benefits of antidepressant medication for children and adolescents with major depressive disorder and anxiety disorders likely outweighed any potential risks.

- For more information see [http://www.nimh.nih.gov/healthinformation/antidepressant\\_child.cfm](http://www.nimh.nih.gov/healthinformation/antidepressant_child.cfm)
- (E) (NIMH)

**Interventions and Services for Youth with Mental Illness Who Are Transitioning to Adulthood:** The transition to adulthood for youth with mental illness is often a period in which care is compromised, with a host of negative outcomes. In 2006, NIH launched an initiative to stimulate research on refining and testing interventions in service delivery models for youth transitioning to adulthood. Four applications were funded.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-07-050.html>
- <http://www.nimh.nih.gov/science-news/2007/new-research-to-help-youth-with-mental-disorders-transition-to-adulthood.shtml>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIMH)

**Alzheimer’s Disease Neuroimaging Initiative (ADNI):** ADNI is an innovative public-private partnership for examining the potential for serial MRI, PET, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer’s disease. Early results suggest that researchers may be able to reduce



the costs associated with clinical trials by improving imaging and biomarker analysis. One ADNI study found that a standard model can be used to monitor the performance of MRI scanners at multiple clinical sites, ensuring the accuracy of the MRI images. In another study, investigators compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and Alzheimer's disease and found that scans correlated with symptoms of each condition and that images were consistent across sites, suggesting the validity of PET scans for monitoring the effectiveness of therapies in future clinical trials. More than 200 researchers have already accessed a public database containing thousands of brain images and related clinical data obtained through blood and cerebrospinal fluid analyses.

- For more information, see <http://www.loni.ucla.edu/ADNI>
- (E) (NIA, NIBIB)

**Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE):** This recent multicenter study in community-dwelling seniors showed that certain mental exercises can offset expected declines in thinking skills of older adults and show promise for maintaining the cognitive abilities needed for tasks such as shopping, making meals, and handling finances. The ACTIVE study is the first randomized, controlled trial to demonstrate long-lasting, positive effects of brief cognitive training in older adults. Although training did not improve the participants' ability to tackle other everyday tasks, their cognitive skills declined less than with untrained seniors. Additional research is needed to translate these findings from the laboratory into interventions that prove effective at home.

- For more information, see <http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20061219ACTIVE.htm>
- (E) (NIA)

**Lifestyle Interventions and Independence for Elders:** Results of several studies have suggested that physical exercise may prevent physical disability, including impaired mobility, in both healthy and frail older adults. To develop definitive evidence regarding the effectiveness of such interventions, NIH designed the Lifestyle Interventions and Independence for Elders (LIFE-P) pilot study, a clinical trial that tested the effects of a physical activity program versus a health education program in preventing major disability. The study involved 424 participants age 70 to 89 who were at risk of disability. These individuals were followed for at least 1 year at four locations around the country: Wake Forest University School of Medicine in Winston Salem, North Carolina; the University of Pittsburgh in Pennsylvania; the Cooper Institute in Dallas, Texas; and Stanford University in Palo Alto, California. At various points in the physical exercise intervention, study participants were tested for their performance on a battery of lower-extremity function tests and the time required for them to walk 400 meters. At the end of the study, participants in the intervention group demonstrated significant improvement over controls. This successful pilot study was completed in 2005 and showed both feasibility and positive preliminary data to permit the design and consideration of a large-scale clinical trial.

- (I, E) (NIA)

**Inflammation in the Elderly:** Inflammatory processes, particularly those mediating chronic inflammation, have been implicated as predictors or initiators of or contributors to a number of

chronic diseases and conditions of aging. NIH currently supports research to determine relationships of age-related changes in inflammation and inflammatory mediators to physiologic and pathophysiologic aging changes, risks and progression of age-related morbidity and disability, and changes in tissue and organ function. Funded projects include studies of vascular inflammation and neurotoxicity in the aging brain and inflammatory responses to sleep loss.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-05-011.html>
- (E) (NIA)

**Neuroeconomics of Aging:** Scientists in the emerging field of neuroeconomics seek to explain the psychological mechanisms that guide economic decisions and the neurobiological pathways that underlie them. NIH is currently supporting research to examine the social, emotional, cognitive, and motivational processes and neurobiological pathways of economic behavior as they (1) influence social, financial, and health-related decisions affecting the well-being of middle-aged and older adults and (2) inform the development and refinement of integrative economic theories of utility, learning, and strategic choice relevant to aging.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-06-011.html>
- (E) (NIA)

**National Long-Term Care Survey (NLTCs):** NLTCs is an ongoing longitudinal study supported by NIA to examine changes in the health and functional status of older Americans and track health expenditures. The study is one of the Nation's preeminent resources for understanding and analyzing national disability trends and other demographic trends to inform public health policy. Efforts are currently under way to make the data publicly available.

- For more information, see <http://www.nltcs.aas.duke.edu/index.htm>
- (E) (NIA)

**Improving Communication About End-of-Life Care in the ICU Reduces Symptoms of Stress, Anxiety, and Depression in Family Members:** A clinical trial supported in part by NIH found that an intervention to improve communication between intensive care unit clinicians and family members of a dying patient significantly reduced feelings of stress, anxiety, and depression in the family members. In the randomized controlled trial, researchers examined communication guidelines that follow the mnemonic VALUE: to Value what the family members said, Acknowledge their emotions, Listen, Understand the patient as a person, and Elicit family member questions. From interviews conducted 3 months after the death of the patient, family members in the VALUE group were found to have lower scores for stress, anxiety, and depression than those in the customary-practice group. The finding indicated that improving communication in end-of-life family conferences in the intensive care unit helped family members express their views and emotions, accept a more realistic goal of care, and improve their long-term psychological outcomes.

- [Lautrette A, et al. \*N Engl J Med.\* 2007;356:469-78, PMID: 17267907](#)
- For more information, see <http://www.nih.gov/news/pr/feb2007/ninr-01.htm>
- (E) (NINR)

**Improving End-of-Life Care: Special Supplement to the *Journal of Palliative Medicine*:** In FY 2005, NIH sponsored the State-of-the-Science Conference on Improving End-of-Life Care. This conference addressed the current state of end-of-life care and proposed important new directions for end-of-life research. Key conclusions to emerge from the conference included: the rapid increase in older adults facing the need for end-of-life care requires the development of research infrastructure to better examine end-of-life issues; enhanced communication between patients, families, and providers is crucial to end-of-life care; and improved outcome measures are needed to better conduct end-of-life research. In FY 2006, a special issue of the *Journal of Palliative Medicine* presented a series of papers developed from this workshop on a wide variety of topics. The supplement includes articles on measuring end-of-life care outcomes; analyzing racial, cultural, and ethnic factors that influence end-of-life care; improving care for dying children and their families; and examining factors in the health care system that influence end-of-life care.

- [Grady PA. \*J Palliat Med.\* 2005;8:S1-3](#), PMID: 16499457
- For more information, see <http://www.liebertonline.com/toc/jpm/8/supplement+1>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NINR)

**Centers in Self-Management or End-of-Life Research:** Future progress in improving the ability of those with chronic disease at all stages of life to manage their own illness, as well as improving the care of patients at the end of life, will require the development of enhanced research capacity, in terms of both people and institutions. In early 2007, NIH solicited applications for the Centers in Self-Management or End-of-Life Research. These Centers are expected to enhance research and training capacity for interdisciplinary, biobehavioral efforts in end-of-life and self-management science.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-004.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-005.html>
- (E) (NINR)

## Rehabilitation Research

**Neural Prosthesis Program:** Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. The NINDS Neural Prosthesis program pioneered the development of this technology beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants for the hearing impaired, respiratory and hand grasp devices for people with spinal cord injuries, and deep brain stimulation for patients with Parkinson's disease, among other contributions. Current work aims to restore standing and voluntary bowel and bladder control after spinal cord injury, to allow paralyzed persons to control devices directly from their brains, and to control seizures. Ongoing research also seeks to improve cochlear implants and to advance deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community, now including private-sector companies, and represents a

cooperative effort among several NIH Institutes, which coordinate their efforts with programs now under way in the Department of Veterans Affairs and DoD.

- For more information, see <http://www.ninds.nih.gov/funding/research/npp/index.htm>
- For more information, see <http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*.
- (E) (NINDS, NIBIB, NIDCD, NICHD, NEI)

**Upper Limb Rehabilitation:** To improve the process of restoring function in the upper limbs, NIH is developing robotic exoskeletons for rehabilitation of upper-extremity paralysis. Recent studies demonstrate that practicing tasks repetitively with feedback can enhance recovery of arm function for selected populations of stroke survivors. This type of practice typically requires the assistance of a trained physical therapist. However, the development of low-cost robotic exoskeletons holds the promise of providing therapeutic activities at home and in a variety of settings to help a wider range of stroke patients improve functioning more efficiently.

- (E) (NICHD, NIBIB) (GPRA Goal)

**High-Tech Replacements for Damaged Limbs:** NIH is investing strategically to develop improved prosthetic devices that can help soldiers and other individuals who have lost limbs resume normal activities. The latest developments and research activities include a new, “intelligent” artificial knee joint that enables a user’s lower-leg prosthesis to adjust automatically to hills, stairs, and other variable surfaces, offering greater mobility. Scientists are also working on developing a prototype “bionic arm,” controlled by microprocessors that read signals through nerves that have been rerouted from the neck to the chest. Investigators are also seeking ways to implant an artificial limb directly into the bone of the residual limb, doing away with the need for a socket device, which often causes painful, chronic irritation.

- [Johansson JL et al. \*Am J Phys Med Rehabil.\* 2005;84:563-75](#), PMID: 16034225
- [Kuiken TA et al. \*Lancet.\* 2007;369:371-80](#), PMID: 17276777
- [Pitkin M et al. \*J Rehabil Res Dev.\* 2006;43:573-80](#), PMID: 17123195
- (E) (NICHD)

**New Medical Adhesive Boasts Unique Wet-Dry Abilities:** One day, tissue engineering will make it possible to regenerate lost facial components. Until then, victims of massive craniofacial trauma or extensive surgeries due to cancer often must depend on maxillofacial prosthetics to provide the form and function needed to resume their day-to-day lives. Current adhesives are not always retentive over long periods or changing conditions. The loss of retention can result in visible margins or even dislodgement of the prosthesis. Now NIH-supported scientists report they have merged two of nature’s most elegant strategies for wet and dry adhesion. As reported in *Nature*, the scientists designed a synthetic material that starts with the dry adhesive properties of the gecko lizard and supplements it with the underwater adhesive properties of a mussel. The hybrid material, which they call a geckel nanoadhesive, proved in initial testing to be adherent under dry and wet conditions and also adhered much longer under both extremes than previous gecko-based synthetic adhesives, a major issue in this area of research. According to the authors, their findings mark the first time that two polar opposite adhesion strategies in nature have been merged into a manmade reversible adhesive. It is envisioned that the new adhesive will be used

for many medical applications, including enhancing the retention of oral and maxillofacial prosthetics.

- [Lee H. et al. \*Nature\*. 2007;448:338-41](#), PMID: 17637666
- For more information see <http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2007/PR07182007.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*.
- (E) (NIDCR)

**Engineering Stem Cells to Repair or Replace Damaged Tissues:** Guiding a person's own stem cells to repair or replace damaged tissues with healthy tissue is the goal of multiple NIH-supported tissue engineering projects. For example, one team previously reported success creating three-dimensional mandibular (jaw) joints using rodent tissue; their continuing work on the project addresses pragmatic questions that must be answered in order to create functional human joints. Other teams are working on regeneration of the temporomandibular disk, which acts as a cushion between the bony components of the jaw joint and on the tissue engineering of skeletal muscle. Tissue engineering holds great promise for regeneration or replacement of dental, oral, and craniofacial structures lost due to trauma, disease, or congenital anomalies. The progress seen in this area will also inform tissue engineering solutions for degeneration in other articular surfaces, such as knee, hip, and shoulder joints.

- [Mao JJ. et al. \*J Dent Res\* 2006;85:966-79](#), PMID: 17062735
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)

**Maintaining Physical Function in Older Populations:** Chronic disability among older Americans has dropped dramatically, and the rate of decline has accelerated during the past two decades, according to recent analysis of data from the NIH National Long-Term Care Survey (NLTCS), which examined disability changes within three age groups (65–74, 75–84, and 85+) and found that the prevalence of chronic disability among people age 65 and older fell from 26.5 percent in 1982 to 19 percent in 2004/2005. The proportion of people without disabilities increased the most in the oldest age group, rising by 32.6 percent among those age 85 and older. The findings suggest that older Americans' health and function continue to improve at a critical time in the aging of the population. The question of how best to maintain and accelerate the trend of declining disability, especially in the face of increasing rates of obesity, will be addressed at a workshop sponsored by the National Academies and commissioned by NIH. NIH currently supports large, multidisciplinary research programs that focus, in part, on rehabilitation research for older people. For example, one of the Claude D. Pepper Older Americans Independence Centers conducts exercise and motor learning-based rehabilitation research to optimize the recovery of older adults who have suffered a stroke, hip fracture, or other chronic debilitating disease and translate these findings into effective community-based rehabilitation programs (see Chapter 4). The Edward R. Roybal Centers for Applied Gerontology conduct applied research to keep older persons independent, active, and productive in later life.

- [Manton KG, et al. \*Proc Natl Acad Sci U S A\*. 2006;103:18374-9](#), PMID: 17101963
- (E) (NIA)

**International Collaborative Trauma and Injury Research Training Program:** Each year, more than 5 million deaths and countless disabilities result from injuries. This program is strengthening the scientific expertise in developing countries in human injury-related research and funds 11 collaborations between institutions in high-income countries and low- or middle-income countries. These collaborations support research training in applied science, the epidemiology of risk factors, acute care and survival, rehabilitation, and long-term mental health consequences of trauma and injury. The program is also supported by the World Health Organization, the Pan American Health Organization, and CDC.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/trauma/index.htm](http://www.fic.nih.gov/programs/training_grants/trauma/index.htm)
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (FIC)

**Cochlear Implants:** One of the more groundbreaking biomedical achievements in the last 30 years has been the cochlear implant, an electronic device that provides a sense of sound to individuals who are profoundly deaf or severely hard-of-hearing. Cochlear implants process sounds from the environment and directly stimulate the auditory nerve, bypassing damaged portions of the inner ear. Nearly 100,000 individuals worldwide have been fitted with cochlear implants. In the United States, approximately 22,000 adults and nearly 15,000 children have received them. Derived in part from NIH-funded research that dates back to the early 1970s and continues today, this remarkable technology has enabled deaf and severely hard-of-hearing individuals to enjoy an enhanced quality of life. NIH-supported scientists showed that profoundly deaf children who receive cochlear implants at an early age develop language skills at a rate comparable to that of children with normal hearing. They also found that the benefits of the cochlear implant in children far outweigh its costs. Scientists can now study the large groups of children who were identified early for hearing loss and use this knowledge to document how treatments such as cochlear implants can lead to improved speech and language acquisition, academic performance, and economic outcomes for these children.

- [Nicholas JG, Geers AE. \*Ear Hear\* 2006;27:286-98](#), PMID: 16672797
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*.
- (E) (NIDCD)

## **NIH Strategic Plans Pertaining to Life Stages, Human Development, and Rehabilitation Research**

### **National Institute of Child Health and Human Development (NICHD)**

- [From Cells to Selves Strategic Plan for the NICHD, 2000](#)
- [Reproductive Health for the 21st Century, 2001](#)
- [Developmental Biology, 2001](#)
- [Genetics and Fetal Antecedents of Disease Susceptibility, 2001](#)
- [Biobehavioral Development, 2001](#)
- *Targeting Sudden Infant Death Syndrome (SIDS): A Strategic Plan, 1995, 1998, 2001*
- [Demographic and Behavioral Sciences Branch Goals and Opportunities, 2002-2006](#)
- [Pregnancy and Perinatology Branch Strategic Plan, 2005-2010, 2003](#)



**Branch Reports to Council with Future Scientific Directions:**

- [\*Mental Retardation and Developmental Disabilities \(MRDD\) Branch, Report to the NACHHD Council, June 2005\*](#)
- [\*National Center for Medical Rehabilitation Research \(NCMRR\) Report to the NACHHD Council, January 2006\*](#)
- [\*Developmental Biology, Genetics and Teratology Branch Report to the NACHHD Council, September 2006\*](#)
- [\*Pediatric, Adolescent, and Maternal AIDS Branch \(PAMAB\), NICHD, Report to the NACHHD Council, June 2007\*](#)
- [\*Reproductive Sciences Branch, NICHD Report to the NACHHD Council, January 2007\*](#)
- [\*Demographic and Behavioral Sciences, NICHD Report to the NACHHD Council, September 2007\*](#)
  - [\*Demographic and Behavioral Sciences \(DBS\) Branch Long-Range Planning 2006-2007: Highlights from a Panel Discussion\*](#)

**National Cancer Institute (NCI)**

- [\*NCI Strategic Plan for Leading the Nation\*](#)

**National Institute of Dental and Craniofacial Research (NIDCR)**

- [\*NIDCR Strategic Plan\*](#)
- [\*NIDCR Implementation Plan\*](#)

**National Institute on Aging (NIA)**

- [\*Living Long and Well in the 21st Century: Strategic Directions for Research on Aging\*](#)

**National Institute on Drug Abuse (NIDA)**

- [\*NIDA Draft Strategic Plan\*](#)

**National Institute on Deafness and Other Communication Disorders (NIDCD)**

- [\*NIDCD Action Plan on Research Careers for Deaf Individuals\*](#)

**National Institute on Alcohol Abuse and Alcoholism (NIAAA)**

- [\*National Institute on Alcohol Abuse and Alcoholism Five-Year Strategic Plan FY08-13\*](#)

**Recommendations of the NIAAA Extramural Advisory Board (EAB)**

- [\*Fetal Alcohol Spectrum Disorders Research\*](#)
- [\*Mechanisms of Behavioral Change\*](#)

**National Institute of Nursing Research (NINR)**

- [\*NINR Strategic Plan: Changing Practice, Changing Lives\*](#)

**Office of Dietary Supplements (ODS)**

- [\*Promoting Quality Science in Dietary Supplement Research, Education, and Communication: A Strategic Plan for the Office of Dietary Supplements, 2004-2009\*](#)

**Trans-NIH Strategic Plans**

- *NIH Research Plan on Down Syndrome*  
(**NICHD**, NCI, NHLBI, NIA, NIAID, NIDA, NIDCD, NIDCR, NIMH, NINDS)
- *NIDDK Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*  
(CC, CSR, NCCAM, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)

## MINORITY HEALTH AND HEALTH DISPARITIES

*The Medical Committee for Civil Rights (later the Medical Committee for Human Rights) was formed in the early 1960s and participated in the 1963 March on Washington, where Dr. Martin Luther King gave his famous “I have a dream” speech. The group succeeded in highlighting racial inequalities in American medicine during a time when racial segregation in professional medical associations, hospitals, and medical education was commonplace. It was at the second National Convention of the Medical Committee for Human Rights that Dr. King made a less well-known but equally profound speech, stating, “Of all the forms of inequality, injustice in health is the most shocking and the most inhumane.”*

### Introduction

Despite remarkable progress in the biomedical sciences in recent years—understanding diseases and their mechanisms and enhancing the ability to prevent, diagnose, and treat disease—significant segments of the U.S. population still are more likely than others to suffer elevated morbidity and mortality and disproportionate incidence of diseases and adverse outcomes such as cancer, cardiovascular disease, diabetes, HIV/AIDS, and infant mortality. Collectively, the term *health disparity populations* refers to racial and ethnic minorities (African Americans, Hispanics, American Indians, Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islanders) and medically underserved populations, including individuals of low socioeconomic status and those living in rural areas.

Characterization of the root causes of these health disparities has been and will continue to be the focus of considerable NIH research. As results of investigations in this area have been published over the years, a broad-brush portrait has begun to emerge of the overall causal factors contributing to the creation and persistence of health disparities. It is clear at this point that these problems are often complex and multifactorial—the unfortunate end results of an interwoven and sometimes overlapping array of disparate factors, including societal, biological, behavioral, and environmental effects. For example, studies have shown that poverty and lack of education correlate with poor health and reduced life expectancy. There is well-documented evidence that discrimination based on racial, ethnic, and linguistic differences persists in the United States and has been shown to be a biological stressor as well as an ongoing barrier to access to and quality of health care. Those barriers all too often coalesce with lack of access to health care or access only to substandard health care. In addition, some racial and ethnic minority groups are genetically susceptible to certain diseases, and this places them at increased risk when such inherited biological vulnerabilities combine with adverse social and environmental factors (e.g., poor diet, chemical exposures, economic stress). These are but a few of the many interrelated factors that contribute to the existence of unacceptable health disparities in the United States, which emphasizes the need for population research.

Thus, as the U.S. population in general has become significantly healthier in recent decades, too many individuals have continued to suffer poor health, disability, and/or premature death due to

factors beyond their immediate control and conditions beyond their personal choice. Overcoming health disparities is the Nation's foremost health challenge—a formidable challenge, no doubt, but one that can and will be met through gains in knowledge and the application of that knowledge in forthright, effective interventions.

In keeping with its role as the steward of medical and behavioral research for the Nation, NIH is firmly committed to reducing and ultimately eliminating health disparities in the United States. To achieve the vision of a time when all have the opportunity for long, healthy, and productive lives, NIH incorporates the goals of improved minority health and reduced health disparities in its support of biomedical and behavioral research, research training, research capacity, outreach, and research information dissemination.

Many of these activities are multidisciplinary collaborations involving several ICs, the entire NIH, or NIH working with other entities. Efforts are guided by the *NIH Health Disparities Strategic Plan, Fiscal Years 2004-2008*, a comprehensive, continuously evolving document that sets the overarching health disparities agenda for the entire agency. The plan, approved by the National Advisory Council on Minority Health and Health Disparities but awaiting formal clearance, focuses on three major goals: (1) to conduct and support intensive *research* on the pathophysiological, epidemiological, and societal factors underlying health disparities; (2) to expand and enhance *research capacity* to create a culturally competent workforce; and (3) to engage in aggressive, proactive *community outreach, information dissemination, and public health education*. All NIH ICs have a minority health/health disparities strategic plan, and those plans are captured within the NIH-wide plan. NCMHD takes the lead on NIH's health disparities agenda related to those three goals.

Established in 2000 to conduct and support research, training, dissemination of information, and other programs with respect to minority health conditions and other populations with health disparities, NCMHD's mission is to promote minority health and to lead, coordinate, support, and assess NIH efforts to eradicate health disparities. For example, NCMHD supports 76 Centers of Excellence across the Nation devoted to health disparities research, training, and outreach and has supported more than 400 collaborative research projects by creating partnerships with ICs and other agencies within DHHS.

## **Burden of Illness and Related Health Statistics**

Ongoing health disparities affecting racial and ethnic minorities are well documented and are seen in a broad spectrum of diseases and adverse outcomes. The findings consistently have shown that minorities are less likely than Whites to receive needed services, including clinically necessary procedures. These disparities are sometimes associated with socioeconomic differences and tend to diminish significantly and, in a few cases, disappear altogether when socioeconomic factors are controlled. However, some racial and ethnic disparities remain even after adjustments are made for socioeconomic differences and other factors related to health care access.<sup>94</sup>

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<sup>94</sup> Institute of Medicine. *The Unequal Burden of Cancer: An Assessment of NIH Research and Programs for Ethnic Minorities and the Medically Underserved*. Washington, DC: National Academy Press, 1999.

Despite remarkable reductions in cardiovascular morbidity and mortality over the past four decades, minorities still bear a disproportionate share of the burden. Heart disease rates have been consistently higher for the African American population than for Whites. In 2004, heart disease age-adjusted death rates for African American men (342.1 per 100,000) and African American women (236.5 per 100,000) were 30 and 37 percent higher than for White men and women, respectively.<sup>95</sup> Similarly, in the period 1999-2004, stroke affected 3.4 percent of the African American population under 75 years old, versus 1.9 percent of Whites under 75.<sup>96</sup> Stroke mortality in that age group was two to three times higher in African Americans than in Whites.<sup>97</sup> Death certificate data from 2002 showed that mean age at stroke death was younger among African Americans, American Indians/Alaska Natives, and Asians/Pacific Islanders than among Whites and was also younger among Hispanics than non-Hispanics.<sup>98</sup>

Cancer deaths vary by gender, race, and ethnicity, but certain racial and ethnic groups have been shown to have lower survival rates than Whites for most cancers. For example, colorectal cancer incidence and death rates are higher among African Americans than among Whites. African American men have the highest rates of prostate, lung, colon/rectum, and oropharyngeal cancers.<sup>99</sup>

African Americans comprised approximately 13 percent of the U.S. population but accounted for 49 percent of the estimated 38,096 new HIV/AIDS diagnoses in 2005 in the 33 states with long-term, confidential name-based HIV reporting. In 2005, HIV/AIDS rates were 72.8 per 100,000 among African Americans, 28.5 among Hispanics, 10.6 among American Indians/Alaska Natives, 9.0 among Whites, and 7.6 among Asians/Pacific Islanders.<sup>100</sup>

In 2004, infant mortality rates showed a persistent disparity between African Americans (13.7 deaths per 1,000 live births) and Whites (5.7 deaths per 1,000 live births).<sup>101</sup> Rates of premature birth are also higher for minority groups. Data from 2003 show that the rate of premature birth was 17.6 percent among African Americans and 13.5 percent among American Indians, whereas the rate for Whites was 11.5 percent and the rate for Asians and Pacific Islanders was 10.5 percent. For African Americans, there is also a higher percentage of low-birth-weight babies. In 2003, 13.4 percent of African American babies were born at low birth weight, compared with 6.9 percent of White babies.

The prevalence of type 2 diabetes in the African American population is nearly 70 percent higher than among Whites. American Indians and Alaska Natives have a diabetes rate more than twice that of Whites. Other health disparity populations, such as Hispanics and Asians/Pacific Islanders, also suffer disproportionately from diabetes and its complications. Hispanics are twice

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<sup>95</sup> For more information, see <http://www.cdc.gov/nchs/data/hus/hus06.pdf>

<sup>96</sup> For more information, see <http://www.nhlbi.nih.gov/resources/docs/cht-book.htm>

<sup>97</sup> For more information, see <http://www.cdc.gov/nchs/data/hus/hus06.pdf>

<sup>98</sup> For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5419a2.htm>

<sup>99</sup> For more information, see [http://seer.cancer.gov/csr/1975\\_2004](http://seer.cancer.gov/csr/1975_2004)

<sup>100</sup> For more information, see <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2005report/>

<sup>101</sup> For more information, see [http://www.cdc.gov/nchs/data/nvsr/nvsr54/nvsr54\\_19.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr54/nvsr54_19.pdf)

as likely to die from diabetes as are Whites and also have higher rates of obesity and high blood pressure.<sup>102</sup>

The prevalence of asthma among non-Hispanic African Americans was approximately 30 percent higher than among non-Hispanic Whites and approximately double that of Hispanics.<sup>103</sup>

Disease burden associated with mental disorders varies across ethnic minority populations. Native American and Alaska Natives, for example, not only suffer disproportionately from depression but also experience a higher rate of suicide than other populations.<sup>104</sup> Although African Americans are less likely than Whites to experience a major depressive disorder, when they do, it tends to be more severe and lasts nearly 50 percent longer.<sup>105</sup> Differences also exist within minority populations. Second- or later-generation Caribbean Black, Latino, and Asian immigrants have been found to have higher rates of mental disorders than do first-generation immigrants.<sup>106</sup>

Many oral and dental diseases, including early childhood caries, oral clefting, oral cancers, and some types of periodontitis are more common, more severe, and more often untreated in disadvantaged populations, such as racial and ethnic minorities, low-income families, and inner-city and rural residents.<sup>107</sup>

Clearly, these and the many other disproportionate burdens of disease suffered by racial and ethnic minorities and other disadvantaged population groups in the United States reinforce the importance of addressing health disparities through research, clinical care, public health, and health policy.

## **NIH Funding for Minority Health and Health Disparities Research**

In FYs 2006 and 2007, NIH funding for minority health and health disparities was \$2.766 billion and \$2.744 billion respectively. The table at the end of this chapter indicates some of the research areas involved in this investment (see “Estimates of Funding for Various Diseases, Conditions, and Research Areas”).

### **Summary of NIH Activities**

NIH has made a strong commitment to reduce and ultimately eliminate health disparities in the United States. Given the multifactorial causes of health disparities, the complex array of their manifestations in vulnerable populations, and the multidisciplinary approaches required to

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<sup>102</sup> For more information, see <http://www.cdc.gov/nchs/nhis.htm>; [http://www.cdc.gov/nchs/products/elec\\_prods/subject/nhanes3.htm](http://www.cdc.gov/nchs/products/elec_prods/subject/nhanes3.htm); [http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2003.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2003.pdf); <http://www.cdc.gov/mmwr/preview/mmwrhtml/00055489.htm>

<sup>103</sup> For more information, see <http://www.niaid.nih.gov/publications/minorityhealth.pdf>

<sup>104</sup> For more information, see <http://www.cdc.gov/ncipc/pub-res/natam.htm>

<sup>105</sup> Joe S, et al. *JAMA*. 2006;296:2112-23, PMID: 17077376

<sup>106</sup> Takeuchi DT, et al. *Am J Public Health*. 2007;97:11-12, PMID: 17138903

<sup>107</sup> For more information, see <http://www.nidcr.nih.gov/DataStatistics/SurgeonGeneral/Report/ExecutiveSummary.htm>



effectively address them, it is appropriate that this commitment is embodied in a wide variety of programs and initiatives, many of which address multiple elements, including population research. Although Research, Outreach, and Research Capacity are the major categories addressed in the *NIH Health Disparities Strategic Plan, Fiscal Years 2004-2008*, many NIH research projects span two or all three of those endeavors. This section will address each of the major categories, providing illustrative examples, along with discussion of several important exemplary programs and/or accomplishments that do not conform to a single category.

## **Research**

### ***Basic, Clinical, and Translational Research***

One of the most important steps on the path to eradicating health disparities is to gain useful new knowledge regarding the causes, mechanisms, natural history, prevention, and treatment of diseases in which disparities have been demonstrated. As the Nation's leader in biomedical research, NIH conducts and supports basic, clinical, and translational research designed to illuminate the relationship between disease and disparities and improve patient quality of life.

For example, sickle cell disease, caused by a genetic defect, afflicts mainly African Americans, 1 in 12 of whom carries the trait. NIH funds 10 [Comprehensive Sickle Cell Centers](#) (CSCCs), which focus on multidisciplinary programs of basic, applied, and clinical research and also provide relevant patient services in diagnosis, counseling, and education concerning sickle cell disease and related disorders. The CSCCs also support multicenter Phase II clinical trials, neuroimaging studies, and the development of a collaborative database of individuals from participating centers who are potentially eligible for inclusion in any sickle cell research study. Ten centers are funded through FY 2007, and the program will be renewed in FY 2008.

The [Jackson Heart Study](#), a partnership of NIH and three local academic institutions, is the largest investigation of cardiovascular disease that has been undertaken in an African American population—a cohort of more than 5,000 African Americans in the Jackson, Mississippi, area. Death rates for cardiovascular disease in the United States are considerably higher among African Americans. Cardiovascular disease death rates in Mississippi are the highest in the Nation and are particularly high among African Americans. One important component of this longitudinal study is the use of new imaging techniques to assess physiological characteristics that may yield a significant additional understanding of heart disease in this minority population.

The Centers of Research Translation program translates basic research discoveries into clinical trials for diagnostic approaches and treatments. The focus of one of the current centers is on lupus, an autoimmune disease that disproportionately affects African American women as well as women of Hispanic, Asian, and Native American descent. Investigators are examining the role of different cell types in the origin and development of lupus and developing markers of disease activity and severity with the goal of identifying new targets for treatment.

### ***Epidemiological/Population Research***

NIH fosters considerable epidemiological and population research conducted mainly to identify, quantify, and characterize health disparities among populations, to test and monitor the effectiveness of potential interventions, and to monitor the health status of minority groups.

Four large-scale epidemiological studies help to demonstrate NIH activities in this sector. The Hispanic Community Health Study, launched in 2006, is the largest long-term epidemiological study of health and disease in Latin American populations living in the United States. As many as 16,000 subjects of Hispanic origin—4,000 at each of four sites—will undergo a series of physical examinations and interviews to help identify the prevalence of and risk factors for a wide variety of diseases, disorders, and conditions. They also will be followed over time to monitor the occurrence of disease. The study will seek to determine the role of cultural adaptation and disparities in the prevalence and development of disease. It also will investigate why Hispanics are experiencing increased rates of obesity and diabetes and yet have fewer deaths from heart disease than non-Hispanics, and why asthma is more common in certain Hispanic groups.

The need to understand the sources of persistent health disparities in overall longevity, cardiovascular disease, and cerebrovascular disease has led to the development of the [Healthy Aging in Neighborhoods of Diversity across the Life Span](#) (HANDLS) study. By posing fundamental questions about differences in rates and risks for pathological conditions associated with aging, the study aims to disentangle the relationship between race, socioeconomic status, and health outcomes. HANDLS will include 4,000 subjects drawn from socioeconomically diverse African American and White adults in Baltimore, Maryland. The cohort will be followed over a 20-year period to allow longitudinal assessment of aging-related variables and their potential impact on health disparities.

The [Reasons for Geographic and Racial Differences in Stroke](#) (REGARDS) study is an observational study to explore the role of race and geographic differences on stroke risk factor prevalence and stroke incidence and mortality. Thirty thousand individuals, about 50 percent African American and 50 percent White, are participating in REGARDS, which has already yielded important new information about disparities in stroke.

NIH is collaborating on and supporting the Collaborative Psychiatric Epidemiology Surveys, large national surveys exploring the prevalence and characteristics of mental health disorders in the United States. The National Comorbidity Survey-Replication (Harvard Medical School), the National Latino and Asian American Study (Cambridge Health Alliance/Center for Multicultural Mental Health Research), and the National Survey of American Life (Program for Research on Black Americans/University of Michigan's Institute for Social Research) will each contribute important information on disparities in the incidence of psychiatric illnesses and mental health service usage and access among racial and ethnic minorities.

## Outreach

Outreach encompasses many forms of activity, with information and intervention campaigns targeted to a wide variety of audiences, including patients, health care providers, public health educators and officials, policymakers, professional and patient advocacy organizations, and community-based groups. Disseminated information may be oriented toward a particular disease (e.g., diabetes, oral cancer, stroke), a particular group (e.g., African American men, Hispanics at high risk of HIV/AIDS, women of reproductive age), or both. Along with communications, outreach initiatives also include activities such as consultations, internships, and partnerships and collaborations with various public and private organizations.

For example, NIH and CDC work together in a grassroots education campaign called [Know Stroke in the Community](#), which enlists community leaders to become “Stroke Champions” to educate their neighbors about the signs and symptoms of stroke. The program focuses on reaching African Americans, Hispanics, and seniors (see also the section “Health Communication and Information Campaigns and Clearinghouses” in Chapter 3). Additionally, NIH collaborates with the National Coalition of Ethnic Minority Nurses Associations to increase awareness of NIH research opportunities for underserved investigators.

A wide variety of programs conduct interventions and education directly in communities in need. NIH’s Oral Health Disparities Centers, which use innovative, low-cost approaches to address severe early childhood caries and oral cancer, are an excellent example of this approach. With the promising achievements of the five currently funded centers and the ongoing need to reverse severe disparities in oral health among some populations, NIH announced in May 2007 that it will fund a competing renewal of the initiative.

Many programs aim to increase health literacy among affected groups and/or to help disparity populations overcome existing barriers to access to health care. Cultural relevancy is an important factor in the success of these efforts to effectively communicate science-based medical and health information to minorities and underserved populations.

In some instances, the approach can be as straightforward—and as powerful—as communicating important information in another language. For example, [infoSIDA](#) is a Spanish-language version of the comprehensive *AIDSinfo* Web site administered by NIH. Some health disparities outreach efforts are segments of wider campaigns. Others expand upon successful campaigns by incorporating culturally relevant scenarios. For example, rather than translating its “Learn the Link” public service announcement about the link between noninjection drug abuse and HIV, NIDA created a culturally relevant public service announcement that would resonate with Hispanic audiences and released both Spanish-language and bilingual versions for English-language stations with large Hispanic audiences. The [National Diabetes Education Program](#) (NDEP) and the [National Kidney Disease Education Program](#) (NKDEP) both tailor materials for minority groups at high risk. With diabetes rates soaring within the Hispanic population, NDEP’s action plan encourages Hispanics to manage the “ABCs” of diabetes—**A**1C (a test that measures 120-day blood glucose levels), **B**lood pressure, and **C**holesterol—to lower their risk for cardiovascular disease and other diabetes complications to improve their health and the health of future generations. NKDEP targets certain materials to African Americans, who are

disproportionately vulnerable to kidney disease due in large measure to their elevated rates of diabetes and high blood pressure. More comprehensively, the National Network of Libraries of Medicine, with more than 5,800 full and affiliate members, is a key component of NIH'S outreach program and its efforts to reduce health disparities and improve health information literacy, particularly for underserved populations.

Enhanced access and improved care are the goals of the [Patient Navigation Research Program](#), an initiative that provides individualized attention to cancer patients, survivors, families, and caregivers, to help them access and then chart a course through the complexities of the health care system and overcome any barriers to quality care. The [Community Networks Program](#) aims to reduce and eliminate cancer health disparities among racial and ethnic minorities. Twenty-five projects across the United States and American Samoa address cancer disparities among African Americans, American Indians, Alaska Natives, Native Hawaiians and other Pacific Islanders, Asians, Hispanics, and rural underserved populations.

## **Research/Outreach**

Many NIH activities that address minority health and health disparities incorporate a synergistic blend of research and outreach. These projects may involve one or more outreach elements such as education, awareness, recruitment of study/clinical trial subjects, and a variety of clinical and preventive interventions, often translational in nature. Frequently, programs provide information and interventions to targeted populations on a pilot basis, so that researchers can collect valuable data and feedback on how effectively the initiative is addressing the problem of interest. Many such programs incorporate community-based participatory research, in which scientific inquiry is conducted in partnership with the community of patients, caregivers, and other stakeholders who participate in the research.

[Head Off Environmental Asthma in Louisiana](#) (HEAL), funded in part by NIH, illustrates these concepts in its activities in post-Katrina New Orleans. Childhood asthma is on the rise in the United States, especially among minority inner-city children. Up to 24 percent of minority children living in cities like New Orleans may have asthma. The rapidly increasing rates of asthma are thought to be related in part to increases in allergies and environmental exposures, such as mold, moisture, and other allergens. Lack of access to health care may be another contributing factor. Those problems are especially prevalent in post-Katrina New Orleans, where HEAL conducts research on the effects of exposure to mold and other indoor allergens on children with asthma, as well as inherited differences in their responses. HEAL research will yield important biomedical knowledge about a growing public health problem while contributing to improved care for children with asthma in a challenging environment.

The Gila River Indian Community Longitudinal study of Pima Indians of Arizona, who have the highest prevalence of diabetes in the world, has made substantial progress in identifying genetic, physiologic, and behavioral factors that contribute to obesity and diabetes. The community has benefited from improved treatment and prevention services, leading to better blood glucose control and blood pressure among the Pima with diabetes.

The [Look AHEAD \(Action for Health in Diabetes\)](#) multicenter clinical trial is following 5,100 obese subjects with type 2 diabetes for 11.5 years. The study's objective is to compare the effects on cardiovascular outcomes of a long-term intensive lifestyle intervention designed to achieve and maintain weight loss, as well as a control program of diabetes education and support. The project includes considerable outreach activities to help subjects improve their health.

Low health literacy is a widespread problem, affecting more than 90 million adults in the United States, many of whom are members of disparity populations facing several other barriers to care. *Understanding and Promoting Health Literacy*, a Program Announcement by NIH and the Agency for Healthcare Research and Quality, is designed to encourage empirical research on health literacy concepts, theory, and interventions, to help accomplish the DHHS *Healthy People 2010* objective of improved national health literacy by the decade's end.

## Research Training

Promoting diversity in education and research is an essential component of the NIH mission to improve health through research. NIH and ICs provide several intramural and extramural programs to promote diversity in research training, increasing the breadth of representation and participation of groups that have been shown to be underrepresented, including individuals from underrepresented racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds. These programs address all career levels in the biomedical and behavioral sciences workforce and include clinical research training. The Minority Biomedical Research Support's (MBRS's) Support of Competitive Research (SCORE) Institutional Development Award program supports research projects that foster diverse faculty and student participation in biomedical research, thereby helping to create a growing and diverse cadre of scientists who are making important contributions in the health sciences. The Research Initiative for Scientific Enhancement (RISE) program develops the research potential of faculty and students. NIGMS also supports several research training programs to increase diversity in the biomedical research workforce: the Minority Access to Research Careers (MARC) Undergraduate Student Training in Academic Research (U-STAR) program, predoctoral fellowships, faculty fellowships and Visiting Scientist Fellowships, ancillary training activities, and the Post-Baccalaureate Research Education Program (PREP). The MBRS and MARC programs are institutional programs and do not use race or ethnicity as a criterion for individuals supported by the program. Many of these programs are offered by the NIGMS's Division of Minority Opportunities in Research, which maintains a [Web site](#) that provides centralized information and an [overview of programs by career stage](#). Other examples of extramural and intramural programs include the NIH Academy; the Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research, as mandated by Federal law (Section 487(a)(4) of the Public Health Service Act, as amended); the Undergraduate Scholarship Program (UGSP), as mandated by Federal law (Section 487D of PHS Act, as amended); and the Research Supplements to Promote Diversity in Health-Related Research (Diversity Supplements; PA 05-015).



## Research Capacity

To accomplish its mission to reduce and ultimately eliminate health disparities in the United States, NIH believes that it is imperative to increase and enhance research capacity in this area in order to ensure that current and future needs are addressed. The ultimate goals are to support research, expand opportunities in training, foster career development, and increase research funding for health disparities research. A variety of projects address the need to recruit, retain, and provide career development opportunities for all scientists (particularly those from underrepresented backgrounds), as well as to expand the number of investigators pursuing health disparities research. Such programs provide direct support to individuals and also fund expansion and infrastructure improvements at numerous institutions, including historically Black colleges and universities and others commonly referred to as minority-serving institutions.

Many ICs have existing programs that contribute to increased research capacity in the area of minority health and health disparities. NCMHD leads the Federal effort at NIH to stimulate new research and promote programs aimed at expanding the participation of underrepresented minorities in all aspects of biomedical and behavioral research. The [Research Infrastructure in Minority Institutions](#) (RIMI) research infrastructure grant program is designed to strengthen the research environment of predominantly minority-serving academic institutions through grant support to develop and/or expand existing capacities for institutional and/or individual faculty-initiated basic, biomedical, social, and/or behavioral research programs. Two NIH loan repayment programs seek to recruit and retain highly qualified health professionals who have doctorate degrees and are from health disparity populations and disadvantaged backgrounds to pursue health disparities or clinical research; they are [Loan Repayment Program for Minority Health Disparities Research](#) and the [Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds](#).<sup>108</sup> Today, the NIH has 71 [Health Disparities Centers of Excellence](#) across the Nation. These Centers of Excellence, now located in 26 States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands, support health disparities research, research training, and community involvement to identify factors that contribute to health disparities and to develop and implement new diagnostic, treatment, and prevention strategies (see Chapter 4).

The [Research Centers in Minority Institutions](#) (RCMI) Program began in 1985 in response to congressional report language (House Report 98-911, on the Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill for FY 1985 [July 26, 1984, pages 78-79]) directing funds to “establish research centers in those predominantly minority institutions which offer doctoral degrees in the health professions or the sciences related to health.” RCMI support includes funds to recruit established and promising researchers, acquire advanced instrumentation, modify laboratories for competitive research, and to fund core research facilities and other research support. The [Institutional Development Award](#) (IDeA) program fosters health-related research and increases the competitiveness of investigators at institutions in 23 states and Puerto Rico, which have historically low aggregate success rates for grant awards from NIH. The program facilitates multidisciplinary collaborations, provides workforce development, enhances research infrastructure, and supports research to reduce health disparities

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<sup>108</sup> Sec. 485 G of PHS Act, as amended; Sec. 487 E - F of PHS Act, as amended.



in minority populations within IDeA-eligible states, such as among American Indians, Alaska Natives, Hispanics, and Native Hawaiians and other Pacific Islanders. Each of these and many similar programs throughout NIH contribute to eliminating health disparities in the United States by addressing the national need to develop a diverse, strong, and culturally competent scientific workforce, and by fostering increased research activity focused on health disparities.

## Conclusion

The goal of reducing and ultimately eliminating health disparities in the United States remains one of NIH's top priorities in its efforts to improve and protect the health and well-being of all Americans. Every IC has its own strategic plan to combat health disparities in its area of influence. Agency-wide activities are guided by the comprehensive *NIH Health Disparities Strategic Plan, Fiscal Years 2004-2008*, with NCMHD serving as the focal point for planning and coordinating minority health and health disparities research. NIH is also committed to broadening collaborative relationships developed through partnerships between NIH and institutions and researchers from all populations.

Health disparities arise due to a complex matrix of physical and cultural influences, and a robust, integrative, sustained approach is required to meet the profound challenges they represent. As has been seen in this chapter, that is precisely the approach being taken by NIH in its efforts to eradicate one of the Nation's most perplexing and intransigent public health problems.

## Notable Examples of NIH Activity

### Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

## Basic, Clinical, and Translational Research

**Sildenafil for Pulmonary Hypertension in Adult Patients with Sickle Cell Disease:** In 2006, NIH began a new study to evaluate a course of treatment with sildenafil in patients with sickle cell disease who have pulmonary hypertension. A randomized, double-blind, placebo-controlled, Phase II clinical trial is testing the drug's safety and efficacy in improving exercise capacity, symptoms, and measures of circulatory function. The trial involves approximately 180 patients at extramural sites and at the NIH Clinical Center. Because pulmonary hypertension occurs frequently in persons with sickle cell disease and confers a high risk of death, a positive outcome of this trial would represent an important step toward improved patient care.

- For more information, see <http://www.clinicaltrials.gov/ct2/show/NCT00492531?term=sildenafil>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NHLBI)

**Comprehensive Sickle Cell Centers (CSCCs):** The CSCCs were established in 1972 in response to a Presidential initiative and a Congressional mandate to support multidisciplinary research to expedite development and application of new knowledge for improved diagnosis and treatment of sickle cell disease. In addition to basic research, training, and patient services activities, the CSCCs currently support multicenter Phase II trials, neurocognitive and neuroimaging studies, development of a collaborative database, and a study on the epidemiology of priapism (painful, prolonged erection) among sickle cell patients. Ten centers were funded through FY 2007, and the program was in FY 2008.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-008.html>
- For more information, see <http://www.sicklecell-info.org/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (NHLBI)

**Jackson Heart Study:** The Jackson Heart Study, a large epidemiological study of cardiovascular disease (CVD) among over 5,300 African American residents of Mississippi, has been renewed through FY 2013. The project is exploring genetic, biological, and environmental factors that influence the development and course of CVD in African Americans. It is also seeking to expand minority participation in public health and epidemiological research by providing classes and hands-on training to interested undergraduate students. Moreover, a community health education component is using data derived from the study cohort to develop and disseminate up-to-date information on reduction of risk factors, practice of healthy lifestyles, and adherence to proven risk-reducing therapies.

- For more information, see <http://jhs.jsums.edu/jhsinfo/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NHLBI, NCMHD)

**Centers of Research Translation (CORT):** NIH launched its CORT program to unite basic and clinical research in a way that translates basic discoveries into diagnostic approaches and treatments. The first set of centers, focusing on lupus, orthopaedic trauma care, scleroderma, and a genetic form of rickets (a childhood disorder characterized by a softening and weakening of bones), began in FY 2006 and are funded through FY 2011.

- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Press\\_Releases/2006/11\\_08.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/11_08.asp)
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIAMS)

**Translational Research for the Prevention and Control of Diabetes and Obesity:** NIH is supporting research projects to explore ways to bring knowledge from successful clinical research into medical practice and community settings. Studies are seeking to develop effective, sustainable, and cost-effective methods to prevent and treat type 1 and type 2 diabetes and

obesity in clinical health care practice and other real-world settings. Many of these studies focus on minority populations disproportionately burdened by type 2 diabetes and obesity.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK)

**Trans-NIH Management and Coordination of HIV/AIDS Research in Racial and Ethnic Populations:** In the United States, AIDS disproportionately affects racial and ethnic minority populations. NIH response to the HIV/AIDS epidemic is a unique and complex multi-institute, multidisciplinary research program. NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection and its associated co-infections, opportunistic infections, malignancies, and other complications that are prevalent in or specific to racial and ethnic populations in the United States. This research transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every NIH IC. The Office of AIDS Research (OAR), located within the NIH Office of the Director, coordinates the scientific, budgetary, and policy elements of NIH AIDS research and has established a specific focus on the epidemic in minority communities. The Racial and Ethnic Minorities section of OAR has established the Ad Hoc Working Group on Minority Research, which includes representatives from key ICs, other DHHS agencies, and non-Government experts and community representatives to assist in the development of an annual strategic plan and for collaboration and information exchange about scientific priorities and opportunities. Through its unique, trans-NIH planning, budgeting, and portfolio assessment processes, OAR ensures that research dollars are invested in the highest-priority areas of scientific opportunity, allowing NIH to pursue a united research front against the epidemic in U.S. minority populations.

- For more information, see <http://www.oar.nih.gov>
- (OAR)

**Osteoarthritis:** African Americans have a higher risk of both bilateral radiographic (x ray-defined) knee and hip osteoarthritis than Whites. Two NIH-funded studies have revealed that mechanical stress can increase the production and release of osteoarthritis-related biomarkers. The research highlights the importance, when analyzing biomarkers, of considering the type and degree of physical activity in which patients with osteoarthritis participate.

- [O’Kane JW, et al. \*Osteoarthritis Cartilage\*. 2006;14:71-6, PMID: 16188465](#)
- [Piscocya JL, et al. \*Osteoarthritis Cartilage\*. 2005;13:1092-9, PMID: 16168680](#)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIAMS)

**Systemic Lupus Erythematosus (Lupus):** The incidence of lupus is three times higher in African American women than in White women, and it is also more common in women of Hispanic, Asian, and Native American descent. NIH-supported researchers have reported that, for most women with moderate lupus that is inactive or stable, taking estrogen—whether as oral contraception or hormone replacement therapy—appears to have no detrimental effect on disease activity. Additionally, researchers working in mice have shown that blocking the effects of two proteins, which normally recognize viruses and bacteria and activate immune cell responses

against them, produced different and unexpected effects on disease severity, suggesting these proteins might be new targets for lupus treatment.

- [Petri M, et al \*N Engl J Med.\* 2005;353:2550-8](#), PMID: 16354891
- [Christensen SR, et al. \*Immunity.\* 2006;25:417-28](#), PMID: 16973389
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Press\\_Releases/2005/12\\_22.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2005/12_22.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2007/proteins\\_lupus.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/proteins_lupus.asp)
- (E) (NIAMS, NCMHD, NCRR, NIAID, ORWH)

**Vitiligo:** Vitiligo is a skin disease characterized by a loss of pigment in all people who are affected. The psychological and social consequences can be particularly profound in affected people of color. A study of 133 families with vitiligo found that family members, even those who do not have vitiligo, are also predisposed to other, potentially more serious autoimmune diseases.

- [Jin Y, et al. \*N Engl J Med.\* 2007;356:1216-25](#), PMID: 17377159.
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Press\\_Releases/2007/04\\_10.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/04_10.asp)
- This example also appears in Chapter 2: *Autoimmune Diseases*.
- (E) (NIAMS, NIAID, NIDDK)

## Epidemiological/Population Research

**Multi-Ethnic Study of Atherosclerosis (MESA):** In an ancillary study to the NHLBI-sponsored MESA, retinal disease was assessed in more than 6,000 African American, Hispanic, White, and Asian subjects in this large, population-based study of cardiovascular health. The eyes of African American and Hispanic study subjects are more likely to have signs indicative of diabetic eye disease, whereas the eyes of White and Chinese subjects are more likely to show signs of age-related macular degeneration. Other analyses demonstrate racial and/or ethnic differences in the relative size and characteristics of the blood vessels lining the back of the eye, which are associated with various cardiovascular profiles. Future analyses will expand on these results and will consider the impact of genes, alone and in combination with differential exposure to environmental factors, such as cigarette smoke and air pollution, on retinal health.

- For more information, see <http://www.mesa-nhlbi.org/default.aspx>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E/I) (NHLBI, NEI)

**Value of early HIV Screening, Testing, and Counseling:** HIV/AIDS disproportionately affects several minority groups, particularly African Americans. Although adult and adolescent African Americans make up approximately 13 percent of the population, they accounted for half of the new HIV/AIDS diagnoses in 2001-2005. This disparity is particularly striking because African Americans do not have higher rates of addiction or intravenous drug use than Whites. One contributing factor is that African Americans are often diagnosed with HIV infection at a later point in the illness, increasing their likelihood of progressing to AIDS and of transmitting the disease. As part of efforts to prevent late diagnosis and HIV spread, NIH is working to identify and address the cultural barriers to making HIV screening more acceptable and to strengthen the

link between education, testing and counseling, and treatment within all ethnic groups. Indeed, NIH-supported modeling research has shown that routine HIV screening, even among populations with prevalence rates as low as 1 percent, is as cost-effective as screening for other conditions, such as breast cancer and high blood pressure. These findings have important public health implications, recognized by CDC, which has called for increased HIV screening as part of its recommended guidelines. NIH is eager to advance new HIV rapid-screen technologies and counseling in community drug treatment programs and in criminal justice settings.

- For more information, see <http://www.drugabuse.gov/ResearchReports/hiv/hiv.html>
- For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDA)

**Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS):** HANDLS is a community-based study to evaluate health disparities in socioeconomically diverse African American and white adults in Baltimore. Recruitment to date, which has resulted in almost 2,000 subjects in the Baltimore area, will continue for 2 additional years to complete cohort recruitment of 4,000 subjects. Scientists are using mobile medical research vehicles to make possible on-site bone density and carotid artery imaging, physical examination and blood sampling, physical and cardiovascular performance, subject interviews, cognitive testing, and psychophysiological testing. HANDLS will also include studies of other variables, including: nutrition, environment and neighborhood effects, genetic make-up, family history, access to health care. Subjects will be followed over a 20-year period to allow researchers to gain insights into the physical, genetic, biologic, demographic, and psychosocial traits that may be most critical for healthy aging.

- For more information, see <http://handls.nih.gov>
- (I) (NIA)

**National Epidemiologic Survey on Alcohol and Related Conditions (NESARC):** This nationally representative survey collected comprehensive, detailed data from approximately 40,000 individuals on alcohol consumption, use of 10 categories of drugs, and symptoms of alcohol and specific drug use disorders, as well as mood, anxiety, and personality disorders. In addition to diagnostic criteria, NESARC assessed indicators of impairment and distress due to each disorder, as well as disorder-specific treatment and help seeking. Analysis of these data is ongoing and continues to provide valuable information such as prevalence and comorbidity of mental health and substance use disorders. In addition, because NESARC data includes a representative sample of ethnic and racial minority populations in the United States, a better assessment of the needs of specific populations can be made. One recent study using this data examined differences in the use of alcohol treatment services across the three largest ethnic groups in America. It showed Hispanics and African Americans with higher levels of problem severity were less likely to have used treatment services than Whites with problems of comparable severity, providing useful information about disparities in treatment utilization.

- [Schmidt LA, et al. \*Alcohol Clin Exp Res\* 2007;31:48-56](#), PMID: 17207101
- For more information, see <http://pubs.niaaa.nih.gov/publications/arh29-2/toc29-2.htm>

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E/I) (NIAAA)

**A Look at Drug Abuse Trends: Local to International:** Several major systems of data collection are helping to identify substance abuse trends locally, nationally, and internationally: Monitoring the Future Survey (MTF), the Community Epidemiology Work Group (CEWG), and the Border Epidemiology Work Group (BEWG). All help to surface emerging drug abuse trends among adolescents and other populations and guide responsive national and global prevention efforts. The MTF project, begun in 1975, has many purposes, the primary one being to track trends in substance use, attitudes, and beliefs among adolescents and young adults. The survey findings are also used by the president's Office of National Drug Control Policy to monitor progress toward national health goals. The MTF project includes both cross-sectional and longitudinal formats—the former given annually to 8th, 10th, and 12th graders to see how answers change over time, and the latter given biennially, or every 2 years (until age 30, then every 5 years) to follow up on a randomly selected sample from each senior class. CEWG, established in 1976, provides both national and international information about drug abuse trends through a network of researchers from different geographic areas. Regular meetings feature presentations on selected topics, as well as those offering international perspectives on drug abuse patterns and trends. A recently established Border Epidemiology Work Group represents a collaboration of researchers from both sides of the U.S.-Mexico border. Of special interest are drug abuse patterns and problems in geographically proximal sister cities/areas. Development of a Latin American Epidemiology Network is under way. NIH has also provided technical consultation for the planning and establishment of an Asian multicity epidemiological network on drug abuse.

- For more information, see <http://www.monitoringthefuture.org>
- For more information, see <http://www.drugabuse.gov/about/organization/CEWG/CEWGHome.html>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDA)

**HEALTHY:** The HEALTHY multicenter clinical trial aims to prevent risk factors for type 2 diabetes in middle-school children. A pilot study for HEALTHY found that an alarmingly high 15 percent of students in middle schools enrolling mainly minority youth had three major risk factors for diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease risks for obesity and diabetes. In the full-scale HEALTHY trial, 42 enrolled middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. More than 80 percent of the enrolled students are from minority populations.

- For more information, see <http://www.nih.gov/news/pr/aug2006/niddk-28.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDDK)



**Head Off Environmental Asthma in Louisiana:** Nearly 20 million people, 6.5 million of them children, suffer from asthma in the United States, and minorities are disproportionately represented. NIH and others, co-fund the Head Off Environmental Asthma in Louisiana (HEAL) project to assess the impact on asthma of environmental health conditions that were caused and exacerbated by Hurricane Katrina in New Orleans children, as well as implement an intervention program to address these problems. The Project's three main goals are (1) to conduct an extensive epidemiology study to assess the nature of the environmental and psychological impacts on children in New Orleans of Hurricane Katrina and subsequent flooding; (2) to examine the genetic and environmental risk factors for asthma, including genetic susceptibility to mold toxins, and gene interactions; and (3) to design, implement, and evaluate a case management program to meet the health care needs of children with asthma in a disrupted and highly challenging environment. The project has a clear plan for informing the community of the goals, implementation, and outcome, as well as for receiving input from the community.

- For more information, see <http://www.niehs.nih.gov/heal>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (NIEHS, NCMHD)

**NIH Collaborative Psychiatric Epidemiology Surveys (CPES):** Through cooperative agreements, NIH supports the National Comorbidity Survey Replication (NCS-R), the National Latino and Asian American Study (NLAAS), and the National Survey of American Life (NSAL). These studies are large, nationally representative surveys assessing the prevalence and correlates of mental health disorders. The NLAAS provides national information on the similarities and differences in mental illness and service use of Latinos and Asian Americans. The objectives of the NSAL are to investigate the nature, severity, and impairment of mental disorders among national samples of the African American and non-Hispanic White populations in the United States.

- For more information, see <http://www.hcp.med.harvard.edu/ncs>
- For more information, see <http://www.multiculturalmentalhealth.org/nlaas.asp>
- For more information, see <http://www.icpsr.umich.edu/cocoon/ICPSR/STUDY/00190.xml>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIMH)

**Hispanic Community Health Study:** In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Latin American heritage living in the United States. The project, which will include about 16,000 subjects, is designed to identify factors that predispose individuals to develop heart disease, stroke, asthma, COPD, sleep disorders, dental disease, hearing loss, diabetes, kidney disease, liver disease, cognitive impairment, and other chronic conditions. Characteristics such as diet, physical activity, obesity, smoking, blood pressure, blood lipids, acculturation, socioeconomic status, psychosocial factors, occupation, health care access, environment, and use of medications and dietary supplements will be assessed.

- For more information, see <http://www.nhlbi.nih.gov/new/press/06-10-12.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NHLBI, NCMHD, NIDCD, NIDCR, NIDDK, NINDS, ODS)

**Jackson Heart Study Advanced Imaging Component:** The Jackson Heart Study is a longitudinal study of heart disease and cardiovascular disease in about 5,000 African Americans in the Jackson, Mississippi area. Data collection for this study began in 2000. New imaging techniques that include dynamic MRI of the heart to assess cardiac function and computed tomography (CT) imaging to assess visceral abdominal fat and calcification of the aorta and coronary vessels. These imaging data can provide significant additional understanding of heart disease in this minority population. NIH is in the process of adding these valuable components to the study of heart disease. The CT studies began in spring of 2007, and the MRI studies will begin in early 2008.

- For more information, see <http://www.nhlbi.nih.gov/about/jackson/index.htm>
- (E) (NIBIB, NCMHD, NHLBI)

**U.S.-Born Children of Immigrants May Have Higher Risk for Mental Disorders Than Parents:** In the first studies to examine the effects of immigration and years of residence on the mental health of Caribbean Black, Latino, and Asian populations in the United States, NIH-funded researchers found that immigrants in general appear to have lower rates of mental disorders than their U.S.-born counterparts.

- For more information, see [http://www.nimh.nih.gov/press/immigrant\\_mentalhealth.cfm](http://www.nimh.nih.gov/press/immigrant_mentalhealth.cfm)
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIMH)

**Retinopathy Occurs in Middle-Aged Adults Even Without Diabetes:** Signs of retinopathy are common in the eyes of the elderly, particularly in those with diabetes. In the Atherosclerosis Risk in Communities (ARIC) Study, African American subjects were significantly more likely to have signs of retinopathy (13 percent) than were White subjects (5.5 percent). Among people with diabetes, 27 percent had signs of retinopathy. Unexpectedly, retinopathy signs were also observed in 4.3 percent of people who did not have frank diabetes but tended to have elevated blood pressure. Future studies will examine whether these signs of retinopathy result from high blood pressure and whether they indicate an increased risk of systemic cardiovascular disease or predict a subsequent diagnosis of diabetes.

- [Wong TY et al. \*Am J Ophthalmol\* 2007;143:970-6](#), PMID: 17399675
- For more information, see <http://www.csc.unc.edu/aric>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E/I) (NHLBI, NEI)

## Outreach

**Disseminating Evidence-based Health Information on Diabetes and Digestive and Kidney Diseases:** The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational material on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take “small steps” to prevent type 2 diabetes. NKDEP encourages African American families to discuss kidney disease at family reunions. Both Programs tailor materials for minority groups at high risk. Information Clearinghouses also provide key health information for the public. Recent

campaigns raised awareness of celiac disease and interstitial cystitis. The Weight-Control Information Network provides science-based information on topics such as obesity and nutrition.

- For more information, see <http://www2.niddk.nih.gov/HealthEducation/>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (NIDDK, CDC)

**National Network of Libraries of Medicine:** With more than 5,800 full and affiliate members, the National Network of Libraries of Medicine is the core component of the National Library of Medicine's outreach program and its efforts to reduce health disparities and to improve health information literacy. The Network also seeks to build and improve collaborations with community-based organizations as an effective means of reaching these populations. A major new initiative is the development of a nationwide emergency plan to ensure backup health library services in the aftermath of a disaster and to establish librarians as key community resources in disaster planning and response. In 2006, new 5-year contracts were signed for eight Regional Medical Libraries in the Network.

- For more information, see [www.nlm.gov](http://www.nlm.gov)
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (I) (NLM)

**Patient Navigation Research Program (PNRP):** PNRP is an intervention that addresses barriers to quality standard care by providing individualized assistance to cancer patients and survivors and their families. The program's aim is to decrease the time between a cancer-related abnormal finding, definitive diagnosis, and delivery of quality standard cancer care. PNRP will focus on the four cancers with the greatest disparity in screening and follow-up care: breast, cervical, prostate, and colorectal. Nine PNRPs reach African Americans, American Indians, Asians, Hispanics/Latinos, and rural underserved populations.

- For more information, see <http://crchd.cancer.gov/pnp/pnpr-index.html>
- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI)

**SIDS Outreach in Minority Communities:** Since 1994, when NIH launched its campaign to reduce the risks of sudden infant death syndrome (SIDS), rates have declined more than 50 percent. Yet the disparities in the SIDS rates that existed 13 years ago continue. Today African American infants are twice as likely to die from SIDS as White infants. To help eliminate this disparity, NIH collaborated with national African American women's organizations whose members are conducting community and neighborhood workshops to highlight important yet easy steps to help reduce the risk of SIDS. In Mississippi, where the infant mortality and SIDS rates are among the highest in the country, small stipends from NIH help community organizations conduct SIDS risk reduction workshops in rural parts of the state.

- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NICHD)

**Reducing Disparities in Stroke:** NIH is actively engaged in a number of research projects designed to identify risk factors for stroke in minority populations and enhance prevention and treatment in these groups. The **REasons for Geographic and Racial Differences in Stroke (REGARDS)** Study is an observational study to explore the role of race and geographic differences on the prevalence of stroke risk factors and on stroke incidence and mortality. To date, researchers have recruited approximately 27,000 of a projected 30,000 individuals (about 50 percent African American and 50 percent White) and have already published a number of important findings on their baseline data. NIH has also established an acute stroke research and care center at the Washington Hospital Center, a community hospital in Washington, DC, where more than 75 percent of stroke patients are African American or Hispanic. The Center will collect data to aid in stroke prevention programs and will run two clinical trials, one on secondary stroke prevention and another on increasing the use of tissue plasminogen activator among minorities. The program directly addresses GPRA Goal SRO-8.9.2: “By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities.”

- For more information, see <http://www.regardsstudy.org/index.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NINDS)

**Promoting Early Detection of Oral Cancer in African American Men:** NIH is developing a new series of oral cancer education materials specifically for African American men, who have the highest risk of oral cancer and the lowest 5-year survival rate (only 35.6 percent) of any population in the United States. This is the first national-level effort of its kind. The first piece in the series, “Are You at Risk for Oral Cancer? What African American Men Need to Know,” is now being pretested in Washington, DC; Chicago; Los Angeles; and Columbia, South Carolina. The brochure—along with other complimentary education tools, such as fact sheets, posters, and both print and audio public service announcements—will be distributed to African American community groups around the country.

- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (NIDCR, NCI)

**Science Education Partnership Award (SEPA) Program:** SEPA increases the public’s understanding of medical research by (1) increasing the pipeline of future scientists and clinicians, especially from minority, underserved, and rural kindergarten to grade 12 (K-12) students and (2) engaging and educating the general public on the health-related advances made possible by NIH-funded research. By creating relationships among educators, museum curators, and medical researchers, SEPA encourages the development of hands-on, inquiry-based curricula that inform subjects about timely issues, including obesity, diabetes, stem cells, and emerging infectious diseases. Additionally, SEPA projects are designed to enhance public trust by focusing on topics such as the clinical trials process, patient safeguards, and medical research ethics. Through SEPA exhibits at science centers and museums, the program provides educational and community outreach activities to tens of thousands of people every year. Moreover, SEPA is helping to bridge the educational gap and provide the next step in research and clinical pipelines for K-12 students interested in pursuing a career in biomedical science and providing

professional development opportunities for teachers. Culturally appropriate projects have been developed to enhance the participation of African American, Hispanic, Alaska Native, American Indian, and Native Hawaiian communities. In FY 2007, SEPA supported 70 projects, of which 50 targeted middle- and high-school students and 20 were based in science centers and museums.

- For more information, see <http://www.ncrrsepa.org/>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NCRR)

**Cancer.gov in Español:** This Spanish-language version of the NCI Web site is designed to reach the Hispanic-Latino population—the fastest-growing online audience in the country—to communicate the message that cancer can be prevented and treated and to offer information on all aspects of the disease. The site is specifically tailored for Hispanics and Latinos, and pages are organized around issues of greatest concern. The site will be updated with evidence-based approaches and emerging technologies to ensure that accurate, relevant, and audience-appropriate information is provided. The site demonstrates the commitment to reducing cancer health disparities by making information readily available to underserved populations.

- For more information, see <http://www.cancer.gov/espanol>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NCI)

## Research/Outreach

**Community-Based Participatory Research (CBPR) Program:** NIH supports the development, implementation, and evaluation of intervention research by using community-based participatory research (CBPR) principles and methods in targeting diseases of major public health importance in health disparity communities. This unique multiyear CBPR initiative promotes participatory research collaborations between scientific researchers and their community partners and will engage communities in all stages of the research process for a total of 11 years. This initiative began in FY 2005 with the award of 25 3-year research planning grants. The participatory partnerships formed between researchers and the community are expected to (1) transform the research questions from researcher to community centered; (2) focus the research area, strategies, and methods to address those diseases and conditions of highest community interest and need; and (3) accelerate the identification and testing of interventions that are likely to make the largest difference in the health of the community. This phase will be followed by a competition for 5-year intervention research grants to be awarded in FY 2008 and will conclude with a 3-year research dissemination grant to be awarded in FY 2013. The current CBPR planning grantees are conducting needs assessments, focus groups, and pilot intervention studies for addressing health disparities in diabetes, cancer, cardiovascular diseases, HIV, depression, dental caries, and other diseases and conditions among health disparity populations in 20 states. In May 2007, RFA MD-07-003, “NCMHD Community-Based Participatory Research (CBPR) Initiative in Reducing and Eliminating Health Disparities,” was issued for the 5-year intervention research phase. Awards for this phase will be made in FY 2008. Current CBPR pilot intervention research studies include:



- ▷ Obesity prevention using individual, family, and community-level interventions among Native Hawaiian and Pacific Islanders in Hawaii
  - ▷ Diabetes prevention among Hispanic communities in border areas in Texas
  - ▷ Dental caries prevention among American Indian children in North and South Dakota, Nebraska, and Iowa
  - ▷ Cancer prevention among African Americans in Denver, Colorado by working with churches and faith-based organizations
  - ▷ Hypertension prevention among Filipino Americans in New York City and New Jersey
  - ▷ HIV/AIDS prevention among African Americans in North Carolina
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/rfa-md-07-003.html>
  - (E) (NCMHD)

**Centers of Excellence Program:** The congressionally mandated NCMHD Centers of Excellence Program<sup>109</sup> leads the effort in supporting biomedical and behavioral research in minority health and health disparities research. Launched in 2002, this program has created new partnerships that enable institutions at all levels of research capability to initiate new research programs or build new institutional and community capacity for improving minority health, eliminating health disparities, providing research training, and engaging health disparity communities in efforts to improve their health. The Centers of Excellence Program has supported 88 centers since its inception and has created hundreds of unique partnerships focused on health disparities with hospitals; tribal groups; health plans; health centers; community and faith-based organizations; civic and nonprofit health organizations; and local, city, and State Governments. Of the 88 centers, 31 Exploratory Centers and 26 Comprehensive Centers are currently active. The research conducted by NCMHD Centers of Excellence and its community partners is contributing to both the scientific and lay knowledge base through numerous publications in the peer-reviewed scientific literature; press releases; television spots; other media, including Web sites and local and regional newsletters; and training of community members as lay health advisors. The NCMHD Centers of Excellence and associated grants are located in 31 States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. In FY 2007, new or continuing awards establishing NCMHD Centers of Excellence were made to 40 institutions. Examples of NCMHD Centers of Excellence program projects include:

- ▷ Perceived Discrimination in Healthcare Among American Indians/Alaska Natives
  - ▷ Religious Outlook on Organ and Tissue Sharing: Inflammation and Asthma
  - ▷ Impact of Coronary Heart Disease Risk Perception on Health Behaviors
  - ▷ Physical Activity Assessment in Multi-Ethnic Women
- (E) (NCMHD)

**Research Partnerships:** Fostering partnerships is a key component of the multifaceted NIH strategic approach to eliminating health disparities. The NCMHD funds a broad range of collaborations with the other NIH ICs, DHHS, and other Federal agencies. Through these co-funded projects, the NCMHD magnifies its reach by leveraging the existing strengths, resources,

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<sup>109</sup> Pub. L. No. 106-525, Section 485F



and research potential of its key Federal research partners through an extensive array of research and training initiatives. Since its creation in 2001, NCMHD has provided more than \$300 million to support several hundred research, training, community outreach, and capacity-building projects. The NCMHD will continue to build and support viable partnerships with emphasis on engaging faith-based and community-based organizations in research and outreach. Examples of research partnerships include:

- ▷ *Jackson Heart Study* (with NHLBI), a longitudinal epidemiological study of African Americans, examines genetic, biological, and environmental risk factors for the development and progression of cardiovascular disease.
- ▷ *Sister Study* (with NIEHS) is a national study that investigates environmental and genetic breast cancer risk factors in living or deceased sisters with breast cancer.
- ▷ *Hispanic Community Health Study* (with NHLBI and others) is the largest epidemiological study of health and disease in U.S. Hispanic populations.
- ▷ *Health Disparities Bench-to-Bedside Program* (with the NIH Clinical Center) fosters collaborations between basic and clinical investigators and enhanced recruitment and retention of racial and ethnic minorities in NIH clinical research.
- ▷ *Bridges to the Future Program* (with NIGMS) promotes partnerships leading to improvement in the pool of underrepresented students being trained as the next generation of scientists.
- ▷ *Tribal Epidemiology Centers Program* (with the Indian Health Service) provides epidemiological analysis, interpretation, and dissemination of information and the development and implementation of disease control and prevention programs aimed at eliminating health disparities experienced by American Indians and Alaska Natives.
- ▷ *Racial and Ethnic Approaches to Community Health (REACH 2010)* (with CDC) is a national program for limited large-scale population surveys and surveillance systems to monitor the health status of minority populations.

- (E) (NCMHD)

**Look AHEAD (Action for Health in Diabetes):** This multi-center NIH-led clinical trial is examining the health effects of an intensive lifestyle intervention designed to achieve and maintain weight loss over the long term, through decreased caloric intake and increased physical activity. The impact of the intervention on the incidence of major cardiovascular events will be evaluated in 5,100 overweight or obese subjects with type 2 diabetes. Look AHEAD is one of four trials that collectively address GPRA Goal SRO-6.2.

- [The Look AHEAD Research Group. \*Diabetes Care\* 2007;30:1374-83](#), PMID: 17363746
- For more information, see <http://tinyurl.com/2xaypk>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NIDDK, CDC, NCMHD, NHLBI, NINR, ORWH) (GPRA Goal)

**Community Networks Program (CNP):** This program aims to reduce and eliminate cancer disparities among racial minorities through community-based research, education, and training. The goals of the program are to significantly improve access to and the utilization of beneficial cancer interventions in communities with cancer disparities. A total of 25 projects across the

United States and in American Samoa were launched in May 2005 to address cancer disparities among African Americans, American Indians/Alaska Natives, Hawaiian Natives and other Pacific Islanders, Asians, Hispanics/Latinos, and rural underserved populations. Ten grantees work in local areas, 10 in regional areas, and 5 in national programs. Visit:

<http://crchd.cancer.gov/cnp/overview.html>.

- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI)

**Collaborative Community-Based Research:** NIH is focusing on strategies and best practices for conducting collaborative community-based clinical and translational research, particularly in minority communities and other medically underserved communities where health disparities persist. The Institutional Development Award (IDeA) and Research Centers in Minority Institutions (RCMI) programs are encouraging efforts to build and strengthen partnerships among Government agencies and academic and private-sector organizations that are also working to improve community health outcomes. Translational, community-based research funded in several IDeA states and RCMI-supported Centers, in both urban and rural settings, is focusing on:

- ▷ Enhancing recruitment and retention of research subjects through community buy-in
- ▷ Implementing practical and effective research protocols in community health care settings
- ▷ Developing versatile and sustainable core research infrastructure to encourage community participation and leverage existing resources

In addition, in FY 2007 NIH conducted two workshops to gather specific recommendations from the community that will help shape future initiatives to enhance clinical and translational research in minority and other medically underserved communities ([www.esi-bethesda.com/nccrworkshops/Fostering/index.aspx](http://www.esi-bethesda.com/nccrworkshops/Fostering/index.aspx)). Workshop subjects included other DHHS-agencies, such as AHRQ, CDC, the Indian Health Service, and HRSA.

- For more information, see [www.ncrr.nih.gov/research\\_infrastructure](http://www.ncrr.nih.gov/research_infrastructure)
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCRR)

**Health Partnership Program and Community Health Center:** The Health Partnership Program (HPP) is a community-based, collaborative research program between NIH and Washington, DC, area representatives. Through research with underrepresented patients affected by arthritis and other rheumatic diseases, the HPP studies health disparities and their causes and provides direction for improving the health status and outcomes of affected minority communities. Its Community Health Center (CHC) is the platform for HPP's research, education, and training activities. The Washington, DC, Center provides the community with access to specialized care and health information and NIH researchers with access to patients

most affected by rheumatic diseases. Recently, NIH published “Exploring Perceptions About the Ethics of Clinical Research in an Urban Community.”

- [Grady C et al. \*Am J Public Health\*. 2006;96:1996-2001](#), PMID: 17018826
- For more information, see [http://www.niams.nih.gov/About\\_Us/Mission\\_and\\_Purpose/Community\\_Outreach/Health\\_Partnership/default.asp](http://www.niams.nih.gov/About_Us/Mission_and_Purpose/Community_Outreach/Health_Partnership/default.asp)
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (NIAMS)

**Oral Health Disparities Centers Initiative:** In May 2007, NIH announced plans to fund a competing renewal of the Oral Health Disparities Centers Initiative due to the promising achievements of currently funded centers and the magnitude of the need for scientific advancement to eliminate disparities. Despite the remarkable improvement in the Nation’s oral health over the years, not all Americans have benefited equally. Oral, dental, and craniofacial conditions remain among the most common health problems for low-income, disadvantaged, and institutionalized Americans. Unfortunately, there is no easy, one-size-fits-all solution. Much remains to be learned about the complex array of cultural, economic, genetic, and other contributory factors to these disparities and how best to overcome them. The five currently supported Centers have devised innovative, low-cost approaches to address severe early childhood caries, oral cancer, poor diet, and malocclusion.

- For more information, see <http://grants1.nih.gov/grants/guide/rfa-files/RFA-DE-08-008.html>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIDCR)

**The Gila River Indian Community Longitudinal Study:** The NIH’s Phoenix Epidemiology and Clinical Research Branch studies type 2 diabetes as it occurs among Pima Indians of Arizona, who have the highest prevalence of diabetes in the world. Working closely with Pima volunteers, the Branch has made substantial progress in identifying genetic, physiologic, and behavioral factors that lead to obesity and diabetes. The Branch also has facilitated improved treatment and prevention services in this community, leading to improved blood glucose control and blood pressure in Pima with diabetes. One important result is that the rate of kidney failure due to diabetes in Pima 45 years of age and older has declined since 1990.

- For more information, see [http://intramural.niddk.nih.gov/research/labbranch.asp?Org\\_ID=503](http://intramural.niddk.nih.gov/research/labbranch.asp?Org_ID=503)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIDDK)

**Rural and Frontier Mental Health:** In 2006 and 2007, NIH held several technical assistance workshops in frontier communities, such as Anchorage, Alaska, in order to improve the competitiveness of research grant applications submitted by rural mental health researchers. NIH also convened workshops in Mississippi to enable community mental health workers to cope with the aftereffects of hurricanes.

- (E) (NIMH)

**Know Stroke in the Community Educational Campaign:** In 2004, NIH entered a first-time partnership with the Centers for Disease Control and Prevention (CDC) to launch a new grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders called “Stroke Champions” who worked to educate communities about the signs and symptoms of stroke. The program focuses on reaching African Americans, Hispanics and seniors in communities that have the health care systems in place to treat stroke. In 2005-2006, the program had been implemented in 11 cities, educating 168 Stroke Champions who have conducted more than 600 community events.

- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses* and Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NINDS)

**InfoSIDA:** NIH introduced *infoSIDA*, a Spanish-language version of the *AIDSinfo* Web site, a DHHS-established site that offers the latest federally approved information on HIV/AIDS clinical research, treatment and prevention, and medical practice guidelines. *InfoSIDA* features a customized home page and a search engine that locates Spanish-language resources within *AIDSinfo*. The steering group spans NIH (OAR, NIAID, and NLM), FDA, HRSA, the Center for Medicare and Medicaid Services, and CDC.

- For more information, see <http://aidsinfo.nih.gov/infoSIDA>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (I) (NLM)

**Minority Health:** NIH works in a number of ways to share health information and develop the capacity of minority-serving educational institutions to access and use health information. NLM-sponsored programs focused on historically Black colleges and universities, the National Medical Association and their more than 25,000 physicians and associated patients of African descent, health information networks for refugees, special Web sites with health information for specific populations (Asian Americans, American Indians, peoples of the Arctic), and information fellowships for representatives from American Indian tribes, Native Alaskan villages, and the Native Hawaiian community.

- [Dutcher G. et al., \*J Med Libr Assoc.\* 2007;95:330-6, PMID: 17641769](#)
- For more information, see <http://sis.nlm.nih.gov/outreach.html>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (I) (NLM)

**Community-Based Participatory Research (CBPR):** CBPR is scientific inquiry conducted in communities and in partnership with researchers. Persons affected by the health condition or issue under study, or other key stakeholders in the community’s health, fully participate in each phase of the work. This input offers CBPR the potential to generate better-informed hypotheses, develop more effective interventions, and enhance the translation of research results into practice. The Program Announcement “Community Participation in Research” supports CBPR on health promotion, disease prevention, and health disparities. CBPR is also the theme of the annual NIH Research on Social Work Interventions and Health Summer Institute (July 2007).

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-283.html>
- For more information, see <http://obssr.od.nih.gov/summerinstitute2007/index.html>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (OBSSR, AHRQ, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINR, NIOSH)

**Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery:** A recent report from the Institute of Medicine on unequal treatment, as well as several other recent reviews, show that racial/ethnic minorities less frequently receive appropriate care, which has an adverse impact on their health outcomes, including higher recurrence rates, morbidity, and mortality. This Program Announcement supports research directed at developing methodology and defining the specific ways in which institutional or personal bias influence the health status, health outcomes, and utilization of health services among racial/ethnic minority patients. The Funding Opportunity Announcement also supports the development of interventions designed to reduce racial/ethnic bias or perceptions of racial/ethnic bias in the health care setting.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-206.html>
- (E) (OBSSR, NCI, NHLBI, NIBIB, NIDA, NIDDK)

**Understanding and Promoting Health Literacy:** The DHHS Healthy People 2010 initiative established a national health objective to improve health literacy by the decade's end. Although many diseases and conditions can be prevented or controlled, too often people with the greatest health burdens have few fact-finding skills, the least access to health information, and least effective communication with health care providers. This Program Announcement supports research that increases our understanding of the health literacy problem and its relationship to health disparities, as well as the development of interventions to overcome the adverse consequences of low health literacy.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-020.html>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (OBSSR, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

**Understanding and Reducing Health Disparities: Behavioral and Social Sciences Research Contributions:** This October 2006 conference highlighted three broad areas of action influencing health disparities: policy, prevention, and health care. These themes are the focus of "Behavioral and Social Science Research on Understanding and Reducing Health Disparities." These Program Announcements invite applications for basic research on the behavioral, social, and biomedical pathways giving rise to disparities in health as well as applied research on the development, testing, and delivery of interventions to reduce disparities in these three action areas. They encourage a multilevel, analytic framework (i.e., ranging from individuals to societies) and systems analytic approaches. They include research relevant to a wide range of population groups (e.g., variation by socioeconomic status, race/ethnicity, and rural-urban locality) residing in the United States. Consideration is given to multiple public health issues and

their interactions (e.g., multiple morbidities rather than single illnesses) and to risk factors or causal processes common to various health conditions (e.g., smoking, diet, exercise, access to health care).

- For more information, see <http://obssr.od.nih.gov/HealthDisparities/index.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-07-379.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-07-380.html>
- (E) (OBSSR, CDC, NCCAM, NCI, NCMHD, NEI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS, NINR, NLM)

**Minority Participation in Clinical Trials:** NIH researchers recently reported several trust-enhancing strategies identified through a process of community engagement that may help scientists successfully recruit clinical research subjects in medically underserved populations. Open communication, ensuring confidentiality, and being attentive to the patient's rights before, during, and after the clinical trial are key.

- [Grady C et al. \*Am J Public Health\*. 2006;96:1996-2001](#), PMID: 17018826
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/trial\\_participation.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/trial_participation.asp)
- (NIAMS, CC)

**Culturally Sensitive Educational Program Promotes HIV Prevention Among Latino Adolescents:** In the first randomized, controlled trial of a culturally tailored HIV risk reduction program for Hispanic adolescents, NIH-supported investigators reported long-term success in reducing risk behaviors. HIV and AIDS disproportionately affect Hispanic adolescents; the incidence of AIDS for adult and adolescent Hispanics in 2001 is more than three times higher than among their non-Hispanic White counterparts. Subjects in the study were randomly assigned to one of two interventions: a general health promotion program or the HIV education/prevention program called “¡Cuidate!” (“Take Care of Yourself”). Both programs presented Hispanic cultural values as an important context that supports positive health behaviors. The study found that the adolescents who received the HIV prevention program reported a lower frequency of sexual intercourse, fewer sexual partners, and an increased use of condoms during intercourse for up to 12 months after completing the program. Results also suggested that it is beneficial to provide education on both abstinence and safe sex practices.

- [Villarruel AM, et al. \*Arch Pediatr Adolesc Med\*. 2006;160:772-7](#), PMID: 16894074
- For more information, see <http://www.nih.gov/news/pr/aug2006/ninr-07.htm>
- (E) (NINR)

## Research Training

**Minority Biomedical Research Support/Research Initiative for Scientific Enhancement MBRS/RISE):**<sup>110</sup> MBRS was created in response to a legislative mandate to “increase the numbers of underrepresented minority faculty, investigators and students engaged in biomedical and behavioral research, and to broaden the opportunities for underrepresented minority faculty

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<sup>110</sup> Section 301(a)(3) of the PHS Act, as amended [42 U.S.C. 241 (a)(3)].



and students for participation in biomedical and behavioral research.” Hence, the objective of the MBR program is to support research projects that foster diverse faculty and student participation in biomedical research, thereby helping to create a growing and diverse cadre of scientists who are making important contributions in the health sciences. To accomplish these goals, RISE provides support for faculty and student development activities, which can include on- or off-campus workshops, specialty courses, travel to scientific meetings, and research experiences at on- or off-campus laboratories. Support is also available for evaluation activities. RISE also offers some support for institutional development, which includes limited funds for the renovation or remodeling of existing facilities to provide space for an investigator to carry out developmental activities, limited equipment purchases, and the development of research courses.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-05-127.html>
- (E) (NIGMS)

**Minority Access to Research Careers (MARC) Undergraduate Student Training in Academic Research (U-STAR):** MARC supports special research training opportunities for students and faculty. MARC programs also enable grantee institutions to develop and strengthen their biomedical research training capabilities. As a result, these schools are able to interest students in, and prepare them for, the pursuit of doctoral study and biomedical research careers. MARC training grants and fellowships include U-STAR institutional grants, predoctoral fellowships, faculty predoctoral and senior fellowships, and a visiting scientist program.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-337.html>
- (E) (NIGMS)

**Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research:**<sup>111</sup> The goal of this program is to provide biomedical and behavioral research and research training programs that will result in the recruitment of women and individuals from disadvantaged backgrounds (including racial and ethnic minorities) in an effort to ensure that diverse pools of highly trained scientists will be available in appropriate research areas to carry out the Nation’s biomedical, behavioral, health services, and clinical research agenda. The means used is to improve the diversity of the health-related research workforce by supporting the training of predoctoral students from groups that have been shown to be underrepresented. Such candidates include individuals from underrepresented racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds. These fellowships will enhance the diversity of the biomedical, behavioral, health services, and clinical research labor force in the United States by providing opportunities for academic institutions to identify and recruit students from diverse population groups to seek graduate degrees in health-related research and apply for this fellowship.

- For more information, see <http://grants1.nih.gov/grants/guide/pa-files/PA-07-106.html>
- (E) (OD/OER, NCI, NCCAM, NCR, NEI, NHLBI, NHGRI, NIA, NIAID, NIAMS, NIBIB, NICHD, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NIGMS, NIMH, NINDS, NINR, ODS)

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<sup>111</sup> Section 487(a)(4) of PHS Act, as amended.

**NIH Research Supplements to Promote Diversity in Health-Related Research:** These research supplements, formerly known as Research Supplements for Underrepresented Minorities and Research Supplements for Individuals with Disabilities, have broad eligibility criteria that include consideration of a larger number of backgrounds that could disadvantage individuals. The primary aim of this supplement is to promote diversity in the biomedical, behavioral, and clinical and social sciences research workforce through the recruitment and retention of (1) individuals from racial and ethnic groups shown by the National Science Foundation to be underrepresented in the health-related sciences, (2) individuals with disabilities, and (3) individuals from disadvantaged backgrounds. NIH recognizes a unique and compelling need to promote diversity in the biomedical, behavioral, clinical, and social sciences research workforce. NIH expects efforts to diversify the workforce to lead to (1) the recruitment of the most talented researchers from all groups, (2) an improvement in the quality of the educational and training environment, (3) a balanced perspective in the determination of research priorities, (4) an improved capacity to recruit subjects from diverse backgrounds into clinical research protocols, and (5) an improved capacity to address and eliminate health disparities.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-05-015.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-05-015.html>
- (E) (NCMHD) All NIH ICs participate in this program.

**Minority Institutional Research Training Program:** The purpose of this Kirschstein-NRSA training program is to support training of graduate and health professional students and individuals in postdoctoral training at minority schools that have the potential to develop meritorious training programs in cardiovascular, pulmonary, hematologic, and sleep disorders.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-027.html>
- For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-043.html>
- (E) (NHLBI)

**Minority Institutions' Drug Abuse Research Development Program (MIDARP):** This program aims to support minority institutions wishing to develop their capacity to conduct drug abuse research. Two programs funded under this PA have focused on Hispanic issues in drug abuse. New MIDARP programs have been established at Universidad del Caribe, Hampton University, and Florida International University. MIDARP is based on a program developed approximately 20 years ago. The current program was developed according to the definition of “minority institutions” that is commonly used by NIH and other DHHS agencies, for example, historic designations such as “historically Black colleges and universities” and student enrollment data. In addition, since this is a capacity development program, consideration is given to the applicant organization’s history of sponsored research in drug abuse and addiction. The program will be reviewed to ensure that it furthers NIDA’s science and scientific workforce needs and NIH expectations and policies regarding equitable access to research opportunities for all population groups.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-05-069.html>
- (E) (NIDA)

**NINR Mentored Research Scientist Development Award for Underrepresented or Disadvantaged Investigators:** NINR recognizes a unique and compelling need to promote diversity in the biomedical, behavioral, clinical, and social sciences research workforce, specifically in nursing research investigators. This award program is one approach to increasing the diversity of nurse investigators and enhancing the research capabilities of historically underrepresented or disadvantaged scientists in nursing research by providing additional research career development opportunities with financial support. These awards train scientists in a mentored setting in the development of research programs, in preparation for becoming independent investigators. NINR also recognizes the lack of diversity of qualified nurse scientists in research settings. This award program seeks to address this problem by enhancing the research capabilities of underrepresented or disadvantaged nurse investigators so that these individuals may establish research laboratories and research programs in nursing science. There is abundant evidence that the research, biomedical, and health enterprise will directly benefit from this broader inclusion. The focus of activities for the awardees in this program is mentored research experience to enhance the candidate's career or to gain expertise in a research area new to the candidate.

- For more information, see <http://grants1.nih.gov/grants/guide/pa-files/PAR-05-135.html>
- (E) (NINR)

#### **Minority Health and Health Disparities International Research Training (MHIRT)**

**Program:** In 2006, NIH provided funding for the Minority Health and Health Disparities International Research Training (MHIRT) Program, which allowed 24 academic institutions to implement international training opportunities in health disparities research for more than 150 undergraduate and graduate students. The MHIRT Program contributes to the elimination of health disparities in the United States by developing researchers who better understand health disparities issues from various international perspectives. Many MHIRT subjects are engaged in research that investigates genetic, socioeconomic, behavioral, psychosocial, and fundamental determinants of health disparities. MHIRT trainees are placed worldwide to conduct research and complete their training. The current MHIRT program expires in 2008, and a new MHIRT RFA that will build on the success of the existing program is being developed. In 2006, the majority of MHIRT research projects were focused on biomedical issues related to improving minority health and eliminating health disparities. African American and Latino (Hispanic) undergraduate and graduate students constitute the largest racial and ethnic groups participating in MHIRT training programs.

- (E) (NCMHD)

**Loan Repayment Programs:** To effectively promote a diverse and strong scientific workforce, it is necessary to expand and create transitioning and financial aid programs that help alleviate barriers that often discourage many students from pursuing a research career. The NIH Loan Repayment Programs address this national need by encouraging the recruitment and retention of minority and other scientists in the fields of biomedical, clinical, behavioral, and health services research. Specifically, the Loan Repayment Program for Health Disparities Research (HDR-LRP) is designed to increase the number of highly qualified health professionals in research careers focused on health disparities. Pursuant to Pub. L. No. 106-525, at least 50 percent of the awards will be made to individuals from health disparity populations. The focus of the

Extramural Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds (ECR-LRP) is to increase the participation of highly qualified health professionals from disadvantaged backgrounds in clinical research careers. To develop synergies between the programs and ensure that emphasis is placed on minority health and other health disparities research efforts, the NIH will work to establish links between the LRPs (HDR-LRP and ECR-LRP) and the NIH research priorities.

- (E) (NCMHD, OER)

**NIH Academy:** The NIH Academy provides opportunities for recent college graduates to spend a year engaged in biomedical investigation at the NIH campus. The mission of the Academy is to enhance research dedicated to the elimination of domestic health disparities through the development of a diverse cadre of biomedical researchers. Participants in this program work side by side with some of the leading scientists in the world in an environment devoted exclusively to biomedical research. Seminars and workshops round out the training experience.

- For more information, see <http://www.training.nih.gov/student/pre-irta/previewacademy.asp>
- (I) (OD/OIR)

**Undergraduate Scholarship Program (UGSP):** The NIH Undergraduate Scholarship Program (UGSP) for students from disadvantaged backgrounds was authorized by statute in 1994 and established in 1996. UGSP participants, as mandated under section 487D of the Public Health Service Act, receive up to \$20,000 in scholarship support to defray educational expenses. Scholarship recipients are required to be employees at the NIH IRP for 10 weeks during the summer for each year of scholarship support and to have 1 year of research employment for each year of scholarship support after their graduation. The 1-year service payback can be deferred until the receipt of a terminal degree (Ph.D., M.D., M.D/Ph.D., etc). The aim of the program is to provide students from disadvantaged backgrounds the opportunity to be trained and hired as employees in the NIH Intramural Research Program. To date, 102 students have been awarded scholarships.

- For more information, see <http://www.ugsp.nih.gov/home.asp?m=00>
- (I) (OD/OIR)

**Biomedical Research Training Program for Underrepresented Minorities:** This program has provided minority undergraduate, graduate, and health professional students majoring in the life sciences with the opportunity to receive training in the NHLBI intramural laboratories. This program has been renamed and re-announced as the NHLBI Biomedical Research Training Programs for Individuals from Underrepresented Groups (BRTPUG) to reflect broadened eligibility criteria for the recruitment and participation of diverse individuals in research and research training programs.

- For more information, see <http://www.nhlbi.nih.gov/funding/training/redbook/brtpug.htm>
- (E/I) NHLBI

**Diversity Inventory:** This work in progress is an effort to catalogue existing programs, described in the NIH Health Disparities Strategic Plan, that aim to create a culturally competent workforce by expanding opportunities for research training, career development, and institutional research capacity and infrastructure. This searchable database will be made available online as a comprehensive source of information for potential applicants or other constituents who are interested in NIH programs that are designed to promote diversity in the biomedical research workforce. This inventory will serve as a baseline for the diversity workgroup that was formed to identify and address gaps and needs in the current diversity recruitment practices.

- (NIGMS, NCMHD, OER, OWH)

## Research Capacity

**The Minority Institution/Cancer Center Partnership (MI/CCP):** The MI/CCP program, initiated in April 2000 as a collaboration between NCI and NCMHD, is focused on developing comprehensive partnerships between NCI-designated Cancer Centers and institutions where students who are underrepresented in the biomedical sciences make up a significant proportion of the enrollments as designated by the U.S. Department of Education as Minority-Serving Institutions (MSI). The aims of these partnerships are (1) to provide cancer research training and education to qualified underrepresented students and investigators to strengthen diversity in the cancer research professions and to encourage recruitment of the most talented researchers to pursue careers in research in cancer and cancer health disparities; (2) to improve the quality of the outreach, training, and educational environment for cancer research at the partnering institutions; (3) to improve the ability to recruit subjects from diverse backgrounds into clinical research protocols; and (4) to strengthen the National Cancer Program by broadening the perspective of the cancer research community in setting cancer research priorities and improving the Nation's capacity to address and eliminate health disparities.

- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI)

**Research Endowment Program:** The NCMHD Research Endowment Program specifically targets "Section 736 [Public Health Service Act] Institutions with currently funded Programs of Excellence in Health Professions Education for Underrepresented Minority Individuals." Congress provided for the creation of this unique program, which makes significant investments in the education and training of underrepresented minority and socioeconomically disadvantaged individuals. The Research Endowment Program is an important priority and represents one of the NCMHD cornerstone programs. NCMHD-endowed institutions are using endowment funds to enhance research capacity and infrastructure for research and training, which include strengthening teaching programs in the biomedical and behavioral sciences and related areas, making physical plant improvements, establishing endowed chairs and programs, obtaining equipment for instruction and research, enhancing student recruitment and retention, providing merit-based scholarships, recruiting and retaining faculty and developing instruction delivery systems and information technology in areas that enhance minority health and health disparities research activities, and training minority and disadvantaged scientists in the behavioral and biomedical sciences.

- (E) (NCMHD)

**Research Infrastructure in Minority Institutions (RIMI) Program:** The Research Infrastructure in Minority Institutions Program (RIMI) program was originally created by the NIH National Center for Research Resources (NCRR) and the NIH Office of Research on Minority Health (ORMH), the predecessor to the NCMHD. The RIMI research infrastructure grant program is designed to strengthen the research environment of predominantly minority-serving academic institutions through grant support to develop and/or expand existing capacities for institutional and/or individual faculty initiated basic, biomedical, social, and/or behavioral research programs. The program is flexible and allows institutions to pursue, for example, research efforts that address health disparities among racial and ethnic minorities and the medically underserved, including those who reside in the Southwest Border States, rural communities, Appalachia Region, Mississippi Delta, Frontier States and urban centers of the United States. Further, the RIMI Program helps non-doctoral degree institutions to develop and enhance their capacity and competitiveness to conduct biomedical or behavioral research and develop their research infrastructure, primarily through collaborations with research-intensive universities.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-07-002.html>
- (E) (NCMHD)

**Institutional Development Award (IDeA) Program:** The NIH IDeA program fosters health-related research and improves the competitiveness of investigators in 23 states and Puerto Rico that historically have not received significant levels of competitive research funding from NIH. The IDeA program supports multidisciplinary centers and State-wide collaborative partnerships that increase institutions' capacity to conduct cutting-edge biomedical research. IDeA supports faculty development and enhancement of research infrastructure at institutions and also promotes collaborative community-based research, particularly in minority communities and other medically underserved communities where health disparities persist. The IDeA program supports the IDeANet initiative, which is expanding access to high-performance computational resources for data-intensive science applications and providing bioinformatics software tools and training to investigators. IDeANet began with Lariat, a pilot program that has enabled connectivity in six states (Alaska, Hawaii, Idaho, Montana, Nevada, and Wyoming). IDeANet ultimately will enable all institutions in the IDeA program, as well as subjects in NIH's Research Centers in Minority Institutions program, to engage in national and international collaborations.

- For more information, see [http://www.ncrr.nih.gov/research\\_infrastructure/institutional\\_development\\_award](http://www.ncrr.nih.gov/research_infrastructure/institutional_development_award)
- For more information, see IDeA program evaluation GPRA goal 8.4
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCRR) (GPRA Goal)

**Research Centers in Minority Institutions (RCMI):** The Research Centers in Minority Institutions (RCMI) Program began in 1985 in response to Congressional report language (House Report 98-911, on the Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill for FY 1985 (July 26, 1984, pages 78-79)) directing funds to “establish research centers in those predominantly minority institutions which offer doctoral degrees in the health professions or the sciences related to health.” RCMI support includes funds to recruit established and promising researchers, acquire advanced instrumentation, modify laboratories for competitive research, and to fund core research facilities and other research support. Because



many investigators at RCMI institutions study diseases that disproportionately affect minorities, NCCR support serves the dual purpose of bringing more minority scientists into mainstream research and enhancing studies of minority health. The next step in increasing the research capacity of the RCMIs is to link each of them together.

- For more information, see [www.ncrr.nih.gov/research%5Finfrastructure/research%5Fcenters%5Fin%5Fminority%5Finstitutions/](http://www.ncrr.nih.gov/research%5Finfrastructure/research%5Fcenters%5Fin%5Fminority%5Finstitutions/)
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NCCR, NCMHD, NHLBI, NIA, NIAID, NIAMS, NICHD, NIDA, NIDDK, NIMH)

**Resource Centers for Minority Aging Research (RCMARs):** Since 1997, RCMARs have provided a venue for increasing the number of researchers who focus on the health of older minority adults, enhancing diversity in the professional workforce by mentoring minorities for careers in research on minority health among older adults, improving recruitment and retention of minority older adults in research studies, and creating culturally sensitive health measures that assess the health status of minority older adults with greater precision and increase the effectiveness of interventions designed to improve their health and well-being. An independent evaluation of the success of the RCMAR program is in progress.

- For more information, see <http://www.rcmar.ucla.edu>
- (E) (NIA)

**Combating Health Disparities:** NIH conducts research designed to identify racial and ethnic disparities in the causes and consequences of alcohol use disorders and to develop treatment and prevention strategies to ameliorate them. NIH contributes to all DHHS and White House initiatives designed to address health disparities by (1) increasing access to and participation in DHHS programs, (2) increasing the capacity of minority institutions to conduct research, and (3) promoting health data collection on racial and ethnic minority populations. For example, between 1998 and 2003, NIH increased the capacity of eight minority or minority-serving institutions to conduct alcohol research, using several cooperative agreement mechanisms. Two of these projects have ongoing activity.

- (E) (NIAAA)

**Collaboration with National Coalition of Ethnic Minority Nurse Associations (NCEMNA):** NIH conducts outreach activities focused on health disparities research through its relationship with the National Coalition of Ethnic Minority Nurse Associations (NCEMNA). Comprising five ethnic nurse associations, NCEMNA strives to increase the number of minority nurses in the United States and increase the amount of minority health-related research. Over the past several years, NIH has provided informational materials to NCEMNA member associations to increase awareness of NIH research opportunities for underserved investigators. In addition, NIH has participated in workshops with NCEMNA members, at which NINR senior leadership has presented information about the Institute, and NINR program directors have met individually with prospective investigators and trainees.

- (E) (NINR)

## NIH Strategic Plans Pertaining to Minority Health and Health Disparities Research

### NIH-Wide Strategic Plan

- [NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities, Fiscal Years 2002-2006](#)

CC, CSR, FIC, NCCAM, NCI, **NCMHD**, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, OAR, OBSSR, OIR, ORD, ORWH

Note: Every IC has a Strategic Plan on Health Disparities. These plans are contained with the NIH plan.

- *NIH Health Disparities Strategic Plan, Fiscal Years 2004-2008*  
(To be published; approved by the National Advisory Council on Minority Health and Health Disparities, but awaiting formal clearance)

### National Institute on Allergy and Infectious Diseases (NIAID)

- [Women's Health in the U.S.: Research on Health Issues Affecting Women \(2004\)](#)

### National Institute on Drug Abuse (NIDA)

- [NIDA Draft Strategic Plan](#)

## **ESTIMATES OF FUNDING FOR VARIOUS DISEASES, CONDITIONS, AND RESEARCH AREAS**

The table below provides insight into NIH research funding on the topics addressed in this chapter. The table is adapted from the most recent<sup>112</sup> version of NIH's Estimates of Funding for Various Diseases, Conditions, and Research Areas (<http://www.nih.gov/news/fundingresearchareas.htm>). That publicly available source table displays information that NIH routinely collects on agency-wide funding in areas of special interest. For each area in which NIH collects data on agency-wide funding, the table below indicates whether some of the funding pertains to the topics in this chapter.

### **Important Notes:**

- The FY 2006 and FY 2007 funding levels are based on actual grants, contracts, intramural research, and other mechanisms of support.
- The figures provided are not allocated or set aside for these areas. Rather, the funding level results from myriad individual decisions.
- Funding included in one area may also be included in other areas; for example, Clinical Research includes Clinical Trials, and Fragile X Syndrome, Genetics, and Intellectual Disability each overlap to some extent, as do Topical Microbicides, HIV/AIDS, and Prevention. Because of this overlap, adding the funding of various areas will yield a false sum.
- For most of the areas listed, only a portion of the funding pertains to the indicated topic. For example, only a portion of NIH funding on Agent Orange and Dioxin pertains to Neuroscience and Disorders of the Nervous System, but because a fraction does, that area is checked.

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<sup>112</sup> February 22, 2007.

**Estimates of Funding for Various Diseases, Conditions, and Research Areas**

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>113</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Acute Respiratory Distress Syndrome	\$74	\$48			X				
Agent Orange & Dioxin	17	18		X					
Aging	2,431	2,462	X	X	X		X	X	X
Alcoholism	511	521	X	X	X		X	X	X
Allergic Rhinitis (Hay Fever)	4	5				X			
ALS	44	39		X					
Alzheimer's Disease	643	645		X				X	
American Indians/Alaska Natives	155	141	X	X	X				X
Anorexia	15	12		X			X	X	
Anthrax	150	105			X				
Antimicrobial Resistance	221	269			X				
Aphasia	15	14		X					
Arctic	17	19			X	X			
Arthritis	355	339		X	X	X	X	X	X
Assistive Technology	182	184		X				X	

<sup>113</sup> Chronic diseases and organ systems pertain to almost every area listed in the table. Instead of checking most areas, only the areas addressed in this chapter's section on chronic disease are checked.

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Asthma	283	294				X	X		X
Ataxia Telangiectasia	9	11		X					
Atherosclerosis	337	347		X	X		X		
Attention Deficit Disorder (ADD)	116	107		X				X	
Autism	108	127		X				X	
Autoimmune Disease	598	587		X		X			X
Basic Behavioral and Social Science	1,062	1,104	X	X	X	X	X	X	X
Batten Disease	8	8		X					
Behavioral and Social Science	3,001	3,060	X	X	X	X	X	X	X
Biodefense	1,766	1,735		X	X				
Bioengineering	1,546	1,469	X	X	X	X	X	X	
Biotechnology	9,974	9,814	X	X	X	X	X	X	X
Brain Cancer	178	193	X	X					
Brain Disorders	4,732	4,670		X	X	X			
Breast Cancer	718	707	X					X	X
Cancer	5,575	5,643	X	X	X	X		X	X
Cardiovascular	2,349	2,370	X	X			X	X	X

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Cerebral Palsy	18	16		X				X	
Cervical Cancer	97	96	X						X
Charcot-Marie-Tooth Disease	7	7		X					
Child Abuse and Neglect Research	38	38		X				X	
Childhood Leukemia	53	55	X					X	
Chronic Fatigue Syndrome	5	4		X		X	X		
Chronic Liver Disease and Cirrhosis	408	379	X		X		X		
Chronic Obstructive Pulmonary Disease	67	91					X		
Climate Change	50	47	X		X				
Clinical Research	8,785	9,116	X	X	X	X	X	X	X
Clinical Trials	2,767	2,949	X	X	X	X	X	X	X
Colorectal Cancer	269	282	X						X
Complementary and Alternative Medicine	301	299	X	X	X		X		X
Conditions Affecting Unborn Children	103	110		X	X			X	
Contraception/Reproduction	335	314						X	
Cooley's Anemia	42	34					X		



Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Cost-Effectiveness Research	143	155	X	X	X				X
Crohn's Disease	64	69				X	X		
Cystic Fibrosis	85	82			X	X	X		
Dental/Oral and Craniofacial Disease	413	417	X	X	X		X	X	X
Depression	335	345		X			X	X	
Diabetes	1,038	1,037		X		X	X	X	X
Diagnostic Radiology	712	694	X	X					
Diethylstilbestrol	8	6	X						
Digestive Diseases	1,252	1,234	X	X	X	X	X		
Digestive Diseases (Gallbladder)	7	6					X		
Digestive Diseases (Peptic Ulcer)	17	23			X	X	X		X
Down Syndrome	14	16		X				X	
Drug Abuse (NIDA only)	990	1,001	X	X	X		X	X	X
Duchenne/Becker Muscular Dystrophy	18	23		X					
Dystonia	19	16		X					
Emerging Infectious Diseases	1,857	1,816	X		X				

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Emphysema	17	21	X				X		
Endometriosis	12	12	X				X	X	
Epilepsy	103	105		X					
Estrogen	153	164	X	X				X	
Eye Disease and Disorders of Vision	705	714		X			X		
Facioscapulohumeral Muscular Dystrophy	2	4		X					
Fetal Alcohol Syndrome	29	34		X				X	X
Fibroid Tumors (Uterine)	15	14	X				X	X	
Fibromyalgia	9	9		X			X		
Food Safety	316	278			X				
Fragile X Syndrome	20	27	X	X				X	
Frontotemporal Dementia	33	31		X				X	
Gene Therapy	356	325	X	X	X	X	X		
Gene Therapy Clinical Trials	32	31	X	X	X	X	X		
Genetic Testing	417	395	X				X	X	
Genetics	4,878	4,878	X	X	X	X	X	X	X
Global Warming Climate Change	58	56			X				

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>113</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Health Disparities	2,766	2,744	X	X	X	X	X	X	X
Health Effects of Climate Change	157	164	X		X				
Health Services	929	1,023	X	X	X	X	X	X	X
Heart Disease	2,087	2,126					X	X	X
Heart Disease: Coronary Heart Disease	398	382					X	X	X
Hematology	1,114	1,128	X		X	X	X		
Hepatitis	177	174	X		X		X		
Hepatitis A	3	2			X				
Hepatitis B	36	42	X		X		X		X
Hepatitis C	122	108	X		X		X		
HIV/AIDS <sup>114</sup>	2,902	2,906	X	X	X			X	X
Hodgkin's Disease	21	17	X						
HPV and/or Cervical Cancer Vaccines	14	20	X		X			X	
Human Fetal Tissue	23	19	X	X	X	X			
Human Genome	1,065	1,099	X	X			X		

<sup>114</sup> Includes research on HIV/AIDS, its associated opportunistic infections, malignancies, and clinical manifestations as well as basic science that also benefits a wide spectrum of non-AIDS disease research.

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Huntington's Disease	48	53		X					
Hyperbaric Oxygen	2	2		X					
Hypertension	395	390		X			X	X	X
Immunization	1,438	1,342	X	X	X			X	X
Infant Mortality/Low Birth Weight	478	464		X	X			X	X
Infectious Diseases	3,132	3,059	X	X	X				X
Infertility	40	51						X	
Inflammatory Bowel Disease	72	80	X			X	X		
Influenza	207	271			X				
Injury (total) Accidents/Adverse Effects	355	403		X				X	X
Injury: Childhood Injuries	28	27						X	
Injury: Trauma (Head and Spine)	233	219		X				X	
Injury: Traumatic Brain Injury	85	82		X				X	
Injury: Unintentional Childhood Injury	25	21		X				X	
Interstitial Cystitis	25	23					X		
Kidney Disease	434	450	X	X	X		X		X

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Lead Poisoning	15	15		X				X	
Liver Cancer	88	90	X						X
Liver Disease	450	423			X		X		
Lung	978	1,013	X				X		
Lung Cancer	266	249	X						
Lupus	97	84		X		X			
Lyme Disease	24	22		X	X				
Lymphoma	170	158	X	X	X	X			
Macular Degeneration	60	70		X			X	X	
Malaria	98	104			X				
Malaria Vaccine	35	36			X				
Mental Health	1,824	1,853		X			X	X	X
Intellectual Disability	188	204		X				X	
Methamphetamine	45	45		X			X		X
Mind and Body	136	133	X	X					
Minority Health	2,423	2,407	X	X	X	X	X	X	X
Mucopolysaccharidoses	10	10	X	X			X	X	
Multiple Sclerosis	110	98		X		X			

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Muscular Dystrophy	40	47		X					
Myasthenia Gravis	9	6		X		X			
Myotonic Dystrophy	7	8		X					
Nanotechnology	192	215	X	X	X				
Networking Information Technology R&D	423	507	X				X		
Neurodegenerative	1,217	1,166		X					
Neurofibromatosis	16	13	X	X					
Neuropathy	54	59	X	X			X		
Neurosciences	4,830	4,809	X	X	X	X	X	X	X
Nutrition	1,039	1,075	X	X	X		X	X	X
Obesity	594	661	X	X			X	X	X
Organ Transplantation	363	358	X			X	X		
Orphan Drug	1,255	1,158	X	X	X	X			
Osteogenesis Imperfecta	5	5					X		
Osteoporosis	169	164					X	X	
Otitis Media	17	15			X		X		
Ovarian Cancer	102	103	X						
Paget's Disease	6	4					X		



Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Pain Conditions, Chronic	220	224	X	X			X		
Parkinson's Disease	208	187		X					
Pediatric	3,161	3,173	X	X	X	X	X	X	X
Pediatric AIDS	276	262	X	X	X			X	
Pediatric Research Initiative	141	171		X	X			X	
Pelvic Inflammatory Disease	4	3	X		X			X	
Perinatal: Birth, Preterm (Low Birth Weight)	374	351		X	X			X	
Perinatal: Neonatal Respiratory Distress Syndrome	8	9						X	
Perinatal Period, Conditions Originating in Perinatal Period	407	387		X				X	
Pick's Disease	1	1		X				X	
Pneumonia	145	132			X				
Pneumonia and Influenza	351	405			X				
Polycystic Kidney Disease	32	36	X				X		
Prevention	6,815	6,729	X	X	X	X	X	X	X
Prostate Cancer	348	345	X						X
Psoriasis	8	10				X	X		

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Regenerative Medicine	614	575	X	X	X	X	X	X	
Rehabilitation	324	344	X	X				X	
Rett's Syndrome	5	6		X				X	
Reye's Syndrome	1	1						X	
Rural Health	202	208	X	X	X				X
Schizophrenia	364	358		X				X	
Scleroderma	11	12				X	X		
Septicemia	49	49			X				
Sexually Transmitted Diseases/Herpes	264	288	X	X	X		X	X	X
Sickle Cell Disease	91	94		X			X		
Sleep Disorders	199	190		X					
Smallpox	149	122			X				
Smoking and Health	517	534	X	X			X	X	X
Spina Bifida	11	9		X				X	
Spinal Cord Injury	66	64		X				X	
Spinal Muscular Atrophy	15	11		X					
Stem Cell Research	643	657	X	X	X	X	X	X	

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Stem Cell Research: Human Embryonic	38	42		X	X	X	X	X	
Stem Cell Research: Non-Human Embryonic	110	106	X	X	X	X	X	X	
Stem Cell Research: Human Non-Embryonic	206	203	X	X	X	X	X	X	
Stem Cell Research: Non-Human Non-Embryonic	289	306	X	X	X	X	X	X	
Stem Cell Research Involving Umbilical Cord Blood / Placenta	19	22	X	X	X	X	X	X	
Stem Cell Research Involving Umbilical Cord Blood/Placenta: Human	16	19	X	X	X	X	X	X	
Stem Cell Research Involving Umbilical Cord Blood/Placenta: Non-Human	4	2	X	X	X	X	X	X	
Stroke	342	340		X				X	X
Substance Abuse	1,490	1,523	X	X	X		X	X	X
Sudden Infant Death Syndrome	77	81		X				X	X
Suicide	32	43		X				X	
Teenage Pregnancy	21	16						X	

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems <sup>1,3</sup>	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Temporomandibular Muscle/Joint Disorder	17	15		X			X		
Tobacco	515	536	X	X			X	X	
Topical Microbicides	88	99			X			X	
Tourette Syndrome	13	11		X					
Transmissible Spongiform Encephalopathy	35	43		X	X				
Transplantation	551	534	X	X		X	X		
Tuberculosis	150	166			X				
Tuberculosis Vaccine	22	17			X				
Tuberous Sclerosis	9	12		X			X		
Urologic Diseases	536	526	X		X		X		
Uterine Cancer	28	22	X						
Vaccine Related	1,449	1,358	X	X	X			X	
Vaccine Related (AIDS)	593	597	X		X				
Vector-Borne Diseases	464	424			X				
Violence Research	113	106							X
West Nile Virus	85	69			X				
Women's Health	3,498	3,470	X	X	X	X	X	X	X



# Chapter 3

## Summary of Research Activities by Key Approach and Resource

### FIELDS AND APPROACHES

#### EPIDEMIOLOGICAL AND LONGITUDINAL STUDIES

*In the midst of a devastating cholera outbreak in 1854, John Snow systematically mapped the distribution of deaths in the Soho neighborhood of London and pinpointed water from the now-famous Broad Street pump as the source of the disease. In addition to helping curb future outbreaks by advancing the notion that cholera is transmitted through contaminated water, Snow's efforts helped lay the foundation for modern epidemiological studies, which collect data and test hypotheses relative to a vast range of factors that affect diseases—from genetic variability to socioeconomic status—with the ultimate goal of improving public health.*

#### Introduction

Epidemiological studies examine the causes of health and disease in human populations using a broad range of approaches. Persons or groups can be followed over time in longitudinal studies, or a snapshot of information can be collected at a single point in time. Studies can be done retrospectively, examining outcomes that have already occurred and factors that may have contributed to health or disease, or they can be done prospectively by beginning to monitor a population of interest before a particular disease-related outcome occurs. Some epidemiological studies, such as randomized controlled clinical trials, are experiments that actively test an intervention; others, however, are observational in nature, collecting information about and comparing groups—called cohorts—made up of individuals who share a characteristic of interest (e.g., tobacco use, age, educational status).

The varied approaches to epidemiological research can be employed to answer a broad range of questions, such as:

- “What genetic and environmental factors interact to cause cancer?”
- “What environmental or behavioral factors have led to increased rates of obesity?”
- “How well does vaccination protect elderly people from influenza?”
- “Do patterns of adolescent drug use vary by geographic region?”

In order to address these questions, epidemiological research draws on expertise from a number of disciplines, including, but not limited to, epidemiology, social and behavioral sciences such as economics and demography, genetics, and public health. Although some epidemiological studies may be adequately addressed within a single discipline, collaboration among scientists with a



variety of expertise is necessary to unravel the multifarious factors that contribute to a complex disease such as cancer or diabetes.

Epidemiological research—particularly the large prospective studies with longitudinal followup that are usually the most robust and informative—is time-consuming and expensive, but NIH investment in this type of research over the past half-century continues to yield invaluable results. For example, two generations of offspring born to the original subjects in the [Framingham Heart Study](#), which was initiated in 1948 and identified high blood pressure, smoking, and other now well-known risk factors for cardiovascular disease, are now being followed to identify hereditary factors that contribute to cardiovascular disease. Moreover, repositories of data and biospecimens collected years ago in long-running epidemiological and longitudinal studies are allowing researchers to answer the research questions of today. For example, the NIH [Genes, Environment, and Health Initiative](#) is using DNA samples collected from persons who participated in past studies to systematically identify disease-related genes and gene variants. The combination of genetic and longitudinal data should help elucidate the complex gene-environment interactions that contribute to disease.

NIH is leveraging its past investments as well as its position as one of the foremost research hubs in the world to spur the next generation of truly “big science.” Although technological advances are contributing to this effort, its success is even more deeply rooted in the growing number of scientists working together in a truly interdisciplinary fashion. Such a collaborative approach permits the integration of diverse data from a variety of sources to improve understanding of the factors that converge to cause disease and of the interventions that may reduce disease risk. Equally important, this culture of cooperation is characterized by a willingness to make results publicly available in a timely manner for the benefit of the entire research enterprise.

Beyond interdisciplinary collaboration, however, NIH also recognizes the great potential of a systems approach that integrates genetics, biology, and the social sciences, as well as multilevel studies that illuminate the mechanisms linking features of societies and communities to individual behaviors and health outcomes, often on a global level. This approach often requires an understanding of economic trends and their relationships to both acute and chronic diseases, and it demands explicit consideration of the environment in which health and disease are being studied. It recognizes that factors such as public health policy and neighborhood design may be just as important as genetic variation and individual behavior, and that addressing any of these factors in isolation will result in an inadequate understanding of health and disease. One example of a systems approach to studying disease is the [International Epidemiologic Databases to Evaluate AIDS \(IeDEA\) consortium](#), which is working to harmonize HIV/AIDS data from a number of sources worldwide to gain a better understanding of HIV/AIDS pathogenesis as well as the efficacy of treatment and prevention strategies within different settings and populations.

Building on its past investment, NIH currently supports numerous epidemiological and longitudinal studies to increase understanding of diseases ranging from cancer to Alzheimer’s disease to influenza. Through interdisciplinary efforts and integration of data from a variety of disciplines, NIH is helping to usher in an era of personalized medicine in which the genetic, biological, and behavioral risk factors of an individual are considered within the context of the sociocultural and physical environment. The following section provides an overview of NIH-supported epidemiological and longitudinal studies, followed by “notable examples” of NIH

work in this field across different disease areas. Detailed information on clinical trials, one type of experimental epidemiological study, can be found in the section on Clinical and Translational Research in Chapter 3.

## **Summary of NIH Activities**

The NIH mission encompasses a broad range of activities, from the pursuit of fundamental knowledge about the nature and behavior of living systems to the application of that knowledge to extend healthy life and reduce the burdens of illness and disability. As part of this continuum from basic to applied research, epidemiological and longitudinal studies are critical for the translation of research findings to real-world application at the population level. In addition to testing hypotheses generated through basic, translational, and clinical research, these types of studies often result in the formulation of new or modified hypotheses, spurring new laboratory and clinical studies. Thus, epidemiological and longitudinal studies are essential for linking bench to bedside to population and help ensure that public investment in research delivers tangible value by providing an empirical perspective on the accrual and application of scientific knowledge. Numerous prior and ongoing NIH studies have yielded results with meaningful implications for the health of the population. This progress has been due to a variety of factors, including a longstanding and continuous investment in epidemiological and longitudinal research, a deeply entrenched culture of cooperation, and a commitment to gaining a comprehensive understanding of health and disease.

## **Investments in the Past Continue to Pay Off**

NIH has been investing in epidemiological and longitudinal studies for more than 50 years. The infrastructure created and the data collected from these studies continue to advance understanding of disease and health in new and exciting ways. Prolonged followup also has enormously increased the value of these studies, and their existence helps form the foundation for extraordinary opportunities in biomedical research today. Below are highlights of select NIH research activities that illustrate how findings from long-term population-based studies have elucidated different facets of important public health issues.

Results of large, national longitudinal studies have helped guide medical recommendations for specific populations, substantially improving their health outcomes. For example, in 1991, NIH launched the [Women's Health Initiative](#) (WHI), a national longitudinal study that included nearly 162,000 women of many racial and ethnic backgrounds—the largest and most comprehensive study of women to date. Over the next 15 years, WHI conducted clinical trials and observational studies to identify strategies for preventing heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. One of the most important discoveries of the original WHI studies was that estrogen plus progestin hormone therapy increases risk of breast cancer and may also increase risk of coronary heart disease, stroke, and pulmonary embolism.<sup>1</sup> This evidence led to a precipitous drop in use of hormone replacement therapy by postmenopausal women, which is thought to have contributed to the 6.7 percent

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<sup>1</sup> [Rossouw JE, et al. JAMA. 2002;288:321-33](#), PMID: 12117397

decline in breast cancer incidence observed in the following year.<sup>2</sup> In addition to pursuing the primary study objectives of WHI, NIH encourages investigators to take advantage of the specimens and data accumulated through WHI. To date, nearly 100 ancillary studies have been funded to research myriad issues that affect older women, from domestic violence to periodontal disease. Many of these studies are carrying earlier WHI results back to the laboratory in order to explain and build upon population-level observations. One group is surveying over 1,000 proteins in specimens collected from WHI subjects with the goal of identifying a small group of proteins that will predict both risk of disease and response to hormone therapy.

Long-term longitudinal studies also can uncover health trends related to people's social and cultural behaviors, and thus suggest new health interventions. For instance, a recent analysis of social network data collected on three generations of [Framingham Heart Study](#) subjects revealed that individuals are significantly more likely to become obese if they have a friend, sibling, or spouse who becomes obese. Interestingly, the strongest association was found between friends, not siblings, suggesting that social relationships play an even more important role in obesity than genetic background. Furthermore, the effect was not observed between neighbors who were not friends, indicating that social relationships are more important than geographic or neighborhood factors.<sup>3</sup> The observation that obesity—commonly attributed to genetic and individual behavioral factors—can also spread through social ties has implications for public health interventions and suggests the possibility of harnessing social networks to spread positive health behaviors.

Long-term population studies also have provided insight into intergenerational influences on health and behavior. For example, NIH facilitated extensive research on linkages between parental factors and child development by building on the U.S. Department of Labor [National Longitudinal Survey of Youth](#)—a longitudinal study designed to further understanding of how young Americans move into productive roles in the economy. In 1979, the U.S. Department of Labor began collecting health, income, and educational attainment information on a cohort of 14- to 22-year-olds. In 1986, NIH expanded the study and began amassing extensive information on children born to women of the 1979 cohort on a biennial basis; these children now range in age from 5 years to 20-something. The resulting intergenerational database combines cognitive, social, and physical information about the children with longitudinal information on family background, education, employment history, and economic well-being. Studies on children of the 1979 cohort have spawned over 1,000 publications on health and other outcomes, from the effects of family income on children's health to the effects of public policy on the investment of fathers in their children.

Longitudinal studies also can be used to inform the decisions of policymakers and assess both short- and long-term effects of policies on health or health-related behaviors. In 1975, NIH launched [Monitoring the Future](#) (MTF), a study that tracks the beliefs, attitudes, and behaviors of adolescents and young adults. MTF surveys approximately 50,000 students in grades 8, 10, and 12 each year. Among other things, MTF gathers information on alcohol and other drug use, and its findings have been used by the Office of National Drug Control Policy to monitor progress toward national health goals. Recent survey results show a 24 percent decline among the three grades combined in recent abuse (i.e., during the past month) of “any illicit drug” between 2001

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<sup>2</sup> [Ravdin PM, et al. \*N Engl J Med.\* 2007;356:1670-4](#), PMID: 17442911

<sup>3</sup> [Christakis NA, Fowler JH. \*N Engl J Med.\* 2007;357:370-9](#), PMID: 17652652

and 2007. Also, during this period, marijuana abuse has decreased roughly 25 percent, and teen cigarette use has declined by a third to be the lowest point in the survey's history. The use of ecstasy has declined by more than half, and methamphetamine use has plummeted by more than 60 percent since 2001.<sup>4</sup> This translates to 860,000 fewer youth using illicit drugs, a testament to the impact of targeted drug abuse prevention efforts, which, by depicting emerging trends, such surveys help to inform.

## **Culture of Cooperation**

Bridging the gap between research and application requires the contributions of numerous scientists with diverse expertise. Recognizing this, NIH fosters a culture of cooperation that has yielded consortia of scientists enthusiastic about working together in interdisciplinary teams and willing to make research results immediately and freely available for the benefit of the whole research enterprise. This emerging "big science" paradigm provides support for interdisciplinary epidemiological and longitudinal studies and also promotes the creation of resources and tools that will help the broader scientific community benefit from and build upon these studies.

NIH supports several studies that bring together expertise from multiple fields to more effectively address research questions and/or simultaneously address multiple research questions. For example, the [National Longitudinal Study of Adolescent Health](#) (Add Health) was initiated in 1994 as a joint effort of 18 NIH Institutes and Federal offices to examine how families, peers, schools, and neighborhoods influence the health-related behaviors of adolescents in grades 7 through 12. A new wave of interviews with the original Add Health cohort, now ages 24-32, will include collection of genetic data and biological markers of disease processes, in addition to basic social, individual, and behavioral data. The new design was developed by a collaborative team representing the fields of epidemiology, cardiology, psychology, sociology, behavioral genetics, nutrition, biostatistics, anthropology, medicine, molecular virology, statistics, and survey research. Working together, these diverse teams will address a broad range of research questions that collectively will yield a deeper understanding of the factors influencing the health of young people.

Other multidisciplinary endeavors at NIH have engendered collective analyses, which extend the power of these studies. As an example, the Magnetic Resonance Imaging (MRI) Study of Normal Brain Development receives contributions from several NIH Institutes and Centers, including NICHD, NIDA, NIMH, and NINDS. Researchers with expertise in child development, neuropsychology, neurology, and imaging work together to increase understanding of normal brain development. This longitudinal effort involves coordination of six Pediatric Study Centers distributed across the country, all of which use cutting-edge technology to monitor brain development in approximately 500 children from 7 days to 18 years of age. Importantly, the Centers have developed and adopted a uniform approach to collecting these images to ensure that their data can be collectively analyzed, extending the power and benefit of the study.<sup>5</sup> Data collected through the study are being used to build the Nation's first normative database of MRI

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<sup>4</sup> Johnston, L. D., O'Malley, P. M., Bachman, J. G. & Schulenberg, J. E. (December 11, 2007). "Overall, illicit drug use by American teens continues gradual decline in 2007." University of Michigan News Service: Ann Arbor, MI. [Online]. <http://www.monitoringthefuture.org/>

<sup>5</sup> [Evans AC, et al. \*Neuroimage\*. 2006;30:184-202.](#) PMID: 16376577

images and accompanying clinical and behavioral data, all of which are being made available to the scientific community. This knowledge will be valuable for future laboratory and clinical studies examining the underlying causes of childhood disorders such as mental retardation, developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases.

The MRI database is only one of the many tools NIH has created to facilitate research community access to emerging scientific information. These resources are particularly relevant for genomic studies. Building on recent knowledge gained through the Human Genome Project and the [International HapMap Project](#), NIH has launched a series of consortia that combine multiple cohorts to create powerful, large-scale studies. One of these consortia, the [Cancer Genetic Markers of Susceptibility](#) (CGEMS) study, is performing genome-wide scans to identify genetic variants associated with risk for developing cancer of the breast, prostate, and colon. The [Pancreatic Cancer Cohort Consortium](#) (PanScan) is conducting an analogous scan for pancreatic cancer, and scans are under way for lung, bladder, and other cancers as well. All of the data collected through these studies will be freely available through [caBIG](#) (the Cancer Bioinformatics Grid), a bioinformatics tool being developed for the explicit purpose of transforming cancer research into a more collaborative, efficient, and effective endeavor. CGEMS researchers recently identified a common genetic variant on chromosome 8 that strongly predicts prostate cancer risk; interestingly, genetic variants in this same region also have been associated with breast and colorectal cancers.<sup>6</sup> These discoveries, made through population-based epidemiological studies, are already spawning new laboratory research, allowing scientists to learn more about the molecular basis of prostate and other cancers.

The NIH investment in genome-wide analyses extends well beyond cancer. The [Database of Genotype and Phenotype](#) (dbGaP) was initiated in December 2006 as a platform to archive and distribute data generated by the increasing number of studies exploring the association between specific genes and disease-related traits. dbGaP already contains data from several studies, including the [Age-Related Eye Diseases Study](#), a prospective study of the clinical course of age-related macular degeneration and cataracts, and the Parkinsonism Study, which collected genetic information on neurologically normal and Parkinson's disease patients. This growing repository of freely available genomic data and other similar resources illustrate a staunch commitment to data-sharing that should help generate new hypotheses and spur discoveries that will eventually be translated into effective therapies.

## **A Comprehensive Understanding of Disease**

NIH recognizes that efficient translation of scientific knowledge to population-level application requires a systems approach that integrates genetics, biology, and the social sciences, and also includes multilevel studies that illuminate the mechanisms linking features of societies and communities to individual behaviors and health outcomes. Performing these studies in diverse contexts, from the community to the global level, contributes to a more comprehensive understanding of health and disease. NIH supports a number of studies in the United States and worldwide aimed at uncovering how these diverse elements interact to influence patterns of disease with the goal of identifying new and effective approaches for prevention and treatment.

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<sup>6</sup> [Yeager M, et al. \*Nat Genet.\* 2007;39:645-9](#), PMID: 17401363



Numerous NIH-supported studies examine how genes, biology, behavior, and environment interact to influence disease risk. For example, the [Jackson Heart Study](#), a prospective epidemiological study of cardiovascular disease among African Americans in the Jackson, Mississippi, metropolitan area, is assessing genetic and other risk factors that underlie cardiovascular disease. The study also is considering how sociocultural factors, such as racism, discrimination, and coping strategies, affect disease in African Americans. In another example, the [National Children's Study](#) will track more than 100,000 children from across the United States from the prenatal period through age 21 to examine factors ranging from natural and man-made environment to biological, genetic, social, and cultural influences. Researchers will analyze how these elements interact with each other to influence health and disease in children throughout development. Plans also are under way for the NIH-wide [Genes, Environment, and Health Initiative](#), which will use genomics, proteomics, and metabolomics to assess how genetic variance and environmental exposures influence disease.

In addition to pursuing multifactorial explanations for disease risk, NIH is examining how diverse factors converge to influence an individual's response to interventions. In 2002, the NIH Diabetes Prevention Program revealed that individuals at high risk of type 2 diabetes could substantially lower disease occurrence through intensive lifestyle intervention. Extensive followup of the same cohort through the [Diabetes Prevention Program Outcomes Study](#) also resulted in the identification of a genetic variant that predisposes people to type 2 diabetes. Importantly, researchers found that people with the high-risk genetic variant benefited as much or more from intensive lifestyle intervention as did those without the variant. These types of studies are becoming increasingly important as personalized medicine becomes a tangible reality. Multilevel studies will lay the groundwork for the informed selection of preventive or therapeutic interventions according to genetic, biological, behavioral, and environmental factors.

NIH also uses longitudinal and epidemiological studies to gather information on global patterns of infectious diseases. These efforts not only will advance understanding of the causes of these diseases, but also should contribute to the development of interventions to lessen disease burden in the United States and worldwide. One illustration of this is the Multinational Influenza Seasonal Mortality Study, an NIH-led collaborative that is analyzing national and global epidemiological patterns associated with influenza virus circulation. The goals of this large-scale collaboration are to evaluate and compare public health strategies to alleviate the impact of seasonal influenza in different countries and better understand the global circulation patterns of influenza and their impact on populations. To this end, 20 countries have contributed data on mortality, virus surveillance, genomics, and influenza control strategies. A more comprehensive understanding of influenza epidemiology worldwide will result in the development of better vaccines as well as other types of strategies to avoid future influenza pandemics.

A global perspective is also being acquired through [IeDEA](#) (the International Epidemiological Databases to Evaluate AIDS). This regional collaborative of centers on five continents is focused on the harmonization and integration of data in order to pursue population-level research questions about HIV/AIDS that cannot be addressed in single cohorts. Topics of research will include HIV variants and resistance, HIV pathogenesis in different settings, success of



antiretroviral therapy, treatment history of HIV in different populations, success of prevention strategies, and vaccines.

## **Conclusions**

Epidemiological and longitudinal studies are essential to NIH efforts in bridging the results of basic, translational, and clinical studies to applications in the general population. In addition to testing hypotheses at the population level, observations gathered through these studies help optimize existing interventions and stimulate novel laboratory and clinical research. Many NIH epidemiological and longitudinal studies have had substantial influence on public health. This success is due to a number of factors, including investment in long-term studies, promotion of a culture of cooperation, and pursuit of a comprehensive view of disease. The studies presented here represent only a fraction of NIH efforts in this area. Although still not comprehensive, additional notable examples of NIH-supported epidemiological and longitudinal studies, as well as further information about the activities mentioned above, are found in the following section.

## **Notable Examples of NIH Activity**

### **Key for Bulleted Items:**

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

## **Investments in the Past Continue to Pay Off**

**Framingham SNP-Health Association Resource (SHARe):** The Framingham SHARe is a comprehensive new effort by NIH and the Boston University School of Medicine to pinpoint genes underlying cardiovascular and other chronic diseases. The program builds on the Framingham Heart Study (FHS), which was begun in 1948 to identify factors that contribute to cardiovascular disease, and on other NIH-funded research demonstrating that common but minute variations in human DNA, called single nucleotide polymorphisms (SNPs), can be used to identify genetic contributors to common diseases. The initiative will examine over 500,000 genetic variants in 9,000 study subjects across three generations. NIH will develop a database to make the data available to researchers around the world. The database will help researchers to integrate the wealth of information collected over the years in the FHS with the new genetic data, resulting in an increased understanding of genetic influences on disease risk, manifestation, and progression. Because of its uniqueness in including three generations of subjects with comparable data obtained from each generation at the same age, the FHS is the first study to be included in the SHARe initiative. NIH is currently considering expansion of SHARe to include other large longitudinal studies such as the Jackson Heart Study and the new Hispanic Community Health Study.

- For more information, see <http://www.nhlbi.nih.gov/new/press/06-02-06.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (NHLBI, NLM)

**Women's Health Initiative:** In January 2007, NIH awarded support for a dozen 2-year research projects to apply genomics, proteomics, and other innovative technologies to improve understanding of several major diseases that commonly affect postmenopausal women. The new endeavor builds on results of the long-running Women's Health Initiative, which conducted several clinical trials and an observational study to examine strategies for preventing heart disease, breast and colorectal cancers, and osteoporosis in a cohort of over 160,000 subjects. Investigators will use stored blood, DNA, and other biological samples and clinical data to analyze genetic factors and biological markers that may be useful in predicting disease outcomes or the effects of therapeutic and preventive regimens in postmenopausal women.

- For more information, see <http://www.whiscience.org/baa/2006.php>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (NHLBI)

**Baltimore Longitudinal Study of Aging (BLSA):** In 2008, NIA will celebrate the 50th anniversary of the BLSA, America's longest running scientific study of human aging. More than 1,400 men and women ranging in age from their twenties to their nineties have been study volunteers. The BLSA has generated significant findings to elucidate the normal course of aging and disentangle the effects of disease from the normal aging process.

- For more information, see <http://www.grc.nia.nih.gov/branches/blsa/blsa.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (I) (NIA)

**Osteoporosis:** NIH supports several longstanding prospective cohort studies, including the Study of Osteoporotic Fractures (SOF) in women and Mr. OS, a study of osteoporosis and other age-related diseases in men. Major contributions from the SOF, which began in 1986, include findings that bone mineral density of the hip is one of the best predictors of fracture for women. Recently, Mr. OS researchers identified specific lifestyle, medical, and demographic characteristics associated with low bone mass and fracture risk in older men.

- For more information, see [www.niams.nih.gov/News\\_and\\_Events/Advisory\\_Council\\_Minutes/2006/sum01\\_06.asp](http://www.niams.nih.gov/News_and_Events/Advisory_Council_Minutes/2006/sum01_06.asp) (Section VII - Study of Osteoporotic Fractures)
- See [www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2007/bonemass\\_men.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/bonemass_men.asp)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIAMS, NIA)

**Population Research:** Given the Nation's increasing diversity and changing demographics, it is critical to understand how trends in such areas as immigration, fertility, marriage patterns, and family formation affect the well-being of children and families. NIH research in these areas allows policymakers and program planners to better address public health needs. For instance:

- ▷ The Fragile Families and Child Well-Being Study follows children born to unmarried parents to assess how economic resources, father involvement, and parenting practices affect children's development.

- ▷ The New Immigrant Survey follows the first nationally representative sample of legal immigrants to the United States, providing accurate data on legal immigrants' employment, lifestyles, health, and schooling before and after entering the country.
- ▷ The National Longitudinal Survey of Youth (1979 cohort) continues to assess the work, educational, and family experiences of a nationally representative cohort of young men and women who were 14-22 years old when they were first studied in 1979. The study also follows children born to female subjects up through age 20, creating the opportunity to study intergenerational influences on child development, health behaviors, and educational attainment.

- For more information, see <http://www.fragilefamilies.princeton.edu/index.asp>
- For more information, see <http://nis.princeton.edu/>
- For more information, see <http://www.bls.gov/nls/nlsy79ch.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NICHD, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

**A Look at Drug Abuse Trends: Local to International:** Several major systems of data collection are helping to identify substance abuse trends locally, nationally, and internationally: Monitoring the Future Survey (MTF), the Community Epidemiology Work Group (CEWG), and the Border Epidemiology Work Group (BEWG). All help to surface emerging drug abuse trends among adolescents and other populations, and guide responsive national and global prevention efforts. The MTF project, begun in 1975, has many purposes, the primary one being to track trends in substance use, attitudes, and beliefs among adolescents and young adults. The survey findings are also used by the President's Office of National Drug Control Policy to monitor progress towards national health goals. The MTF project includes both cross-sectional and longitudinal formats—the former given annually to 8th, 10th, and 12th graders to see how answers change over time, and the latter given biennially, or every 2 years (until age 30, then every 5 years) to follow up on a randomly selected sample from each senior class. CEWG, established in 1976, provides both national and international information about drug abuse trends through a network of researchers from different geographic areas. Regular meetings feature presentations on selected topics, as well as those offering international perspectives on drug abuse patterns and trends. A recently established Border Epidemiology Work Group represents a collaboration of researchers from both sides of the U.S.-Mexico border. Of special interest are drug abuse patterns and problems in geographically proximal sister cities/areas. Development of a Latin American Epidemiology Network is under way. NIH has also provided technical consultation for the planning and establishment of an Asian multi-city epidemiological network on drug abuse.

- For more information, see <http://www.monitoringthefuture.org/>
- For more information, see <http://www.drugabuse.gov/about/organization/CEWG/CEWGHome.html>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*, and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIDA)

**The Gila River Indian Community Longitudinal Study:** NIH's Phoenix Epidemiology and Clinical Research Branch studies type 2 diabetes as it occurs among Pima Indians of Arizona, who have the highest prevalence of diabetes in the world. Working closely with Pima volunteers, the Branch has made substantial progress in identifying genetic, physiologic, and behavioral

factors that lead to obesity and diabetes. The Branch also has facilitated improved treatment and prevention services in this community, leading to improved blood glucose control and blood pressure in Pima with diabetes. One important result is that the rate of kidney failure due to diabetes in Pima 45 years of age and older has declined since 1990.

- For more information, see [http://intramural.niddk.nih.gov/research/labbranch.asp?Org\\_ID=503](http://intramural.niddk.nih.gov/research/labbranch.asp?Org_ID=503)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (I) (NIDDK)

**The Role of Development in Drug Abuse Vulnerability:** NIH supports a number of longitudinal studies at various stages of development, following cohorts over extended timeframes. Information is gathered on children's cognitive and emotional development, as well as their vulnerability to addiction later in life. These studies have been critical to estimate, for example, the contribution of in utero drug exposure to emotional and cognitive development, vulnerability to substance abuse, and other mental disorders. This knowledge, together with animal studies that provide complementary and validating information while minimizing the confounding factors that are likely to play a role in prenatal effects of drug exposure in humans, will help us to mitigate the deleterious impact of substance abuse on the developing fetus. With regard to later developmental stages, the application of modern brain imaging technologies has generated unprecedented structural and functional views of the dynamic changes occurring in the developing brain (from childhood to early adulthood). The discovery of these changes has been critical to understanding the role of brain development in decision-making processes and responses to stimuli, including early exposure to drugs. Such studies have suggested, for example, that an unbalanced communication between volitional control and emotional circuits may explain some of the impulsive reactions typical of adolescents, who tend to engage in risky behaviors, and are at heightened risk for developing addictions. Collectively, these longitudinal studies, using new imaging and genetics tools, promise a greatly enhanced ability to interpret the effects of myriad environmental variables (e.g., quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics) on brain development and behavior.

- For more information, see [http://www.drugabuse.gov/NIDA\\_notes/NNvol19N3/Conference.html](http://www.drugabuse.gov/NIDA_notes/NNvol19N3/Conference.html)
- For more information, see [http://www.nida.nih.gov/NIDA\\_notes/NNvol19N3/DirRepVol19N3.html](http://www.nida.nih.gov/NIDA_notes/NNvol19N3/DirRepVol19N3.html)
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NIDA, NICHD) (GPRA Goal)

**The Carolina Lupus Study:** Since 1997, NIH supported the Carolina Lupus Study, the first population-based epidemiologic study to examine the influence of hormonal and occupational exposures, in addition to genetic factors affecting immune function and metabolism, on systemic lupus erythematosus (SLE). SLE is a severe, disabling autoimmune disease that can lead to morbidity and mortality from renal and cardiovascular disease. African Americans are two to three times more likely than whites to develop the disease for reasons unknown. The study included 265 patients and 355 people without lupus living in 60 counties in North and South Carolina. The results for analysis of occupational exposure to silica dust in relation to risk for SLE were striking. Other associations were seen with self-reported occupational exposure to

mercury, in mixing pesticides for agricultural work and among dental workers. Weaker associations were seen between SLE and shift work and among health care workers with patient contact.

- For more information, see <http://dir.niehs.nih.gov/direb/studies/clu/home.htm>
- This example also appears in Chapter 2: *Autoimmune Diseases*.
- (I) (NIEHS)

## **Culture of Cooperation**

### **Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer:**

NIH supports several research consortia that are designed to enhance understanding of cancer control across the continuum of prevention, screening, and treatment within the context of health care delivery.

- ▷ The most comprehensive of these initiatives, the [Cancer Research Network \(CRN\)](#), seeks to improve the effectiveness of preventive, curative, and supportive interventions for major and rare tumors. The CRN consists of the research programs, enrolled populations, and data systems of 13 health maintenance organizations covering care for over 9 million enrollees, or 3 percent of the U.S. population. This initiative uses a consortium of delivery systems to conduct research on cancer prevention, early detection, treatment, long-term care, and surveillance. Given its large and diverse populations, the CRN is uniquely positioned to study the quality of cancer care in community-based settings and to explore rare conditions. Seminal research includes, for example, CRN research documenting specific gaps in implementing effective tobacco cessation services among clinicians, reasons for late diagnosis of breast and cervical cancer, more rapid uptake in the use of aromatase inhibitors in comparison to tamoxifen in treatment for breast cancer, and examination of the role of a number of common drugs and cancer outcomes using its large and automated pharmaceutical databases.
- ▷ In the area of the evaluation of cancer screening in clinical care, the [Breast Cancer Surveillance Consortium \(BCSC\)](#) is a collaborative network of mammography registries linked to tumor and/or pathology registries designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. Because of the vast size and continually updated clinical information in this research initiative, the BCSC is responsible for research that for the first time documented the falling incidence of hormone replacement therapy among screened women, quantified the extent of difference in the association of breast density with breast cancer risk among premenopausal and postmenopausal women, and identified that although biopsy rates are twice as high in the United States in comparison to the United Kingdom, cancer detection rates are very similar in the two countries.
- ▷ In an effort to address how characteristics of patients, providers, and care delivery systems affect the cancer management and treatment services that patients receive, as well as the relationship between cancer-related clinical practices and outcomes, including patient-centered outcomes, such as symptom control and quality of life, the [Cancer Care and Outcomes Research Surveillance Consortium \(CanCORS\)](#) was established. It supports prospective cohort studies on 10,000 patients with newly diagnosed lung or colorectal cancers across geographically diverse populations and health care systems and examines



issues related to health outcomes, costs, and patient-centered issues such as symptom control and quality of life.

- For more information, see <http://crn.cancer.gov/>
- For more information, see <http://breastscreening.cancer.gov>
- For more information, see <http://healthservices.cancer.gov/cancers/>
- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Clinical and Translational Research*, and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (I) (NCI)

**Database of Genotype and Phenotype (dbGaP):** Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGaP to house this growing body of information, particularly the results of genome-wide association studies (GWAS), which examine genetic data of subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2007, dbGaP included results from more than a dozen GWAS, including genetic analyses added to the landmark Framingham Heart Study and trials conducted under the Genetic Association Information Network. dbGaP is to become the central repository for many NIH-funded GWAS in order to provide for rapid and widespread distribution of such data to researchers and accelerate the advance of personalized medicine.

- For more information, see <http://view.ncbi.nlm.nih.gov/dbgap>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Genomics*.
- (I) (NLM)

**NIH Collaborative Psychiatric Epidemiology Surveys (CPES):** Through cooperative agreements, NIH supports the National Co-morbidity Survey-Replication (NCS-R), the National Latino and Asian American Study (NLAAS), and the National Survey of American Life (NSAL). These studies are large, nationally representative surveys assessing the prevalence and correlates of mental health disorders. The NLAAS provides national information on the similarities and differences in mental illness and service use of Latinos and Asian Americans. The objectives of the NSAL are to investigate the nature, severity, and impairment of mental disorders among national samples of the African American and non-Hispanic white populations in the United States.

- For more information, see <http://www.hcp.med.harvard.edu/ncs/>
- For more information, see <http://www.multiculturalmentalhealth.org/nlaas.asp>
- For more information, see <http://www.icpsr.umich.edu/cocoon/ICPSR/STUDY/00190.xml>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIMH)

**Genome-Wide Association Studies of Cancer Risk:** Beginning with the Cancer Genetic Markers of Susceptibility (CGEMS) initiative for breast and prostate cancer, NIH has capitalized on its long-term investment in intramural/extramural consortia by creating strategic partnerships to accelerate knowledge about the genetic and environmental components of cancer induction and progression. Using powerful new technology capable of scanning the entire human genome,



these efforts have recently identified unsuspected genetic variants associated with increased risk for developing cancers of the prostate, breast, and colon. Additional scans, either planned or under way, will be directed at cancers of the pancreas, bladder, lung, and other organs. The results of these genome-wide studies, together with the follow-on studies planned to narrow the search for causal gene variants, promise to provide novel clinical strategies for early detection, prevention, and therapy. To expand upon these emerging opportunities, a new Laboratory of Translational Genomics (LTG) has been established to further characterize genetic regions associated with cancer susceptibility, and to identify gene-gene and gene-environment interactions. The LTG will create opportunities for collaboration and data-sharing in order to accelerate the translation of genomic findings into clinical interventions.

- For more information, see <http://cgems.cancer.gov/>
- For more information, see <http://epi.grants.cancer.gov/BPC3/cohorts.html>
- For more information, see <http://cgems.cancer.gov/index.asp>
- For more information, see <http://epi.grants.cancer.gov/PanScan/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Genomics*.
- (E/I) (NCI)

**Hispanic Community Health Study:** In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Latin American heritage living in the United States. The project, which will include about 16,000 subjects, is designed to identify factors that predispose individuals to develop heart disease, stroke, asthma, chronic obstructive pulmonary disease, sleep disorders, dental disease, hearing loss, diabetes, kidney disease, liver disease, cognitive impairment, and other chronic conditions. Characteristics such as diet, physical activity, obesity, smoking, blood pressure, blood lipids, acculturation, socioeconomic status, psychosocial factors, occupation, health care access, environment, and use of medications and dietary supplements will be assessed.

- For more information, see <http://www.nhlbi.nih.gov/new/press/06-10-12.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NHLBI, NCMHD, NIDCD, NIDCR, NIDDK, NINDS, ODS)

**The Rapid Response Program:** In April 2002, the Task Force on College Drinking released its seminal report *A Call to Action: Changing the Culture of Drinking at U.S. Colleges*. As part of its college focus, NIH initiated support of collaborations between university personnel who have responsibility for alcohol programs on various campuses and established college drinking researchers to implement and evaluate programs to reduce underage alcohol use and its consequences.

- ▷ Dec. 2002 - RFA AA-03-008: “Research Partnership Awards for Rapid Response to College Drinking Problems.” Five U01 (cooperative agreement) 5-year grants were awarded.
- ▷ June 2003 - PAR-03-133: “Rapid Response to College Drinking Problems.” Fifteen 3-year grants were awarded.
  - This rapid funding mechanism (U18, cooperative agreement) supports timely research on interventions to prevent or reduce alcohol-related problems among college students. It was intended to support studies of services or interventions that could capitalize on “natural

experiments” (e.g., unanticipated adverse events, policy changes, new media campaigns, campus-community coalitions)

- Each U18 grantee was required to partner with a U01 grantee. Together, these pairs, working with NIH Scientific Staff Collaborators, jointly design, develop, implement, and evaluate college drinking projects on their campuses.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*, and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIAAA)

**Polycystic Kidney Disease (PKD):** The Consortium for Radiologic Imaging Studies of PKD (CRISP) showed that magnetic resonance imaging could accurately track structural changes in the kidneys in people with the more common form of PKD. An extension, CRISP II, will continue to monitor these patients to determine whether these changes in kidney volume predict changes in kidney function. NIH is also conducting two clinical trials of people with the most common form of PKD; one is in patients with early kidney disease and another in patients with more advanced disease. These two trials are the largest multicenter studies of PKD conducted to date and are collectively termed HALT-PKD. They are testing whether optimum blood pressure management, in combination with medication, will slow the progression of PKD.

- [Grantham JJ, et al. \*N Engl J Med.\* 2006;354:2122-30](#), PMID: 16707749
- For more information, see <http://tinyurl.com/2qu94j>
- For more information, see <http://www.pkd.wustl.edu/pkd-tn/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK)

**Health and Retirement Study (HRS):** The HRS is the leading source of combined data on health and financial circumstances of Americans older than age 50 and a valuable resource to follow and predict trends and help inform policies for an aging America. Now in its 14th year, the study follows more than 20,000 people at 2-year intervals and provides researchers with an invaluable, growing body of multidisciplinary data on the physical and mental health of older Americans, insurance coverage, finances, family support systems, work status, and retirement planning. Managed under a cooperative agreement between NIH and the University of Michigan, the study was expanded in 2006 to include additional key constructs in cognitive aging. A substudy will provide the first estimates of cognitive impairment and dementia based on nationally representative data and validation of survey measures. HRS staff will also assemble information on sample and questionnaire design, computer-assisted interview programming, interviewer performance, and data dissemination to improve the quality of data collected and provide an incentive for international partners to follow a harmonized design that will maximize the potential for cross-national behavioral and social research on aging.

- For more information, see <http://hrsonline.isr.umich.edu/>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIA)

**Magnetic Resonance Imaging (MRI) Study of Normal Brain Development:** Understanding healthy brain development is essential to finding the causes of many childhood disorders, including those related to mental retardation, developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases. NIH is creating the Nation's first database of MRI measurements and analytical tools, and clinical and behavioral data to understand normal brain development in approximately 500 children from across the Nation. This large-scale longitudinal study uses several state-of-the-art brain-imaging technologies. The data will be disseminated as a Web-based, user-friendly resource to the scientific community.

- For more information, see <http://www.bic.mni.mcgill.ca/nihpd/info/index.html>
- [Evans AC, et al. \*Neuroimage\*. 2006;30:184-202](#), PMID: 16376577
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NICHD, NIDA, NIMH, NINDS)

**National Longitudinal Study of Adolescent Health (Add Health):** Several NIH Institutes are supporting this study, which integrates biomedical, behavioral, and social science data to discover the pathways that lead to health and/or disease in adulthood. NIH initially funded Add Health in 1994 as a social science study of the causes of adolescent health problems and health-related behaviors. As the cohort of adolescents has moved into early adulthood, the study's focus has shifted to the environmental, behavioral, and biological pathways that lead to the development of adult chronic disease. The study initially incorporated measurements of social environments – peer groups, families, schools, and neighborhoods – that could affect health and also incorporated a sibling-pair design that facilitated quantitative genetic studies. Most recently, in collaboration with other Federal offices, NIH funded a new wave of interviews that will include collection of genetic data and biological markers of disease processes, as well as basic social, individual, and behavioral data. The new design was developed by a collaborative team representing the fields of epidemiology, cardiology, psychology, sociology, behavioral genetics, nutrition, biostatistics, anthropology, medicine, molecular virology, statistics, and survey research.

- For more information, see <http://www.cpc.unc.edu/addhealth>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NICHD, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

**Study of Normal Brain Development:** The NIH Intramural Research Program is conducting studies to explore brain development in healthy children and adolescents using magnetic resonance imaging. Recent studies have addressed brain structure differences related to risk for Alzheimer's disease and sex differences in brain development trajectories.

- [Shaw P, et al. \*Lancet Neurol\* 2007;6:494-500](#), PMID: 17509484
- [Lenroot RK, et al. \*Neuroimage\* 2007;36:1065-73](#), PMID: 17513132
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (I) (NIMH)

## A Comprehensive Understanding of Disease

**National Health and Nutrition Examination Survey (NHANES):** CDC uses rigorous surveys such as NHANES to collect health information and disease burden statistics representative of the entire U.S. population. Surveys also provide insight on health-seeking behaviors, as well as quality of life experiences and priorities. NIH and CDC collaborate to generate stable national estimates of vision impairment. A recent analysis of vision data indicated that 11 million of the estimated 14 million Americans with vision impairment could have their vision improved to normal levels if they had appropriate refractive correction (e.g., glasses or contact lens), including 9 percent of all young adults ages 12-19.

- For more information, see <http://www.cdc.gov/nchs/nhanes.htm>
- For more information, see <http://www.cdc.gov/nchs/nhis.htm>
- (E) (NEI)

**Ocular Epidemiology Panel Report:** The broad aim of National Eye Institute (NEI)-sponsored epidemiology research is to reduce the burden of visual impairment through research into the causes, diagnosis, prevention, treatment, and rehabilitation of the most prevalent blinding diseases. The ability to apply genetic and molecular tools in the context of populations, in connection with behavioral, environmental, and social factors, has transformed the potential contribution of epidemiology to the goal of controlling the major blinding diseases. NEI recently convened an expert panel to assess the unique needs and opportunities in ocular epidemiology that result from these new tools and to make recommendations for their application in future research. The panel's recommendations are contained in its report *Epidemiological Research: From Populations through Interventions to Translation*.

- For more information, see <http://www.nei.nih.gov/funding/nprp.asp>
- (E/I) (NEI)

**Multi-Ethnic Study of Atherosclerosis (MESA):** In an ancillary study to the NHLBI-sponsored MESA, retinal disease was assessed in more than 6,000 African American, Hispanic, White, and Asian subjects in this large population-based study of cardiovascular health. Eyes of African American and Hispanic study subjects are more likely to have signs indicative of diabetic eye disease whereas the eyes of White and Chinese subjects are more likely to show signs of age-related macular degeneration. Other analyses demonstrate racial/ethnic differences in the relative size and characteristics of the blood vessels lining the back of the eye, which are associated with various cardiovascular profiles. Future analyses will expand on these results and will consider the impact of genes, alone and in combination with differential exposure to environmental factors, such as cigarette smoke and air pollution, on retinal health.

- For more information, see <http://www.mesa-nhlbi.org/default.aspx>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (NHLBI, NEI)

**Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD):** The Chronic Renal Insufficiency Cohort (CRIC) study is investigating the relationship between CKD and cardiovascular disease. With approximately 3,000 subjects, this is the largest cohort study of

CKD undertaken to date. The Chronic Kidney Disease in Children Study (C-KiD) is a cohort study of 540 children. It aims to identify novel and traditional kidney disease risk factors for the progression of CKD, and to characterize the impact of a decline in kidney function on neurodevelopment, cognitive abilities, and behavior. The U.S. Renal Data System is a national data system that collects, analyzes, and distributes information about CKD and ESRD in the United States.

- For more information see <http://tinyurl.com/39nk3x>
- For more information, see <http://www.statepi.jhsph.edu/ckid/>
- For more information, see <http://www.usrds.org/>
- (E) (NIDDK, NICHD)

**Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC):** The DCCT demonstrated that intensive control of blood glucose levels reduced complications of the eyes, nerves, and kidneys in type 1 diabetes patients. Long-term findings from the follow-on EDIC study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients should begin intensive therapy as early as possible. EDIC recently found that recurrent hypoglycemia associated with intensive control does not affect patients' long-term cognitive function. After over 20 years of studying this patient cohort, crucial insights continue to emerge.

- For more information, see <http://www.bsc.gwu.edu/bsc/studies/edic.html>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK, NICHD)

**Diabetes Prevention Program Outcomes Study (DPPOS):** The landmark NIH Diabetes Prevention Program clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk. The DPPOS is a long-term followup study of the DPP subjects that is determining the durability of the interventions in preventing disease. DPP researchers recently confirmed that a variant in a gene predisposes people to type 2 diabetes. DPP subjects at highest genetic risk benefited from healthy lifestyle changes as much or more than those who did not inherit the variant. Participants over 60 years of age responded especially well to the lifestyle intervention, showing a 71 percent risk reduction in the incidence of diabetes, as compared to groups treated with metformin or standard medical advice. The lifestyle intervention had greater impact with increasing age (from age 25 to over 60) while the metformin treatment had progressively less impact with increasing age.

- [Florez JC, et al. \*N Engl J Med.\* 2006;355:241-50](#), PMID: 16855264
- For more information, see <http://tinyurl.com/24okog>
- For more information, see <http://tinyurl.com/295h4l>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK, CDC, IHS, NCMHD, NEI, NHLBI, NIA, NICHD, ORWH)

**National Epidemiologic Survey on Alcohol and Related Conditions (NESARC):** This nationally representative survey collected comprehensive, detailed data from approximately

40,000 individuals on alcohol consumption, use of 10 categories of drugs, and symptoms of alcohol and specific drug use disorders, as well as mood, anxiety, and personality disorders. In addition to diagnostic criteria, NESARC assessed indicators of impairment and distress due to each disorder, as well as disorder-specific treatment and help seeking. Analysis of these data is ongoing and continues to provide valuable information such as prevalence and comorbidity of mental health and substance use disorders. In addition, because NESARC data include a representative sample of ethnic and racial minority populations in the United States, a better assessment of the needs of specific populations can be made. One recent study using these data examined differences in the use of alcohol treatment services across the three largest ethnic groups in America. It showed Hispanics and African Americans with higher levels of problem severity were less likely to have used treatment services than Whites with problems of comparable severity, providing useful information about disparities in treatment utilization.

- [Schmidt LA, et al. \*Alcohol Clin Exp Res\* 2007;31:48-56](#), PMID: 17207101
- For more information, see <http://pubs.niaaa.nih.gov/publications/arh29-2/toc29-2.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, and Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (NIAAA, NIDA)

**Boston Area Community Health Study (BACH) Survey:** Interstitial cystitis/painful bladder syndrome (IC/PBS) is a urologic condition whose prevalence is uncertain and which remains difficult to diagnose and treat. The Boston Area Community Health (BACH) Survey is a population-based study of urologic conditions, including IC/PBS, in over 5,500 adults in Boston. Results emerging from BACH about IC/PBS prevalence by demographic group, the role of comorbid conditions, and the impact of IC/PBS on quality of life are providing a clearer picture of the IC/PBS burden in the population and will inform research efforts to reverse this burden.

- [Clemens JQ, et al. \*J Urol\*. 2007;177:1390-4](#), PMID: 17382739
- For more information, see <http://tinyurl.com/35llmz>
- For more information, see <http://tinyurl.com/363842>
- (E) (NIDDK)

**Multinational Influenza Seasonal Mortality Study:** NIH is leading an international collaborative effort to analyze national and global epidemiological patterns associated with influenza virus circulation. Twenty countries have contributed data on mortality, virus surveillance, genomics, and control strategies. The goals of this large-scale collaboration are to evaluate and compare public health strategies to alleviate the impact of seasonal influenza in different countries, and understand the global circulation patterns of influenza and their impact on populations. A better understanding of influenza epidemiology worldwide can inform vaccine strain selection and strategies to mitigate future influenza pandemics.

- For more information, see <http://origem.info/misms/>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (FIC)

**Screening Infants for Congenital CMV Infection (9.4):** “By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life.”



Approximately 1 percent of newborns, or about 40,000 infants each year, are born infected with CMV. As much as 20 to 30 percent of childhood hearing loss is caused by CMV, the most common virus that is passed from a mother to her unborn child. However, 90 percent of CMV-infected children show no symptoms at birth. Due to the compelling but limited data on congenital CMV infection and hearing loss in infants, NIH funded a research contract to the University of Alabama School of Medicine, Birmingham (UAB). The contract funds UAB to lead a multicenter longitudinal study entitled “CMV and Hearing Multicenter Screening” (CHIMES) Study, on the role of congenital CMV in the development of hearing loss in children. A major focus of this research is identifying asymptomatic children and following their progress to determine whether hearing loss develops. The CHIMES study is one of the largest studies of its kind with approximately 100,000 children to be screened at birth for CMV infection. Those who test positive for CMV will undergo followup diagnostic hearing testing to determine the onset, severity, and progression of hearing loss. NIH-supported scientists are combining screening newborns for CMV infection with newborn hearing screening to improve our ability to detect and predict hearing loss in children.

- [Fowler KB, Boppana SB. \*J Clin Virol.\* 2006;35:226-31](#), PMID: 16386462
- (E) (NIDCD) (GPRA Goal)

**International Training and Research Program in Population and Health:** This program supports U.S. universities that provide training to scientists from developing countries in population studies or reproductive biology. Objectives of this program include enhancing population research programs and international collaborative studies on (a) reproductive processes and contraceptive development and (b) demographic processes, including aging, mortality, morbidity, fertility, migration, and linkages between health and economic development; strengthening the ability of scientists from developing nations to contribute to global population research efforts and advance knowledge in support of population policies appropriate for their home countries; and developing and strengthening centers of research excellence in population-related sciences in developing countries.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/itrph/index.htm](http://www.fic.nih.gov/programs/training_grants/itrph/index.htm)
- This example also appears in Chapter 3: *Research Training and Career Development*
- (E) (FIC, NICHD, ODS)

**Jackson Heart Study:** The Jackson Heart Study, a large epidemiological study of cardiovascular disease (CVD) among over 5,300 African American residents of Mississippi, has been renewed through FY 2013. The project is exploring genetic, biological, and environmental factors that influence the development and course of CVD in African Americans. It is also seeking to expand minority participation in public health and epidemiological research by providing classes and hands-on training to interested undergraduate students. Moreover, a community health education component is using data derived from the study cohort to develop and disseminate up-to-date information on reduction of risk factors, practice of healthy lifestyles, and adherence to proven risk-reducing therapies.

- For more information, see <http://jhs.jsums.edu/jhsinfo/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NHLBI, NCMHD)

**Retrovirus Epidemiology Donor Study (REDS):** REDS was begun by NIH in 1989 to determine the prevalence and incidence of HIV infection among blood donors and the risks of transmitting HIV and other viruses via transfusions. In 2004, NIH launched REDS-II to monitor the appearance of newly discovered infectious agents in the blood supply, evaluate the characteristics and behaviors of voluntary blood donors, determine the causes of transfusion reactions of unknown etiology, assess the results of new donor screening methods, assess the effects of new blood banking technologies, and evaluate the donation process. In 2005, an international component was added to REDS-II to conduct research on blood donors in selected countries seriously affected by the AIDS epidemic to ensure the safety and availability of blood for transfusion.

- For more information, see <http://clinicaltrials.gov/ct/show/NCT00097006;jsessionid=7A9763F65A8C734DA771CDB5210D4877?order=7>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NHLBI)

**Improving the Lives of Asthmatic Children in the Inner City:** The NIH Inner-City Asthma Consortium (ICAC) evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children, who are disproportionately affected by asthma. An ICAC longitudinal birth cohort study involving 500 inner-city children is investigating the immunologic causes of the development of recurrent wheezing, a surrogate marker for asthma in children under three. The ICAC is also conducting a multicenter trial to evaluate the safety and efficacy of Xolair (omalizumab) in children with moderate to severe allergic asthma whose symptoms are inadequately controlled with inhaled steroids. Finally, researchers are conducting a clinical trial to determine the safety and dosing levels of a potential new allergy immunotherapy for cockroach allergen, which previous ICAC findings showed are a major determinant of asthma severity among inner-city children.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIAID)

**Therapies to Treat and Prevent Food Allergies:** The NIH Consortium of Food Allergy Research is developing immune-based approaches to treat food allergy, rather than to simply avoid food allergens. Basic studies are ongoing using mouse models to study how modified forms of peanut allergens protect against peanut-induced anaphylaxis. The five clinical sites of the Consortium are developing treatment and prevention strategies for food allergy, and they work to educate parents and health care providers regarding food allergies. An ongoing observational study is examining immune mechanisms, genetic factors, and environmental factors associated with the development of new food allergy to peanut and the loss of egg allergy to high-risk children. An interventional study aims to determine the safety and immunologic effects of giving egg by mouth to egg-allergic children, with the goal of inducing immunological

tolerance. Phase I clinical trials are assessing the safety of treating peanut-allergic subjects with either a modified form of peanut allergen or small amounts of peanut allergen under the tongue.

- For more information, see <http://www3.niaid.nih.gov/healthscience/healthtopics/foodAllergy/ReportFoodAllergy.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIAID)

**Prenatal Alcohol, Sudden Infant Death Syndrome (SIDS), and Stillbirth (PASS) Research Network:** Following a 3-year feasibility study, NIH established this multidisciplinary consortium in order to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of SIDS, stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study will follow 12,000 pregnant high-risk American Indian and South African women and their infants prospectively until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

- For more information, see <http://www.nichd.nih.gov/research/supported/pass.cfm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NICHD, NIAAA)

**Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA):** This 5-year clinical study's longitudinal design will greatly accelerate the identification of better treatments to control the pain of temporomandibular joint and muscle (TMJ) disorders. The OPPERA study marks one of the first prospective clinical studies of a chronic pain disorder. A prospective study is the "gold standard" of medical research: It looks forward in time, monitoring the health of those in the study over several years to track the onset or progression of a disease. With the study's 5-year vantage point, investigators will begin identifying individual genetic, physiologic, and psychological factors that cause or contribute to TMJ disorders and advance virtually all aspects of understanding and caring for these disorders.

- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/Archived/NewsReleases/NRY2005/PR12052005.htm>
- See <http://www.nidcr.nih.gov/Research/ResearchResults/InterviewsOHR/TIS012006.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDCR)

**Studies of Diabetes in Youth:** Previously known as a disease of adults, type 2 diabetes is increasingly being observed in youth. The Treatment Options for Type 2 Diabetes in Youth study is comparing three different treatment strategies for children with the disease. The SEARCH for Diabetes in Youth Study is providing key data on childhood diabetes incidence and prevalence. SEARCH estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. While type 2 diabetes is increasing in children over 10, particularly minorities, type 1 diabetes accounts for most new cases, with an estimated 15,000 youths diagnosed annually.

- For more information, see <http://www.todaystudy.org/index.cgi>
- For more information, see <http://www.searchfordiabetes.org/>

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Clinical and Translational Research*, and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDDK, CDC)

**The Environmental Determinants of Diabetes in the Young:** Pinpointing the environmental factors, such as infectious agents or diet that can trigger type 1 diabetes in genetically susceptible individuals, is crucial to developing prevention strategies. To address this knowledge gap, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. This international consortium is enrolling newborns at high genetic risk and following them until age 15 to identify environmental triggers for type 1 diabetes. The study is amassing the largest set of data and samples in the world for newborns at risk for type 1 diabetes.

- For more information, see <http://teddy.epi.usf.edu/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDDK, CDC, NIAID, NIEHS)

**The Sister Study:** The Sister Study is a major NIH initiative to study environmental and genetic risk factors for breast cancer in a cohort of 50,000 sisters of women who have had breast cancer. The asymptomatic women are being followed over time with periodic health updates. The women who develop breast cancer during the followup period will be compared with those who remained healthy to identify factors associated with increased cancer risk.

- For more information, see <http://www.sisterstudy.org/English/index1.htm>
- This example also appears in Chapter 2: *Cancer*.
- (I) (NIEHS)

**Cognitive and Emotional Health Project: The Healthy Brain:** The purpose of this initiative is to assess the state of longitudinal and epidemiologic research on determinants of cognitive and emotional health in aging adults. The project has completed a comprehensive review of measures that have been (or could be) used in epidemiological research. To help NIH learn what epidemiological data exist on the cognitive and emotional health of adults in the United States, the project polled investigators who are conducting these types of studies and created an online database. In addition, a Critical Evaluation Study Committee conducted an analysis and published a summary of the existing scientific literature pertaining to factors involved in the maintenance of cognitive and emotional health in adults. NIH is discussing new initiatives to expand this project, including promoting the use of existing datasets and developing ancillary studies to examine how cognitive and emotional health influence each other.

- For more information, see <http://trans.nih.gov/CEHP/CriticalEvaluationStudyReport.pdf>
- For more information, see <http://trans.nih.gov/cehp/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS, NIA, NIMH)

**HIV/AIDS Epidemiological and Long-term Cohort Studies:** NIH supports epidemiologic HIV research through a wide range of cohort studies that contribute to our understanding of risk factors that lead to HIV transmission and disease progression. Established in 2005, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) compiles data from NIH-

funded international HIV research to answer population-level questions about HIV variants and resistance, HIV pathogenesis in different settings, success of antiretroviral therapy, treatment history of HIV in different populations, success of prevention strategies, and vaccines. The Pediatric HIV/AIDS Cohort Study (PHACS) established in 2005 addresses two critical pediatric HIV research questions: the long-term safety of fetal and infant exposure to prophylactic antiretroviral chemotherapy and the effects of perinatally acquired HIV infection in adolescents. The Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) are the two largest observational studies of HIV/AIDS in women and homosexual or bisexual men, respectively, in the United States. These studies exceed standard clinical care diagnostics and laboratory analysis on both HIV infected, and importantly, HIV negative controls, which allows for novel research on how HIV spreads, how the disease progresses, and how it can best be treated. The studies focus on contemporary questions such as the interactions between HIV infection, aging, and long-term treatment; cardiovascular disease; and host genetics and its influence on susceptibility to infection, disease progression, and response to therapy.

- For more information, see [www3.niaid.nih.gov/about/organization/daids/daidsepi.htm](http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIAID, NICHD)

**The National Children's Study (NCS):** The NCS promises to be one of the richest information resources available for answering questions related to children's health and development and will form the basis of child health guidance, interventions, and policy for generations to come. The landmark study will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. This extensive research effort will examine factors ranging from those in the natural and man-made environments to basic biological, genetic, social, and cultural influences. By studying children through their different phases of growth and development, researchers will be better able to understand the role of these factors in both health and disease. Specifically, the NCS will identify factors underlying conditions ranging from prematurity to developmental disabilities, asthma, autism, obesity, and more. The study is led by a consortium of Federal agencies including NICHD and NIEHS at NIH, CDC, and EPA.

- For more information, see <http://www.nationalchildrensstudy.gov/>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (I) (NICHD, NIEHS)

**Environmental Health of Mothers and Babies: The Norwegian Mother and Child Cohort Study:** NIH is participating in the Norwegian Mother and Child Cohort Study, which provides a valuable opportunity to assess the role of environmental exposures in the health of women and their children. The Norwegian Mother and Child Cohort Study or MoBa (den norske Mor & barn-undersøkelsen) is an ongoing long-term prospective cohort study of 100,000 pregnant Norwegian women and their children. In collaboration with the Norwegian National Public Health Institute (NIPH), NIH is supporting the collection of additional biologic specimens from the pregnant women. These specimens will be used for the measurement of environmental

exposures. A variety of exposure and health variables on babies, mothers, and fathers are collected. Records from the cohort study will also be linked to routine national health registries.

- For more information, see <http://www.fhi.no/artikler/?id=51488>
- For more information, see <http://dir.niehs.nih.gov/direb/studies/nmc/>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (NIEHS)

**Databases for Cervical Cancer Research:** NIH has developed data analysis and image recognition tools for studying biomedical images of human papillomavirus (HPV) infection and cervical neoplasia. Image data include 100,000 cervicographs (high-definition cervical photograph), Pap test, and histology images. Tools allow the exploration of visual aspects of HPV and cervical cancer, for research, training, and teaching.

- [Castle PE, et al. \*Cancer Res.\* 2006;66:1218-24](#), PMID: 16424061
- [Jeronimo J, et al. \*J Low Genit Tract Dis.\* 2006;10:39-44](#), PMID: 16378030
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*, and Chapter 2: *Cancer*.
- (I) (NLM, NCI)

**U.S.-Born Children of Immigrants May Have Higher Risk for Mental Disorders Than Parents:** In the first studies to examine the effects of immigration and years of residence on the mental health of Caribbean Black, Latino, and Asian populations in the United States, NIH-funded researchers found that immigrants in general appear to have lower rates of mental disorders than their U.S.-born counterparts.

- For more information, see [http://www.nimh.nih.gov/press/immigrant\\_mentalhealth.cfm](http://www.nimh.nih.gov/press/immigrant_mentalhealth.cfm)
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIMH)

**Retinopathy Occurs in Middle-aged Adults Even Without Diabetes:** Signs of retinopathy are common in the eyes of the elderly, particularly in those with diabetes. In the Atherosclerosis Risk in Communities (ARIC) Study, African American subjects were significantly more likely to have signs of retinopathy (13 percent) compared to White subjects (5.5 percent). Among persons with diabetes, 27 percent had signs of retinopathy. Unexpectedly, retinopathy signs were also observed in 4.3 percent of people who did not have frank diabetes but tended to have elevated blood pressure. Future studies will examine whether these signs of retinopathy result from high blood pressure and whether they indicate an increased risk of systemic cardiovascular disease or predict a subsequent diagnosis of diabetes.

- [Wong TY et al. \*Am J Ophthalmol\* 2007;143:970-6](#), PMID: 17399675
- For more information, see <http://www.csc.unc.edu/aric>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (NHLBI, NEI)





## GENOMICS

*In the early 1950s, the race to discover the structure of DNA was on. At Cambridge University, James Watson and Francis Crick made physical models to narrow the possible DNA structure. At King's College in London, Maurice Wilkins and Rosalind Franklin took an experimental approach, looking at x-ray diffraction images of DNA. Based partially on Rosalind Franklin's data, Watson and Crick built a model in which each strand of the DNA molecule was a template for the other, allowing DNA to make identical copies of itself at each cell division. The structure so perfectly fit the experimental data that it was almost immediately accepted. Elucidating the structure of DNA has been called the most important biological work of the last 100 years, and the field it opened may be the scientific frontier for the next 100.*

### Introduction

Genomics is the study of an organism's entire genome—the complete assembly of DNA (deoxyribonucleic acid), or in some cases RNA (ribonucleic acid)—which transmits the instructions for developing and operating a living creature. It focuses not just on individual genes but also on the functioning of the genome as an interrelated network, and it is a new, rapidly expanding field of biological and medical research.

DNA is made up of four chemical compounds called “nucleotides”—adenine, thymine, guanine, and cytosine—denoted by the letters A, T, G, and C. These nucleotides are assembled in two parallel strands that are connected in the form of a double helix, and each nucleotide in one strand always links to the same partner on the other strand: A always pairs with T; C always pairs with G. Each of these pairings is referred to as a “base pair.” The human genome consists of about 3 billion base pairs, packaged into 23 sets of chromosomes, in virtually every cell in the body. Identifying the base pairs—and thus the letters—and the order in which they appear on any stretch of DNA is called “sequencing” that segment. DNA's double helical structure was discovered in 1953, and the human genome was fully sequenced just less than 50 years later, in 2003, after a 13-year, U.S.-led international effort called the Human Genome Project.

The sequencing of the human genome generated immense scientific excitement. It provided a new means of analyzing the functions of cells, tissues, and systems in the body and understanding and attacking the causes of disease. It enabled broad new scientific disciplines such as proteomics, the study of the structure and function of all the proteins produced by the body in response to instructions carried by the genes. It also gave many people the impression that all the questions of biology had been answered and that the genome had been fully decoded. This is not so. Sequencing the genome indicated the order of the letters; the question now is how precisely the words are written and what they mean.

Every human disease or disorder has a genetic component. Some heritable diseases, such as cystic fibrosis or Huntington's disease, result from mutations to single genes—changes that disrupt their proper functioning. The role of genes is more complicated in most other diseases. Some diseases arise as a result of spontaneous gene mutations that occur during a person's lifetime; others are caused by complex cascades of changes in gene expression triggered by

environmental factors. Differences as small as one letter in a stretch of DNA can cause disease directly or make people respond differently to particular pathogens or drugs. A single DNA base change in the “spelling” of the genome sequence—called a single nucleotide polymorphism, or SNP—also can help researchers track down genes involved in disease. Heart disease, asthma, and myriad other diseases appear to have multiple genetic factors, although all the genes involved have not been identified. Many types of cancer are caused by damage to one or more genes that leads to further mutations as cells divide.

## Scope of NIH Activity in Genomics Research

Virtually every NIH IC engages in some genome-related research. NCI sponsors an array of gene-oriented projects, including an effort to compile [The Cancer Genome Atlas](#), a catalogue of the many genetic changes that occur in cancer cells. NHLBI supports a major epidemiological project, the [Framingham Genetic Research Study](#), to search for genetic links to disease in 9,000 study subjects across three generations. NIAID’s [Microbial Genome Sequencing Centers](#) program is sequencing the genomes of many disease-causing microorganisms, including the fast-mutating RNA virus that causes influenza, seeking information that may help design vaccines or therapies to avert worldwide pandemics.

NIH researchers and grant recipients also are sequencing other nonhuman genomes, and not just the genomes of our mammalian relatives such as the chimpanzee, to highlight stretches of DNA that have remained similar across species for millions of years. Such similarities—or small differences in otherwise similar stretches of DNA—can help determine the roles and importance of particular sequences, and also may point the way toward therapies for diseases that affect humans. AIDS, caused by the human immunodeficiency virus, is one such disease.

An international consortium led by NHGRI has begun an effort to identify every functional element in the human genome, called the [Encyclopedia of DNA Elements](#) (ENCODE) project. Initial results reveal that genes do not operate independently but are part of a complex network, and that most of the genome’s “noncoding” DNA, that is, sequences that are not part of a gene, is not “junk” but appears to have important, heretofore unknown, functions.

## Toward an Era of “Personalized Medicine”

ENCODE and other NIH programs also aim to develop new technologies to reduce the cost of genome sequencing and otherwise aid in understanding the human genome. This includes the development of computer techniques and software to organize and analyze immense amounts of data, which are made available free of charge to all qualified researchers via public databases. When the Human Genome Project began in 1990, DNA sequencing cost about \$10 for each base pair. By 2007, that had been reduced to less than 1 cent, or less than \$20 million for sequencing a full human-sized genome.

Ultimately, NIH would like to reduce the cost of sequencing an entire human genome—all 3 billion base pairs—to \$1,000 or less, making possible a new era of “personalized medicine.” When costs are reduced to the point that sequencing an individual patient’s genome is feasible, and when the impact of small genetic changes on disease progression and therapy is better

understood, clinicians will have powerful new methods with which to defend their patients' health.

## Summary of NIH Activities

In fiscal years (FY) 2006 and 2007, NIH made significant progress toward exploiting the raw data of the human genome sequence and translating it into advances in human health. NIH-funded researchers and other scientists have laid the foundation for a scientific revolution—a truly new paradigm that will soon change medical research and the practice of medicine itself, moving beyond a one-size-fits-all approach. Most of the changes in practice and research that will matter for human health and our understanding of basic human traits have not yet happened. However, the next decade will yield the fruits of this foundational work, leading scientists increasingly closer to better means for preventing, diagnosing, and treating disease.

Among NIH's key accomplishments in the field of genomics in the FY 2006-2007 period were:

- Collaborating in the completion of the haplotype map of the human genome, known as the "[HapMap](#)": An international effort, the HapMap identifies the location of more than 3.1 million SNPs along the 3 billion bases of human DNA. SNPs are relatively common variations that serve as markers for whole neighborhoods of gene-carrying DNA. As such, they are signposts by which researchers can compare individuals' genomes and hunt for genetic mutations that may be involved in disease.
- Confirmation that the genome is not a simple string of independent genes, but rather a complex network, for which the elements and functions are still incompletely understood: In a program that is still ongoing, the international ENCODE project (the acronym stands for "[ENCyclopedia Of DNA Elements](#)") conducted multiple analyses of carefully selected DNA segments totaling approximately 1 percent of the human genome—about 30 million base pairs—in an attempt to identify every functional element and to figure out which methods worked best for identifying functional elements. ENCODE's next phase is to determine the functions of the other 99 percent of the genome. NIH has launched a similar project, dubbed "modENCODE," to apply the same strict scrutiny to the genomes of two common laboratory model animals, the fruit fly *Drosophila melanogaster* and the round worm *Caenorhabditis elegans*.
- Full sequencing of additional vertebrate and nonvertebrate animal genomes: Completed vertebrate animal genomes include those of the dog, the horse, the cow, the opossum, the honeybee, and two nonhuman primates—the rhesus macaque and the chimpanzee. By 2007, NIH and NIH-funded centers also had sequenced thousands of different viruses, hundreds of bacteria, and many unicellular parasites, including two that cause malaria—not to mention two mosquito species, one a vector for human malaria, the other for avian malaria. Such data enable scientists to compare the genomes of different organisms and identify elements that are similar in many species. Scientists suspect that genetic elements that have remained similar in different species over millions of years of evolution have important functions; thus, similarities between different species' genomes

may provide clues about human disease processes. Sequencing of other nonhuman genomes also is a major ongoing NIH program.

- Development of new laboratory tools and methods, and new computer algorithms for analyzing immense quantities of data, in order to reduce the cost of genome sequencing: A major goal of NIH sequencing programs is to reduce costs so that in time, physicians will be able to collect and use genomic data from their own patients—moving sequencing from blue-sky science to bedside therapy.
- Confirmation that genetic differences underlie much of an individual's response to medications, and that those genetic differences can be detected and potentially used to develop personalized treatment approaches: For example, in recent research, patients with two copies of a particular version of the serotonin 2A receptor gene responded significantly better to the antidepressant drug citalopram, a selective serotonin reuptake inhibitor, than did patients with different versions of the gene. Some day, such analyses could allow physicians to choose drugs tailored to individual patients rather than by a one-size-fits-all approach.
- New tests for diagnosing once-puzzling diseases and potential new therapies to treat them: Identifying the gene or genes involved in a disease can help scientists understand how the defect results in malfunction and thus point the way toward treatments. This approach is still new, but shows promise. For example, in 2003, NIH researchers identified the gene responsible for Hutchinson-Gilford progeria syndrome, which causes premature aging and heart disease in children and usually causes death by the teen years. They discovered that a single point mutation—a one-letter misspelling—in the gene known as *LMNA* produces a defective structural protein, which in turn causes misshapen nuclei in the patient's cells. Two years later, scientists following up on the discovery showed that an existing anticancer drug might correct the damage. Now, a 3-year clinical trial of this potential therapy for a devastating childhood disease is under way in the NIH Clinical Center.

## The HapMap and Genetic Variation

Completion of the first phase of the HapMap in October 2005 by an international consortium of hundreds of researchers in six countries was one of the most significant developments in genomic research since the sequencing of the human genome in 2003.

The HapMap is the basic platform upon which most current genomic studies of human diversity are now built. It details the location of millions of relatively common single-letter variations in the human genome, that is, variations that occur in at least 5 percent of people. The HapMap achieved two important goals: (1) it discovered most of the common variants in the genome and (2) it determined how these variants travel in “neighborhoods,” or haplotypes, making it possible to track only a small percentage of all of the variants directly, allowing the rest to be inferred. It enables researchers to conduct studies that were simply impossible just a few years ago. When

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the HapMap was published, a commentary in the journal *Nature* noted that it had “succeeded in a spectacular way.”<sup>7</sup>

In the early trailblazing years of genetic research, scientists largely were limited to seeking the single genes involved in classic, Mendelian-inherited diseases. A disease caused by a single damaged or inactive gene—such as cystic fibrosis or sickle cell anemia—could be traced in family history and then laboriously hunted down by trial-and-error comparisons of genetic variation across hundreds of families. However, diseases that involve several genes, where no single gene has a very large effect, have eluded such analysis, and most, if not all, human diseases involve a complex interaction of multiple genes. This is further complicated by the interactions of genes with environmental factors such as exercise, stress, and exposures.

The HapMap, together with advanced sequencing technology, now enables researchers to seek out the genetic roots of common, complex diseases by comparing and contrasting hundreds of thousands of points of variation among people. Thus, NIH-funded researchers have pioneered a whole new approach to genetic studies, called genome-wide association studies (GWAS, pronounced “gee-was”).

### **The Big Picture: Genome-Wide Association Studies**

GWAS examine not just a single stretch of DNA or the expression of a protein in a laboratory dish, but rather points of similarity and difference in the entire DNA sequences of people with or without particular diseases. In a typical GWA study, the genomes of 1,000 or more people with a particular disease are compared with the genomes of a similar number who are free of the disease. (Samples from many thousands of people are better, of course; the greater the number of individuals, the more accurate the study.) Theoretically, the “big picture” comparison of peoples’ genomes will signal the presence of blocks of DNA that carry a gene or genes involved in the disease in question.

In the short time since they were devised, GWAS conducted by NIH or NIH-funded researchers have, among other discoveries:

- Identified a common genetic variation that significantly raises the risk of age-related macular degeneration. The finding strengthened our understanding of the link between the inflammation pathway and a devastating eye disease that often leads to blindness, and suggested a new treatment that is now under clinical study.
- Uncovered several genes that appear to play a role in bipolar disorder. One, which is active in the pathway through which lithium operates on the disorder, suggests a new treatment approach—seeking ways to regulate the enzyme involved, known as DGKH. Others may point scientists toward new directions for research.

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<sup>7</sup> [Goldstein DB, Cavalleri GL. \*Nature\*. 2005;437:1241-2.](#) PMID: 16251937



- Located at least 10 sites of gene variants associated with type 2 diabetes—most of them never before identified. One of the sites includes two genes that had been studied in cancer, but never before associated with diabetes.
- Discovered three gene variants that may affect the ability of a person infected with HIV to control viral load and prevent or delay progression to AIDS. In addition to offering new approaches to anti-AIDS therapy, the apparent involvement of an immune system gene, *HLA-C*, may suggest a new avenue for research aimed at developing an HIV vaccine.
- Identified five new potential sites for breast cancer susceptibility genes. At least three of the five have been implicated in cell growth or cell signaling, rather than DNA repair or hormone metabolism, pointing the way toward new areas for basic research.
- Found a major site associated with prostate cancer risk on chromosome 8, with several different haplotypes that confer risk, and which may explain a substantial fraction of the increased risk in African Americans.
- Discovered additional variants of genes that increase the risk for colon cancer, Crohn's disease, rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, gallstones, celiac disease, atrial fibrillation, glaucoma, lupus, coronary artery disease, and type 1 diabetes, among others.

With support from NIH and other sources, scientists will follow up on these discoveries through further genomic research to confirm and refine findings and, through nongenomic investigations, to discover preventions, diagnostics, and treatments.

A new, large-scale GWA study of cardiovascular and other chronic diseases is now under way in Framingham, Massachusetts. In collaboration with the Boston University School of Medicine, NIH is screening DNA from subjects enrolled in the long-running [Framingham Heart Study](#)—up to 500,000 analyses of DNA from 9,000 people who have been followed over three generations since 1948. The Framingham study has been a key source of knowledge about heart disease, stroke, and other chronic diseases; the new genome-wide association analyses will add immensely to understanding the genetic factors involved.

The genome-wide association approach also is at the heart of a major effort to explore the relationship between genes and the environment in many common diseases. The trans-NIH [Genes, Environment and Health Initiative](#) (GEI), will add an additional step to GWAS: It will monitor the differing environmental factors to which people in the study are exposed, as well as genomic differences, to determine not only which genes may be involved in particular diseases, but also what specific environmental influences trigger disease in susceptible individuals. NIH awarded its first GEI research grants in 2007; in the program's first year, NIH plans to sponsor eight GWAS, two genotyping centers and more than 30 environmental technology projects—including efforts to develop small environmental sensors that people can wear or carry, like cell phones or iPods, to measure environmental exposures. The environment includes not only the

chemical environment but also exposure to the behavioral environments of dietary intake, physical activity, psychosocial stress, and addictive substances.

In 2006, NIH also launched a 3-year series of GWAS seeking genes that raise the risk of prostate and breast cancer, known as the [Cancer Genetic Markers of Susceptibility](#) project.

Supplementing NIH's research efforts, a unique public-private partnership known as the [Genetic Association Information Network \(GAIN\)](#) has begun funding additional GWAS analyses of common diseases, beginning in late 2006 with studies of schizophrenia, bipolar disorder, diabetic nephropathy, attention deficit hyperactivity disorder (ADHD), major depression, and psoriasis. Managed by the nonprofit Foundation for the National Institutes of Health, GAIN is funded by private-sector partners, including Pfizer, Affymetrix, Perlegen Sciences, Abbott, and the Broad Institute of Massachusetts Institute of Technology and Harvard University.

As with other genetic data produced by NIH or NIH-funded researchers, all data from GWAS—including data resulting from the public-private GAIN studies—are made freely available to biomedical researchers worldwide through databases maintained by NIH. The trans-NIH [GWAS Policy](#), released in August 2007, includes establishment of a central data repository of de-identified genetic (genotypic and phenotypic) data, and creates a more uniform approach to expanding investigators' access to GWA study data. Implementation guidance was released to intramural and extramural scientists in November 2007, and the policy became effective on January 25, 2008. Under the new guidelines, information is deposited into databases immediately, rather than being held back for months until it is published in scientific journals. This accelerates data availability, thereby facilitating the development of better diagnostic tools and the design of new, safe, and effective treatments.

## Decoding Cancer

Understanding and developing new treatments for human cancer has long been a major goal of genetic research. Since the 1990s, a growing number of individual genes that predispose an individual to cancer have been identified, such as the breast cancer genes *BRCA1* and *BRCA2*. But it has become clear that cancer is not a disease caused by a single gene. Instead, cancer is known to involve many different forms of out-of-control cell growth and to be influenced by many different genes. A few of these mutations are inherited from a person's parents, but most occur during a lifetime of cell division, or, in some instances, are caused by some external environmental factor. (In some cases, the external factor is known, such as cigarette smoking in lung cancer; however, even smoking does not explain all cases of lung cancer, nor do all smokers get lung cancer.)

In its continuing effort to unravel human cancers, in 2006 NIH launched [The Cancer Genome Atlas](#). In a 3-year pilot project, scientists at more than a dozen institutions will sequence and analyze genetic changes in tissue samples donated by thousands of brain, lung, and ovarian cancer patients. They will try to identify the specific alterations in genes associated with cancer and determine the genetic signatures of different cancer subtypes. Some cancers develop slowly; others are aggressive. Some respond to a particular chemotherapy; others do not. If the effort

succeeds, The Cancer Genome Atlas will be expanded to cover other types of cancer (see also the section on *Cancer* in Chapter 2).

NIH already assembles—and makes available to medical researchers worldwide—a vast collection of genomic data resources and computer tools for accessing and analyzing that data, through such efforts as its [Cancer Genome Anatomy Project](#) and the [Mammalian Gene Collection](#).

## Nonhuman Genomes

NIH also continues to fund sequencing of the genomes of nonhuman organisms. Sequencing projects under way include the orangutan, the gorilla, and the gibbon genomes. In addition, NIH sponsors an ongoing program of sequencing the genomes of microorganisms that prey on humans. These efforts provide insights not only into potential approaches to controlling these organisms, but also into basic understanding of DNA, genes, and genomes. For example, studies of fruit flies and the round worm *C. elegans* have, for decades, been a source of basic knowledge about genes and their function that have enlightened studies in humans. Rats and mice are also key laboratory model animals and are hardly irrelevant to human genetics; more than 99 percent of human genes have analogs in the mouse. Studies of other mammals also can cast light on human disease. For example, a study of the dog genome suggested a possible new connection between human cancer and a gene that had never before been considered as a cancer suspect. The 2007 study revealed that a single gene is the major determinant of a dog's size, from Chihuahua to Great Dane. That gene, *IGF-1*, which codes for the hormone insulin-like growth factor-1, is similar to a gene in humans. If *IGF-1* is so important to size regulation in dogs, researchers say, it also may be involved in cell proliferation, and possibly cancer, in humans.

As is the case with humans, scientists can learn even more when they have data from many representative microbes of the same kind. For example, NIH has collected and sequenced the whole genomes of more than 2,500 human and avian influenza samples. The data from this ongoing project may help researchers anticipate the frequent evolutionary mutations in the virus that make designing a vaccine so difficult. It also may enable them to predict whether, and when, the A/H5N1 avian flu virus will mutate into a form that can easily infect humans, and to design a vaccine to counteract it. The possibility of an avian flu breakout into humans raises fears of a disaster similar to the 1918 Spanish flu pandemic, which is estimated to have killed 1 to 2 percent of the total world population. In 2007, an NIH research team developed a strategy for predicting the mutations that would permit the avian flu virus to adapt to humans—as few as two mutations could do it—and it is now possible to monitor newly isolated viruses to assess whether this possibility is occurring.

## Genome Sequencing and Technology

Virtually all NIH sequencing programs have a dual purpose. Their aim is not just to answer a conventional research question, such as what is the DNA sequence of this organism or that gene, but also to reduce the cost of sequencing itself, and to increase the speed and efficiency of the task of analyzing DNA sequences.

For example, a consortium of 11 teams of investigators known as the ENDGAME consortium—the acronym stands for Enhancing Development of Genome-wide Association Methods—is seeking new approaches to conduct GWAS, aimed specifically at lowering their cost and enhancing their usefulness. The Large-Scale Sequencing Program, which involves several sequencing centers throughout the United States, not only produces sequence data on a wide range of organisms to answer research questions, but also seeks ways to cut sequencing costs.

NIH's Genome Technology Program focuses directly on the development of new methods for transcribing DNA sequences, comparing sequences to identify variations, and determining the effects of such variations on genetic function and thus human health. Such analyses require significant computer backup. Because the human genome comprises more than 3 billion DNA base pairs, there are more than 3 billion possible points of difference between the genomes of any two individuals, and a genome-wide association study may involve several thousand individuals. Without such analytic efforts—which DNA researchers call “annotating,” and could not be accomplished without sophisticated and innovative computer programming—DNA sequences are simply disconnected strings of letters in an alien language.

Currently, the field is undergoing a revolution in sequencing technology. The cost of sequencing the entire genome of an individual human being has been reduced from several billion dollars to between \$100,000 and \$1 million. NIH's goal is to bring that cost down to \$1,000—and to truly bring genomic science to the bedside. That era of personalized medicine may be only a few years away.

### Notable Examples of NIH Activity

#### Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

### The Big Picture: Genome-Wide Association Studies

**Genome-Wide Association Studies (GWAS) and Database of Genotype and Phenotype (dbGaP):** In December 2006, NIH released the initial dbGaP dataset using genome-wide association study data from the Age-Related Eye Diseases Study (AREDS), a landmark study of the clinical course of Age-related Macular Degeneration (AMD) and cataracts. AREDS documents, protocols, and aggregated data are made available with no restrictions. In order to protect patient confidentiality, de-identified individual-level patient characteristics and family data are accessible only by authorized investigators. Correlating phenotype and genotype data provides information about the genetic and environmental interactions involved in a disease process or condition, which is critical for better understanding complex diseases and developing new diagnostic methods and treatments. Using these data, recent studies have linked two genes with progression to advanced AMD. After controlling for other factors, certain forms of the

genes increased risk of AMD progression 2.6- to 4.1-fold; smoking and body weight further increased risk with these gene variants.

- [Seddon JM, et al. JAMA 2007;297:1793-800](#), PMID: 17456821
- For more information, see <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gap>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NEI, NIA, NLM)

**Genetic Association Information Network (GAIN):** GAIN is a public-private partnership initiative that will elucidate the genetic factors influencing risk for many complex diseases. The resulting data will be made available in a central database managed by NIH for no-cost access by the scientific community. Of the six initial studies receiving funding through GAIN, four will target mental disorders: schizophrenia, bipolar disorder, major depression, and attention deficit hyperactivity disorder.

- For more information, see [http://www.fnih.org/GAIN2/home\\_new.shtml](http://www.fnih.org/GAIN2/home_new.shtml)
- For more information, see <http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-07-060.html>
- (NHGRI)

**Genome-Wide Genotyping in Parkinson's Disease (PD):** NIH researchers recently conducted genome-wide genotyping of publicly available samples from a cohort of 267 Parkinson's disease patients and 270 neurologically normal controls to identify any common genetic variability with significant effect on the risk for PD. The project has produced around 220 million data points in the 537 subjects, the largest collection of publicly available genotypes in a case-control cohort. The release of these data facilitates research on PD and other neurodegenerative disorders, and the genotypes from neurologically normal controls can be used as a comparison cohort for other studies, dramatically reducing the cost of future research.

- [Fung HC et al. Lancet Neurology 5:911-6](#), PMID: 17052657
- For more information, see <http://www.nia.nih.gov/NewsandEvents/PressReleases/PR20060927parkinsons.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NIA, NINDS)

**Enhancing Development of Genome-Wide Association Methods (ENDGAME):** The ENDGAME consortium, which comprises 11 interactive teams of investigators, has been initiated to explore new approaches for designing and conducting GWAS of complex diseases. ENDGAME investigators are developing and testing innovative, informative, and cost-effective study designs and analytical strategies and tools for performing the studies. All strategies and tools developed will be made available to the scientific community. Results from ENDGAME are expected to enhance greatly the utility of GWAS for increasing understanding about genetic variations and their role in health and disease.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NHLBI, NCI, NHGRI, NIEHS, NIGMS)

**Population Genomics, GAIN, and GEI:** In February 2006, HHS announced the creation of two related groundbreaking initiatives in which NIH is playing a leading role. The Genetic Association Information Network (GAIN) and the Genes, Environment, and Health Initiative (GEI) will accelerate research on the causes of common diseases. GAIN is a public-private partnership among NIH, the Foundation for the NIH, Pfizer, Affymetrix, Perlegen, the Broad Institute, and Abbott. GEI is a trans-NIH effort combining comprehensive genetic analysis and environmental technology development to understand the causes of common diseases. Both GAIN and GEI are powered by completion of the “HapMap,” a detailed map of the 0.1 percent variation in the spelling of our DNA that is responsible for individual predispositions for health and disease. Data from GAIN will narrow the hunt for genes involved in six common diseases. In June 2007, the first GAIN dataset, on attention deficit hyperactivity disorder, was released. GEI will provide data for approximately another 15 disorders and will develop enhanced technologies and tools to measure environmental toxins, dietary intake, and physical activity, as well as an individual’s biological response to those influences.

- For more information, see <http://www.genome.gov/19518664>
- For more information, see <http://www.genome.gov/19518663>
- For more information, see <http://genesandenvironment.nih.gov/>
- For more information, see <http://www.genome.gov/11511175>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Technology Development*.
- (E/I) (NHGRI)

### **Genetic Roots of Bipolar Disorder Revealed by First Genome-Wide Study of Illness:**

According to NIH-funded research, the likelihood of developing bipolar disorder depends in part on the combination of small effects of variations in many different genes in the brain, none of which is powerful enough to cause the disease by itself.

- For more information, see <http://www.nimh.nih.gov/press/mcmahon-bipolar-genetics.cfm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH)

**Gene Expression Changes in Facioscapulohumeral Muscular Dystrophy (FSHD):** Results from a genome-wide scan of skeletal muscle biopsies suggest a link between eye blood vessel defects and muscle defects that characterize FSHD. Patient participants were recruited from the National Registry for Myotonic Dystrophy and FSHD Patients and Family Members.

- [Osborne RJ, et al. \*Neurology\*. 2007;68:569-77](#), PMID: 17151338
- For more information, see [http://www.niams.nih.gov/Funding/Funded\\_Research/registries.asp#dystrophy](http://www.niams.nih.gov/Funding/Funded_Research/registries.asp#dystrophy)
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIAMS, NCRR, NINDS)

## **Decoding Cancer**

**The Cancer Genome Anatomy Project (CGAP):** The goal is to determine the gene expression profiles of normal, precancer, and cancer cells to improve detection, diagnosis, and treatment for



the patient. The CGAP Web site makes various tools for genomic analysis available to researchers. Through worldwide collaborations, CGAP seeks to increase its scientific expertise and expand its databases for the benefit of all cancer researchers.

- For more information, see <http://cgap.nci.nih.gov>
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NCI)

**Genome-Wide Association Studies of Cancer Risk:** Beginning with the Cancer Genetic Markers of Susceptibility (CGEMS) initiative for breast and prostate cancer, NIH has capitalized on its long-term investment in intramural/extramural consortia by creating strategic partnerships to accelerate knowledge about the genetic and environmental components of cancer induction and progression. Using powerful new technology capable of scanning the entire human genome, these efforts have recently identified unsuspected genetic variants associated with increased risk for developing cancers of the prostate, breast, and colon. Additional scans, either planned or under way, will be directed at cancers of the pancreas, bladder, lung, and other organs. The results of these genome-wide studies, together with the follow-on studies planned to narrow the search for causal gene variants, promise to provide novel clinical strategies for early detection, prevention, and therapy. To expand upon these emerging opportunities, a new Laboratory of Translational Genomics (LTG) has been established to further characterize genetic regions associated with cancer susceptibility, and to identify gene-gene and gene-environment interactions. LTG will create opportunities for collaboration and data sharing in order to accelerate the translation of genomic findings into clinical interventions.

- For more information, see <http://epi.grants.cancer.gov/Consortia/tablelist.html>
- For more information, see <http://epi.grants.cancer.gov/BPC3/cohorts.html>
- For more information, see <http://cgems.cancer.gov/index.asp>
- For more information, see <http://epi.grants.cancer.gov/PanScan/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E/I) (NCI)

**The Cancer Genome Atlas (TCGA):** TCGA is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. The goal of TCGA is to develop a free, rapidly available, publicly accessible, comprehensive catalogue, or atlas, of the many genetic changes that occur in cancers, from chromosome rearrangements to DNA mutations to epigenetic changes - the chemical modifications of DNA that can turn genes on or off without altering the DNA sequence. The overarching goal of TCGA is to improve our ability to diagnose, treat, and prevent cancer.

- For more information, see <http://cancergenome.nih.gov/index.asp>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*.
- (E/I) (NCI, NHGRI)

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## Nonhuman Genomes

**The Dog Genome and Human Cancer:** Cancer is the number one killer of dogs, and studying the major cancers in dogs provides a remarkably valuable approach for developing a better understanding of the development of cancer in humans. The clinical presentation, histology, and biology of many canine cancers very closely parallel those of human malignancies, so comparative studies of canine and human cancer genetics should be of significant clinical benefit to both. Furthermore, information gained from studying the genetic variant involved in dog size can provide important information for studying cell growth in humans and has the potential to be a useful tool in cancer research. A 2007 article by NIH researchers reported a genetic variant that is a major contributor to small size in dogs, followed by a second study finding that a mutation in a gene that codes for a muscle protein can increase muscle mass and enhance racing performance in dogs.

- [Sutter NB, et al. \*Science\*. 2007;316:112-5](#), PMID: 17412960
- [Mosher DS, et al. \*PLoS Genet\* 2007;3:e79](#), PMID: 17530926
- For more information, see <http://www.genome.gov/25520294>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (I) (NHGRI)

**Microbial Genomics:** NIH has made significant investments in two large-scale programs to sequence microbes and genomes over the last decade. Sequenced pathogens include hundreds of bacteria, fungi, parasites, invertebrate vectors of diseases, and viruses (including those pathogens that cause anthrax, influenza, aspergillosis, tuberculosis, gonorrhea, chlamydia, and cholera, and many that are potential agents of bioterrorism). NIH also provides comprehensive genomic, bioinformatic, and proteomic resources and reagents to the scientific community. These include (1) Microbial Genome Sequencing Centers, which rapidly produce high-quality genome sequences of human pathogens and invertebrate vectors of diseases, (2) The Pathogen Functional Genomics Resource Center, which provides functional genomic resources, (3) Bioinformatics Resource Centers, which provide access to genomic and related data in a user-friendly format, and (4) Proteomics Research Centers, which support research on the full set of proteins encoded in a microbial genome. The NIH Influenza Genome Sequencing Project has sequenced over 2,800 human and avian influenza isolates (as of November 28, 2007). NIH scientists recently exploited these data to explain the global spread of resistance to adamantanes, a first-generation class of anti-influenza drug.

- For more information, see <http://www3.niaid.nih.gov/research/topics/pathogen/default.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E/I) (NIAID) (GPRA Goal)

**Tools for Genetic and Genomic Studies in Emerging Model Organisms:** In FYs 2006 and 2007, NIH funded eight grants that create genetic and genomic resources for model organisms whose genomes have been recently sequenced. These organisms include fish, invertebrates, and microbes used to understand human health, development, and disease. The resources include reagents and mutant lines, a center for high-throughput mutagenesis, genetic maps, databases, and stock centers.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-04-135.html>
- (E) (NIGMS)

**Human Microbiome Project:** The human microbiome is the set of microbes that naturally inhabit the human nose, mouth, gut, vagina, and skin. The interactions between human hosts and these microbial communities at multiple body sites are known to be important for health, yet relatively little is known about them. The concept and plan for the NIH Roadmap Human Microbiome Project (HMP) was approved in 2007. By leveraging both the traditional approach to genomic DNA sequencing and the metagenomic approach (which allows the genomic sequencing of all microbes contained in a single sample), the HMP will lay the foundation for further longitudinal studies of human-associated microbial communities. Program initiatives are to characterize the genomes of the indigenous microbes of the human nose, mouth, gut, vagina, and skin, referred to as the “human microbiome,” and determine whether individuals share a core human microbiome; to understand the relationship between the human microbiome and changes in human health; to develop novel technological and analytic tools needed to support these goals; to establish a data analysis and coordinating center and a resource repository; and to address the ethical, legal, and social implications raised by human microbiome research.

- For more information, see <http://nihroadmap.nih.gov/hmp>
- For more information, see <http://www.genome.gov/26524200>
- (E) (Roadmap—all ICs participate)

**Scientists Complete Full Sequence of Opportunistic Oral Bacterium:** Over the last decade, scientists have assembled the complete DNA sequences of several important oral bacteria. Now NIH-funded investigators have decoded and added another important bacterium, *Streptococcus sanguinis*, a key player in the formation of the oral biofilm, to the list. Although not regarded as a pathogen in the mouth, *S. sanguinis* is known to enter the bloodstream where it can colonize heart valves and contribute to bacterial endocarditis, a condition that kills an estimated 2,000 Americans each year. With the bacterium’s genetic blueprint now publicly available online, scientists can better study the dynamics of biofilm formation and possibly tease out new leads to prevent tooth decay and periodontal disease. They also now can systematically identify and target sequences within the DNA of *S. sanguinis* that are critical to the infectious process, providing invaluable information in designing more effective treatments for endocarditis.

- [Xu P, et al. \*J Bacteriol\* 2007;189:3166-75](#), PMID: 17277061
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIDCR)

## Genome Sequencing and Technology

**Genome Technology and the \$1,000 and \$100,000 Genome Initiatives:** DNA sequencing spells out the order in which our chemical building blocks are arranged, making DNA sequencing a powerful resource for biomedical research. Although DNA sequencing costs have dropped by more than three orders of magnitude since the start of the Human Genome Project, sequencing an individual’s complete genome for medical purposes is still prohibitively expensive. Developing technology to make whole-genome sequencing more affordable would enable the sequencing of individual genomes to become part of routine medical care. The

Genome Technology program supports research to develop new methods, technologies, and instruments to rapidly, and at low cost:

- ▷ Transcribe DNA sequences
- ▷ Check sequences for genetic variations (SNP genotyping)
- ▷ Aid research to understand the effects of genetic variations on genomic function

Additionally, NHGRI supports two types of sequencing grants: (1) “Near-Term Development for Genome Sequencing” grants support research aimed at sequencing a human-sized genome at 100 times lower cost than is possible today (\$100,000) and (2) “Revolutionary Genome Sequencing Technologies” grants aim to develop breakthrough technologies that will enable a human-sized genome to be sequenced for \$1,000 or less. Currently, only analyses of ~ 500,000 Single Nucleotide Polymorphisms (SNPs) are being performed commercially at this cost; an individual's complete genome sequence (~ 3 billion base pairs) would offer vastly more information.

- For more information, see <http://www.genome.gov/10000368>
- For more information, see <http://www.genome.gov/19518500>
- This example also appears in Chapter 3: *Technology Development*.
- (E) (NHGRI)

**Large-Scale Sequencing Program:** NIH’s Large-Scale Sequencing Program funds three major research centers in the United States to conduct genetic sequencing. During and since the completion of the Human Genome Project, NIH-funded centers have used their industrial-scale enterprises to improve DNA sequencing methods, thereby substantially decreasing costs and increasing capacity. For many years, the Program has achieved twofold decreases in cost approximately every 20 months. One of the main projects now under way is the sequencing of the genomes of other primates, such as orangutan, baboon, gibbon, and marmoset (in addition to chimpanzee and macaque, which are complete). By comparing the human genome to that of other primates, researchers can find important information about both health and abilities that are uniquely human and those shared with other species. The Program also supports the genomic sequencing of human pathogens (organisms that cause disease in humans) and their vectors (the organisms that carry those pathogens). For other relevant NIH programs see previous section, Microbial Genomics. Also, many mammals are being sequenced to identify elements that are functionally important to human biology. These studies will undoubtedly unveil new biological insights to increase our understanding of how the human genome works.

- [Rhesus Macaque Genome Sequencing and Analysis Consortium, et al. \*Science\*. 2007;316:222-34, PMID: 17431167](#)
- For more information, see <http://www.genome.gov/10001691>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NHGRI)

**How Fast Is Evolution?** Traditionally, scientists thought that evolution happened very slowly. They believed that it is quite rare to have major DNA changes (also called radical mutations) that benefit organisms and are passed on to future generations. Recently, NIH-funded researchers learned that in some cases, evolution can happen very quickly. By analyzing how DNA varies

from person to person, and comparing human and chimpanzee DNA, the researchers discovered that radical mutations undergo a two-step selection process. Most mutations never make it past the first step, and slip out of the gene pool without being passed on to subsequent generations. But the rare mutations that survive this first cut spread rapidly throughout the species. These observations have relevance for our own species because, even though radical mutations represent only 10-12 percent of the differences between human and chimpanzee DNA, they may be responsible for some of the most significant differences between the two species.

- [Gojobori J, et al. \*Proc Natl Acad Sci U S A.\* 2007;104:3907-12](#), PMID: 17360451
- (E) (NIGMS)

## Functional Genomics of Disease

**Longevity Assurance Gene (LAG) Initiative and Interactive Network:** The identification and functional characterization of genes and biological pathways controlling longevity and lifespan have advanced significantly, in large part as a result of the efforts of scientists participating in the NIH-supported LAG Initiative and Network. The LAG Initiative has led to the identification of over 100 new longevity-associated genes, along with many other conserved biological processes and pathways that regulate longevity in a host of divergent species, including humans. These and similar discoveries are helping to illuminate disease processes, identify new predictive biomarkers, and facilitate identification of targets for preemptive drug therapy.

- (E) (NIA)

**Women's Health Initiative:** In January 2007, NIH awarded support for a dozen 2-year research projects to apply genomics, proteomics, and other innovative technologies to improve understanding of several major diseases that commonly affect postmenopausal women. The new endeavor builds on results of the long-running Women's Health Initiative, which conducted several clinical trials and an observational study to examine strategies for preventing heart disease, breast and colorectal cancers, and osteoporosis in a cohort of over 160,000 subjects. Investigators will use stored blood, DNA, and other biological samples and associated clinical data to analyze genetic factors and biological markers that may be useful in predicting disease outcomes or the effects of therapeutic and preventive regimens in postmenopausal women.

- For more information, see <http://www.whiscience.org/baa/2006.php>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NHLBI)

**Inflammatory Bowel Disease Genetics Consortium:** This consortium of researchers in the United States and Canada applies knowledge from the Human Genome Project to the identification of genetic factors influencing the development of inflammatory bowel diseases (IBD). A genome-wide screen of samples collected recently identified three IBD susceptibility genes. The identification of such genetic factors can provide key insights into disease development and targets for designing more effective therapies for IBD.

- [Rioux JD, et al. \*Nat Genet.\* 2007;39:596-604](#), PMID: 17435756

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-011.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK)

**A Multidisciplinary Approach to Nicotine Addiction:** Nicotine addiction is the number one preventable public health threat, with enormous associated morbidity, mortality, and economic costs. NIH-supported research has generated new knowledge to support the development of more effective prevention messages and treatment approaches. Several notable examples characterize NIH's multidisciplinary approach to targeting the best treatment (or combination of treatments) for nicotine addiction. Genomic studies have recently uncovered a series of genes associated with nicotine addiction that could provide new targets for medications development and for the optimization of treatment selection. Pharmacologic studies, critical to understanding the basis of nicotine's mode of action, have recently revealed that its addictiveness may hinge upon its ability to slowly shut down or desensitize the brain's response to nicotine. A recent imaging study indicated that a part of the brain called the insula may play an important role in regulating conscious craving. This exciting finding provides a new target for research into the neurobiology of drug craving and for development of potentially more effective smoking cessation and other addiction treatments. Results of a Phase II clinical trial strongly suggest that a nicotine vaccine, which works by preventing nicotine from ever reaching the brain, may be a particularly useful tool for cessation programs in the not-too-distant future.

- For more information, see <http://www.drugabuse.gov/ResearchReports/Nicotine/Nicotine.html>
- This example also appears in Chapter 3: *Clinical and Translational Research*, Chapter 2: *Cancer*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDA, NCI) (GPRA Goal)

**The Collaborative Study on the Genetics of Alcoholism (COGA):** In its 18th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) who are densely affected by alcoholism. Several genes have been identified including GABRA2, ADH4, ADH5, and CHRM2, which influence the risk for alcoholism and related behaviors such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes influencing vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

- For more information, see <http://zork.wustl.edu/niaaa/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Molecular Biology and Basic Sciences*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIAAA) (GPRA Goal)



**New Genetics Tools Shed Light on Addiction:** NIH-supported research is taking full advantage of the massive databases and rapid technologies now available to study how genetic variations influence disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms and the genetic predispositions underlying diseases like addiction. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as “gene chips” (e.g., the *neurexin* gene has been found to play a role in drug addiction). A next-generation “neurochip” is being developed with 24,000 gene variants related to substance use and other psychiatric disorders. Applying this tool to addiction and other brain disorders will advance our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient’s genetic profile (i.e., a “pharmacogenetic” approach). To complement these efforts, NIH is investing heavily in the emerging field of epigenetics, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. A focus on gene-environment interactions has recently been expanded to incorporate developmental processes, now known to also affect the outcome of these interactions. The resulting Genes, Environment, and Development Initiative (GEDI) seeks to investigate how interactions among these factors contribute to the etiology of substance abuse and related phenotypes in humans.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/rfa-da-07-012.html>
- For more information, see <http://nihroadmap.nih.gov/roadmap15update.asp>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*.
- (E/I) (NIDA, NCI, NIAAA, NIMH) (GPRA Goal)

**Clinical Proteomic Technologies Initiative for Cancer:** The completion of the Human Genome Project in 2003 has been a major catalyst for proteomics research and NIH has taken a leading role in facilitating the translation of proteomics from research to clinical application through its Clinical Proteomic Technologies Initiative for Cancer. The overall objective of this Initiative is to build the foundation of technologies (assessment, optimization, and development), data, reagents and reference materials, computational analysis tools, and infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate discovery research and clinical applications.

- For more information, see <http://proteomics.cancer.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*.
- (E/I) (NCI)

**Medical Sequencing:** The completion of the human genome sequence as well as genomic sequences of numerous other organisms has already made a substantial impact on both biological and medical research. Public access to the raw data produced from these large-scale sequencing efforts has empowered many additional studies about the genomic contributions to disease. To expedite the transition from research data to medical practice, NIH supports initiatives that both drive technology that will make whole genome sequencing affordable and produce data useful to biomedical research. Making the sequencing of any individual’s complete genome affordable

will allow personalized estimates of future disease risk and improve prevention, diagnosis, and treatment of disease. NIH's medical sequencing program is utilizing DNA sequencing to identify the genes responsible for rare, single-gene diseases; sequence all of the genes on the X chromosome to identify the genes involved in sex-linked diseases; and survey the range of variants in genes known to contribute to common diseases.

- For more information, see <http://www.genome.gov/15014882>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E/I) (NHGRI)

**Systems Biology Approach to Salivary Gland Physiology:** Previous research has catalogued the genes and proteins expressed in the salivary glands. This initiative puts those catalogues into context by defining when and where genes and proteins are expressed and how they function as parts of a fully integrated biological system. The initiative combines the power of mathematics, biology, genomics, computer science, and other disciplines to translate this highly detailed information into more precise and practical leads to treat Sjögren's syndrome, a debilitating autoimmune disorder that affects millions of Americans. The initiative also will help in learning to use saliva as a diagnostic fluid for a variety of conditions, from AIDS to cancer to diabetes.

- For more information, see <http://grants2.nih.gov/grants/guide/rfa-files/RFA-DE-08-001.html>
- This example also appears in Chapter 2: *Autoimmune Diseases*, Chapter 2: *Chronic Diseases and Organ Systems*, and Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIDCR)

**Genetics of Kidneys in Diabetes (GoKinD):** This program facilitates investigator-driven research into the genetic basis of diabetic kidney disease through a biospecimen repository. Individuals with type 1 diabetes were screened to identify two subsets, one with clear-cut kidney disease and another with normal kidney function despite long-term diabetes. Nearly 10,000 DNA, serum, plasma, and urine samples—plus genetic and clinical data—from more than 1,700 adults with diabetes have been collected. The entire GoKinD collection is being genotyped for whole genome association studies as part of the previously described Genetic Association Information Network (GAIN).

- [Mueller PW, et al. \*J Am Soc Nephrol\*. 2006;17:1782-90, PMID: 16775037](#)
- For more information, see [http://www.jdrf.org/index.cfm?fuseaction=home.viewPage&page\\_id=B9C33021-1321-C834-0382E079E7865807](http://www.jdrf.org/index.cfm?fuseaction=home.viewPage&page_id=B9C33021-1321-C834-0382E079E7865807)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK)

**Environmental Genomics:** NIH's Environmental Genome Project (EGP) was set up to catalogue all of the common variants, or single nucleotide polymorphisms (SNPs), in the coding and noncoding regions of the selected candidate genes. These candidate genes were chosen to fall into eight categories: cell cycle, DNA repair, cell division, cell signaling, cell structure, gene expression, apoptosis (cell death), and metabolism. Since 2005, EGP has been expanded to

include resequencing of factors controlling epigenetic modification of gene expression and nuclear receptors or other environmentally responsive genes. The newest NIH initiative on Environmental Genomics is supporting studies of the mechanisms of susceptibility to environmentally influenced diseases. This research is focusing on the critical common pathways through which environmental factors influence human health and the determinants of individual and population susceptibility to these stressors. Each application for this program was required to have a cross-stressor, cross-strain, and/or cross-species comparison depending on which comparative biology approach was most appropriate for the system of study. Two distinct approaches to utilizing comparative biology for understanding environmentally induced disease are used: (1) a genetically driven approach to define the genetic-environment interactions that contribute to the pathophysiological responses and individual susceptibility or protection from disease and (2) a pathway and network-driven approach to defining molecular mechanisms that mediate the pathophysiological responses to toxins.

- For more information, see <http://www.niehs.nih.gov/research/supported/programs/egp/>
- (E) (NIEHS)

**The NIH Pharmacogenetics Research Network (PGRN):** NIH established the PGRN in 2000 to study how genes affect the way a person responds to medicines. The network includes 12 interdisciplinary research groups, each focused on a specific problem. Recently, one team (the Pharmacogenetics of Anticancer Agents Research Group) identified 63 genetic variants that regulate human responses to the anticancer drug etoposide. The drug can cause severe side effects, including leukemia. Knowing the genetic basis of these side effects will help scientists develop tests to identify which cancer patients can be treated safely with etoposide.

- [Huang RS, et al. \*Proc Natl Acad Sci U S A.\* 2007;104:9758-63](#), PMID: 17537913
- For more information, see <http://www.nigms.nih.gov/Initiatives/PGRN>
- (E) (NIGMS)

**DNA Test for Charcot-Marie-Tooth Disease:** Charcot-Marie-Tooth disease, one of the most common inherited neurological disorders, affects one in 2,500 people in the United States. Its symptoms start in early adulthood and include progressive arm and leg pain that leads to difficulty walking and manipulating objects. Using a special strain of mice, new genomic technologies, and information from the mouse and human genome sequences, NIH-funded researchers rapidly identified a mutation that causes a subtype of the disease. Knowledge of the specific gene defect will enable development of a DNA test to confirm the diagnosis in patients and predict risk for family members.

- [Chow CY, et al. \*Nature.\* 2007;448:68-72](#), PMID: 17572665
- For more information, see <http://www.med.umich.edu/opm/newspage/2007/charcot.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (NIGMS, NINDS)

**How the Genes in Cells Are Turned On and Off:** In any cell, only a small fraction of the genes are activated. Scientists know that DNA is rolled around protein spools into structures called nucleosomes. They suspect that a gene's position on the nucleosome determines whether it is activated. Recently, NIH-funded investigators used state-of-the-art techniques to discover a DNA

sequence that appears to mark the start of activated genes in yeast cells (a similar sequence is predicted to play the same role in human cells). The sequence appears at the same place on almost all of the thousands of nucleosomes in the study—a location that is accessible to the proteins that activate genes. Improper gene activation is linked to cancer and other diseases, therefore identification of a DNA sequence that regulates gene activation will help researchers prevent, detect, or correct problems with gene activation that are associated with these diseases.

- [Albert I, et al. \*Nature\*. 2007;446:572-6](#), PMID: 17392789
- (E) (NIGMS)

**Gene Influences Antidepressant Response:** Whether depressed patients will respond to an antidepressant depends, in part, on which version of a gene they inherit. Having two copies of one version of a gene that codes for a component of the brain's mood-regulating system increased the odds of a favorable response to an antidepressant by up to 18 percent, compared to having two copies of the other, more common version.

- For more information, see <http://www.nimh.nih.gov/press/stardgene.cfm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH)

**Potential Therapy for Children Afflicted With Progeria Syndrome:** Hutchinson-Gilford progeria syndrome (HGPS) is a genetic disorder of accelerated aging. In addition to other symptoms of aging, HGPS patients suffer from accelerated cardiovascular disease and often die in their teen or even pre-teen years from heart-related illnesses. No treatments are currently available for HGPS; however, recent work led by NHGRI researchers indicates that farnesyltransferase inhibitors (FTIs), a class of drugs originally developed to treat cancer by blocking the growth of tumor cells, are capable of reversing the effects of the defective HGPS protein, lamin A. Ongoing studies in a mouse model have validated the results of preliminary experiments, and a clinical trial of FTIs in children with progeria began in 2007. In FY 2008, researchers plan on expanding the study to investigate whether FTIs are capable of reversing the detrimental effects after progression of the cardiovascular anomalies that are seen in the mouse model. The development of biological assays to assess the effects of FTI treatment on the patients' cells is in progress to monitor potential beneficial effects of the clinical trial. In addition, it has been demonstrated that the progerin protein is present in small amounts in normal aging tissues. The investigation of this phenomenon is being pursued as a contributory factor to the normal aging process.

- [Cao K, et al. \*Proc Natl Acad Sci U S A\*. 2007;104:4949-54](#), PMID: 17360355
- [Capell BC, et al., \*Proc Natl Acad Sci U S A\*. 2005;102:12879-84](#), PMID: 16129833
- For more information, see <http://www.genome.gov/15515061>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (I) (NHGRI)

**Genomic Studies of Autism:** NIH has supported a number of studies that are pointing to potential genetic causes of autism.

- For more information, see <http://www.nimh.nih.gov/science-news/2007/tiny-spontaneous-gene-mutations-may-boost-autism-risk.shtml>
- For more information, see <http://www.nimh.nih.gov/science-news/2007/largest-ever-search-for-autism-genes-reveals-new-clues.shtml>
- For more information, see <http://www.nimh.nih.gov/science-news/2006/gene-linked-to-autism-in-families-with-more-than-one-affected-child.shtml>
- For more information, see <http://www.nimh.nih.gov/science-news/2007/new-tests-may-help-researchers-detect-genetic-basis-for-autism.shtml>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH, NCRR, NICHD, NINDS)

## Resources

**Rodent Model Resources for Translational Research:** Mouse and rat models are the primary testbed for preclinical research and have played a vital role in most medical advances in the last century. Rodent models comprise about 90 percent of all animal studies enabling a wide range of genetic and physiological research on human disease. NIH plays a major role in supporting the availability of normal and mutant mice and rats for translational research. Recent accomplishments include:

- ▷ Knockout Mouse Project (KOMP)—a Trans-NIH initiative to individually inactivate each protein-coding mouse gene to better understand the genetic functions of the estimated 22,000 mouse genes, which are, in many cases, very similar to human genes.
  - ▷ KOMP Repository—established in FY 2007 to acquire and distribute the mouse models produced by the KOMP.
  - ▷ Mutant Mouse Regional Resource Centers—distribution of genetically engineered mice increased by 50 percent in FY 2006 because of increased demand.
  - ▷ Rat Resource and Research Center—acquisition and distribution of rat models increased by 50 percent in FY 2006 because of increased demand.
- For more information, see <http://www.genome.gov/17515708>
  - For more information, see <http://www.genome.gov/25521840>
  - For more information, see <http://www.mmrrc.org/>
  - For more information, see <http://www.nrrrc.missouri.edu/>
  - For more information, see [ncrr.nih.gov/comparative%5Fmedicine/resource\\_directory/rodents.asp](http://ncrr.nih.gov/comparative%5Fmedicine/resource_directory/rodents.asp)
  - This example also appears in Chapter 3: *Clinical and Translational Research*.
  - (E) (NCRR)

**NIMH Genetics Repository:** Over the last 9 years, NIMH has built the infrastructure for large-scale genetics studies through the NIMH Human Genetics Initiative. Through this Initiative, NIMH established a repository of DNA, cell cultures, and clinical data, serving as a national resource for researchers studying the genetics of complex mental disorders.

- For more information, see <http://nimhgenetics.org/>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH)

**Database of Genotype and Phenotype (dbGaP):** Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGaP to house this growing body of information, particularly the results of GWAS, which examine genetic data of subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2007, dbGaP included results from more than a dozen GWAS, including genetic analyses added to the landmark Framingham Heart Study and trials conducted under the Genetic Association Information Network. dbGaP is to become the central repository for many NIH-funded GWAS in order to provide for rapid and widespread distribution of such data to researchers and accelerate the advance of personalized medicine.

- For more information, see <http://view.ncbi.nlm.nih.gov/dbgap>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NLM)

**Candidate Gene-Association Resource:** Over the years, NHLBI has supported a number of major population studies that have collected extensive data on cardiovascular disease and its risk factors and manifestations. To increase the utility of the data for conducting genetic association studies, NIH initiated the Candidate Gene Association Resource program in FY 2006. This new resource will have the capacity to perform high-throughput genotyping for up to 50,000 subjects in cohort studies that have stored samples and data available on a wide array of characteristics (phenotypes) associated with heart, lung, blood, and sleep disorders. The linked genotype-phenotype data will form an invaluable resource for investigators seeking to identify genetic variants related to those disorders.

- For more information, see <http://public.nhlbi.nih.gov/GeneticsGenomics/home/care.aspx>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NHLBI)

**Framingham SNP-Health Association Resource (SHARe):** The Framingham SHARe is a comprehensive new effort by NIH and the Boston University School of Medicine to pinpoint genes underlying cardiovascular and other chronic diseases. The program builds on the Framingham Heart Study (FHS), which was begun in 1948 to identify factors that contribute to cardiovascular disease, and on other NIH-funded research demonstrating that common but minute variations in human DNA, called single nucleotide polymorphisms (SNPs), can be used to identify genetic contributors to common diseases. The initiative will examine over 500,000 genetic variants in 9,000 study subjects across three generations. NIH will develop a database to make the data available to researchers around the world. The database will help researchers integrate the wealth of information collected over the years in the FHS with the new genetic data, resulting in an increased understanding of genetic influences on disease risk, manifestation, and progression. Because of its uniqueness in including three generations of subjects with comparable data obtained from each generation at the same age, the FHS is the first study to be included in the SHARe initiative. NIH is currently considering expansion of SHARe to include



other large longitudinal studies such as the Jackson Heart Study and the new Hispanic Community Health Study.

- For more information, see <http://www.nhlbi.nih.gov/new/press/06-02-06.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NHLBI, NLM)

**Conserved Domain Database and RefSeq:** NIH's Conserved Domain Database (CDD) is a powerful means to deduce the function of newly discovered proteins. CDD is particularly valuable to researchers working on drug development and those requiring a synthesis of information on protein biological function, 3-D structure, and sequence conservation. In FY 2006 NIH met its GPRA goal of developing methods to classify at least 75 percent of proteins from sequenced genomes according to evolutionary origin and biological structure. NIH also met the FY 2006 GPRA goal of building a high-quality collection of reference sequences (the RefSeq database) to provide a unified view of the best available genetic information on organisms.

- [Marchler-Bauer A, et al. \*Nucleic Acids Res.\* 2007;35:D237-40](#), PMID: 17135202
- [Pruitt KD, et al \*Nucleic Acids Res.\* 2007;35:D61-5](#), PMID: 17130148
- For more information, see <http://www.ncbi.nlm.nih.gov/RefSeq/>
- For more information, see <http://www.ncbi.nlm.nih.gov/Structure/cdd/cdd.shtml>
- (NLM) (GPRA Goal)

**ENCODE:** The ENCyclopedia Of DNA Elements (ENCODE) is an international research consortium organized by NIH that seeks to identify all functional elements in the human genome. The initial 4-year pilot phase has just been completed, and the consortium has published a series of papers describing a complex network in which genes and other regulatory mechanisms interact in complex ways. Other insights include the discovery that the majority of DNA in the human genome is transcribed into functional molecules, called RNA, and that these transcripts extensively overlap one another. These findings challenge long-held beliefs that the genome has small sets of genes and vast amounts of “junk” DNA. Until now, most studies have concentrated on the functional elements of specific genes, and have not provided information about functional elements in the vast majority of the genome that does not contain genes. ENCODE's exciting discoveries may well reshape the way scientists think about the genome and pave the way for more effective approaches to both understanding and improving human health.

- [The ENCODE Project Consortium, et al. \*Nature.\* 2007;447:799-816](#), PMID: 17571346
- For more information, see <http://www.genome.gov/10005107>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NHGRI)

**The Knockout Mouse Project (KOMP):** The NIH Knockout Mouse Project (KOMP) is an NIH-wide effort to create a publicly available resource of knockout mouse mutations that can be used to study human disease. Knockout mice are strains of mice in which specific genes have been completely disrupted, or knocked out. By studying these mice, researchers can evaluate the effect of this systematic disruption of different genes on physiology and development. Understanding the effects of gene disruption in mice will provide powerful tools to develop

better models of inherited human disease. NIH has awarded 5-year cooperative agreements for the creation of knockout mice lines to Regeneron Pharmaceuticals Inc. to a collaborative team from Children's Hospital Oakland Research Institute, and to the Wellcome Trust Sanger Institute in England. NIH has also recently awarded \$4.8 million to the University of California, Davis, and the Children's Hospital of the Oakland Research Institute to establish and support a repository for the KOMP. The repository will enable many more researchers to have access to the knockout mice, and will ensure product quality for the 8,500 types of knockout mice currently available.

- [Austin CP, et al \*Nat Genet.\* 2004;36:921-4](#), PMID: 15340423
- For more information, see [www.komp.org](http://www.komp.org)
- This example also appears in Chapter 3: *Technology Development*.
- (E/I) (NHGRI)

**Genetics Home Reference:** The Genetics Home Reference Web site provides basic information about genetic conditions and the genes and chromosomes related to those conditions. Created for the general public, the site was expanded to include summaries for more than 225 genetic conditions, more than 380 genes, all the human chromosomes, and information about disorders caused by mutations in mitochondrial DNA.

- For more information, see <http://ghr.nlm.nih.gov>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (I) (NLM)

**The U.S. Surgeon General's Family History Initiative:** Many people see most diseases as the result of interactions of multiple genes and environmental factors. Health care professionals have known for a long time that common diseases, such as heart disease, cancer, and diabetes, and rare diseases such as hemophilia, cystic fibrosis, and sickle cell anemia, can run in families. In a collaborative effort between the Office of the Surgeon General, NIH, the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), and the Health Resources and Services Administration (HRSA), the U.S Surgeon General's Family History tool was created. The U.S. Surgeon General's Family History tool (available in both English and Spanish) is free, and has proven to be an effective personalized tool for individualizing preventive care and disease prevention—in other words, maintaining good health. Recently updated, this tool allows individuals to record health conditions that have affected their relatives. It utilizes a three-generation pedigree to gather information on health conditions in one's family to help doctors take action to keep individuals and families healthy.

- [Guttmacher AE, et al. \*N Engl J Med.\* 2004;351:2333-6](#), PMID: 15564550
- For more information, see <http://www.hhs.gov/familyhistory>
- For more information, see <https://familyhistory.hhs.gov>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (OD, NHGRI)

**Influenza Virus Resource:** This database of more than 40,000 influenza virus sequences allows researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic, and vaccine

targets. The resource was developed by NCBI using data obtained from NCBI's Influenza Virus Sequence Database and from NIAID's Influenza Genome Sequencing Project, which has contributed sequences of the complete genomes from over 2,500 influenza samples. In FY 2006 more than 11,000 influenza virus sequences were entered into the database, and new search and annotation tools were added to assist researchers in their analyses.

- [Wolf YI, et al. \*Biol Direct\* 2006;1:34](#), PMID: 17067369
- [Chang S, et al. \*Nucleic Acids Res\* 2007;35:D376-80](#), PMID: 17065465
- For more information, see <http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>
- For more information, see <http://www.niaid.nih.gov/dmid/genomes/mscs/influenza.htm>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*, Chapter 2: *Infectious Diseases and Biodefense*, and Chapter 3: *Molecular Biology and Basic Sciences*
- (I) (NLM)

## Ethical, Legal, Social and Behavioral Issues

**Genetic Factors in Health Disparities:** A major concern in the era of genomic health care is to ensure that all racial, ethnic, and cultural groups benefit fully from genomic technology. One GPRA goal is to establish the role of genetic factors in three major diseases for which health disparities are noted. Building on the foundation of the Human Genome Project (HGP), NIH, as part of the International HapMap Consortium, has developed a way to scan large regions of chromosomes for variants (called SNPs, or single nucleotide polymorphisms) associated with increased risk of disease. Understanding the role of genetics in diseases characterized by health disparities will rely on such tools. As an example, the FUSION (Finland-United States Investigation of Non-Insulin-Dependent Diabetes Mellitus Genetics) study collected 820 million genotypes in 2006, which resulted in the identification of at least four new genetic variants associated with increased risk of diabetes and confirmed existence of another six. The findings boost to at least 10 the number of genetic variants confidently associated with increased susceptibility to type 2 diabetes—a disease that affects more than 200 million people worldwide, and a major cause of health disparities.

- [Scott LJ, et al. \*Science\*. 2007;316:1341-5](#), PMID: 17463248
- For more information, see <http://nihperformance.nih.gov/>
- (E/I) (NHGRI) (GPRA Goal)

**Ethical, Legal and Social Implications (ELSI) Centers of Excellence for ELSI Research (CEERs):** This center program has funded four full centers and three exploratory centers involving investigators in a wide range of disciplines to devise and employ interdisciplinary approaches to investigate ELSI issues such as:

- ▷ Intellectual property issues surrounding access to and use of genetic information
- ▷ Factors that influence the translation of genetic information to health care
- ▷ Conduct of genetic research that involves human subjects
- ▷ Use of genetic information and technologies in non-health care settings such as employment, insurance, education, criminal justice, or civil litigation
- ▷ Impact of genomics on concept of race, ethnicity, and individual/group identity

- ▷ Implications of uncovering genomic contributions to human traits and behaviors such as mental illness or aging for how we understand health and illness
- ▷ How different individuals, cultures, and religious traditions view the ethical boundaries for the uses of genomics

The use of CEERs resources and expertise to design and implement multifaceted and multidisciplinary investigations of particularly complex, persistent, or rapidly emerging ELSI issues is an important addition to ongoing genetic, genomic, and ELSI research efforts. Additionally, each CEER trains many young ELSI researchers each year.

- For more information, see <http://www.genome.gov/10001618>
- For more information, see Chapter 4: *NIH Centers of Excellence*.
- (E) (NHGRI)

**Multiplex Initiative:** With the completion of the sequence of the human genome, genetic susceptibility tests that give “personalized” information about risk for a variety of common health conditions are now being developed and marketed. This genetic information ultimately will improve primary care by enabling more personalized treatment decisions for common diseases such as diabetes and heart disease. This information also might motivate patients to change unhealthy behaviors. NIH investigators have teamed with the Group Health Cooperative in Seattle and the Henry Ford Health System in Detroit to launch a study to investigate the interest level of healthy, young adults in receiving genetic testing for eight common conditions. Called the Multiplex Initiative, the study will also look at how people who decide to have the tests interpret and use the results in making health care decisions. One thousand subjects who meet the study’s eligibility requirements will be offered free multiplex genetic testing. The testing is designed to yield information about 15 different genes that play roles in common diseases such as type 2 diabetes and coronary heart disease. Trained research educators will make followup telephone calls to help subjects interpret and understand test results, and subjects will receive newsletters to update them on new developments about the tested genes. This research should provide insights into how best to utilize the powerful tools of genomic medicine to improve health.

- For more information, see <http://www.genome.gov/25521052>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NHGRI)

**Genes, Behavior and the Social Environment: Moving Beyond the Nature/Nurture Debate:** This 2006 Institute of Medicine report was requested in order to examine the state of the science on gene-environment interactions as related to health, with a focus on the social environment. Report recommendations identified approaches and strategies to strengthen the integration of social, behavioral, and genomic research and training needs.

- For more information, see <http://www.iom.edu/CMS/3740/24591/36574.aspx>
- (E) (OBSSR, NHGRI, NIGMS)

**NIH Revision Awards for Studying Interactions Among Social, Behavioral, and Genetic Factors in Health:** These program announcements solicit applications for competitive supplements (revisions) to NIH grants to add a genetics/genomics component to a behavioral or social science project or the converse, i.e., to add a behavioral or social science component to a genetics/genomics project. This ultimate goal of this initiative is to elucidate how interactions among genetic/genomic, behavioral and social factors influence health and disease. The knowledge gained by such research will improve our understanding of the determinants of disease as well as inform efforts to reduce health risks and provide treatment.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-065.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-066.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-08-067.html>
- (E) (OBSSR, NCCAM, NCI, NEI, NHGRI, NIA, NIAAA, NIAMS, NIDA, NICHD, NIDCD, NIDCR, NIDDK, NIMH, NINR, NINDS, ODS)

**Summer Training Institute in Genes, Environment and Behavior Research:** This training institute scheduled for summer of 2009 will target behavioral and social scientists at various career levels. The activity is designed to instruct the subjects in the theoretical and practical foundations of genetics and genomics and to introduce them to research on gene-behavior-environment interactions. The institute will help train a cadre of behavioral and social scientists capable of working in interdisciplinary teams to improve our understanding of how interactions among genes, behaviors, and environments contribute to health and disease.

- (E) (OBSSR)

## MOLECULAR BIOLOGY AND BASIC RESEARCH

*Over 30 years ago, the introduction of recombinant DNA technology as a tool for basic biological research revolutionized the study of life. Molecular cloning allowed the study of individual genes of living organisms; however, this technique was dependent on obtaining relatively large quantities of pure DNA. This problem was solved by the development of the polymerase chain reaction (PCR), which produced large quantities of a specific DNA sequence from a complex DNA mixture. Because of its simplicity and elegance, PCR transformed the way in which almost all studies requiring the manipulation of DNA fragments were performed. As described by Kary Mullis, who was awarded the Nobel Prize for Chemistry in 1993 for inventing PCR, the technique “lets you pick the piece of DNA you’re interested in and have as much as you want.” Because of its simplicity and ability to create hundreds of thousands of copies of a specific DNA sequence of interest, PCR allows for the routine yet highly efficient performance of most major molecular biology techniques including sequencing, cloning, and identifying variations in genes, including gene mutations that cause disease.<sup>8</sup>*

### Introduction

Basic research is a major force driving progress across the biomedical and behavioral sciences, making it possible to understand the causes and progression of disease, intervene to prevent disease from occurring, develop better and more precise diagnostic devices and tests, and discover new treatments and cures. Basic research leads to fundamental insights that, on the surface, might not have an immediate or apparent application to human health, but are essential to understanding basic human biology and behavior in their normal and diseased states. It provides the foundation for responding to unexpected health crises. Whether the new insights come from blockbuster discoveries or an accumulation of incremental advances, history shows that over time, basic research yields inestimable rewards. Thus, it is a critical component of the Nation’s public investment in research and is a central feature of each IC’s research program. The importance of basic research to new interventions cannot be overestimated.

Basic research involves and relies on many scientific disciplines, including genomics, proteomics, endocrinology, immunology, genetics, epidemiology, neuroscience, behavioral, and social science, and cell, developmental, and vascular biology—to name a few. Importantly, basic scientists and clinical researchers frequently work together to translate research findings from bench to bedside and back.

As an influential component of basic research, molecular biology focuses on the formation, structure, and function of macromolecules—very large molecules that consist of many smaller structural units linked together. Macromolecules including proteins and nucleic acids—such as DNA and RNA—are involved in critical biological functions such as cell replication and storing and transmitting genetic information. The study of macromolecules provides information about structures that are essential to life. Such study yields knowledge of the molecular components of

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<sup>8</sup> NIH did not fund Mullis’s Nobel Prize-winning research, although it did fund other research by Mullis, and NIH-funded research laid the foundation that made Mullis’s invention of PCR possible.



the cells of all types of organisms and the complex ways in which these molecules are organized, regulated, and interact, and provides essential insights for understanding and eventually controlling a wide range of human diseases.

Some researchers focus on individual or a few proteins, whose functions or structures, particularly if disrupted, may play key roles in specific diseases. Meanwhile, other researchers are engaged in “proteomics,” which entails integrating analytic technologies to identify and measure levels of large sets of (instead of individual) proteins. Scientists then study their interactions and how their levels fluctuate under various conditions. These basic efforts are helping to determine how such sets of proteins might change with the onset and progression of specific diseases, often providing insights about ways to intervene in the patient.

Molecular biology, like other areas of basic biological research, depends on harnessing the expertise and skills of allied disciplines such as physics, chemistry, mathematics, computer science, and engineering.

Every IC embraces basic research as essential to furthering the NIH mission—improving health. Although many ICs, such as NIAID and NCI, focus on research fundamental to specific diseases and organ systems, others, such as NIEHS and NIGMS, have missions that mandate they support basic research across a wide range of specialized disciplines. Still other ICs, such as NIBIB and NHGRI pursue basic research in more targeted areas.

For example, basic research in infectious disease examines the mechanisms that pathogens use to invade and infect the body, the interactions between pathogens and the bodies they infect, the mechanisms bodies naturally use to fight pathogens, and the environmental and genetic influences on the spread and evolution of pathogens. Insights from such investigations provide the targets for candidate vaccines, diagnostics, and treatments.

Because cancers affect various cells, organs, and tissues throughout the body, basic research in cancer is aimed, for instance, at understanding immune and inflammatory responses, stem cells, DNA repair mechanisms, and the microenvironment enveloping tumors. Discoveries in these areas are leading to medical advances that help patients with particular types of cancer. Not long ago, for example, experts disputed the validity of immunotherapy as a way of treating cancer. (Immunotherapy stimulates or restores the ability of the immune system to fight cancer, infections, and other diseases.) Now, this approach is being used as one standard of care for treating several specific types of cancer, including leukemia, lymphoma, and melanoma. Similarly, efforts to understand basic molecular mechanisms for repairing DNA could help cancer patients recuperate more quickly after receiving radio- and chemotherapy, both of which damage healthy as well as cancer cells.

Efforts to understand the microenvironment of cancer cells complement efforts to learn more about how the broader environment and associated toxic agents can affect human health and contribute to diseases other than cancer. One emergent area of research sponsored by NIEHS involves studying how toxic substances in the environment can impinge on signaling pathways within our cells, sometimes disrupting biochemical pathways and leading to subtle stresses or outright disease.

As part of fulfilling its mission to support a wide spectrum of basic research, NIGMS funded Andrew Fire and Craig Mello, who shared the 2006 Nobel Prize in Physiology or Medicine. In studying the roundworm *C. elegans*, they discovered a type of double-stranded RNA molecule that silences genes in that organism. Other researchers soon learned that similar RNA molecules silence genes in other organisms, including humans. Now these molecules are being studied as potential treatments for specific diseases. Thus, basic research on a roundworm, of no obvious direct medical interest itself, furnished insights that soon could lead to novel treatments for a diverse array of diseases, including Huntington's disease, hepatitis B, and cancer, among others.

The 2007 Nobel Prize in Physiology or Medicine was awarded to two long-time NIH grantees whose work underscores the power of basic research to stimulate progress in the treatment and cure of disease. NIGMS began supporting Mario Capecchi and Oliver Smithies in 1968 and 1973, respectively. Later, other ICs also provided support. Working independently, Capecchi and Smithies created an elegant and powerful gene-targeting method in mice that has become an indispensable tool for biomedical research. The method enables scientists to create "transgenic" mice, which contain specific insertions of extra genes from mice or other organisms. When transferred genes involve human diseases, the transgenic mice can serve as model organisms for studying those human disorders. Researchers also can use the gene-targeting technique to insert defective genes that "knock out" the normal versions. Once these are "knocked out," scientists can understand the importance of these genes to normal function or disease. Mice developed with this technology are used for a wide range of medical research from basic studies of biological processes to investigations of, for example, cancer, heart disease, and cystic fibrosis.

Basic research often relies on studies in "model organisms" such as bacteria, fruit flies, or mice. Because human cells contain the same molecular building blocks and pathways as those of most other living things, researchers can learn much about the way our cells work by studying these simpler organisms. Although seemingly removed from human health, historically, many productive routes to medical discoveries involve organisms that typically are far simpler to study than are humans.

In addition, because candidate diagnostics and therapeutics typically need to be validated in model systems—for example, by studying animals that are susceptible to the same or similar microbial pathogens that cause diseases in humans or that develop diseases similar to humans, the development of animal models of disease is an important element of basic research. NIH-supported researchers have developed animal models for corneal disease, cleft palate, hearing loss, blindness, and even mental retardation. Animal models can lead to the development of promising interventions that then are subject to further refinement and testing before being evaluated in clinical trials. Conversely, fundamental research focused on improving human health also can provide veterinary benefits. For example, basic studies of the role of immune factors in controlling herpes led to a vaccine for a deadly disease in chickens.

The long-term implications of basic research in bioengineering and imaging also are profound. NIBIB is pursuing the tools that will enable tissue engineering and regenerative medicine to become standard medical realities. Basic research in imaging techniques is fueling a wide array of new means of diagnosis and making a quantum leap in structure-based design of drugs, a method that cuts through the cumbersome and expensive screening processes.

Basic science can yield unanticipated benefits, as scientists make so-called serendipitous discoveries. For example, while creating compounds to clog proteasomes—cellular garbage disposal-like structures implicated in muscle wasting—scientists noticed that one of the substances had anticancer properties; this drug (Velcade™) is now used to treat multiple myeloma, the second most common blood cancer. As another example, while studying the structures of complex sugars, scientists developed prototypes of new drugs to help control blood clots, which can cause heart attacks and strokes during surgery. This unpredictability is intrinsic to the interconnectedness of biological systems and the rudimentary stage of our knowledge. And rather than randomness or caprice—serendipity is the beauty of biology. However, as stewards of the Nation’s investment in health science, NIH does not count on the serendipity—that is, NIH never funds or justifies a project based on expectations for serendipity. Rather, serendipitous findings are an added bonus from research projects already deemed meritorious for their intended purposes.

Basic biomedical research also benefits other sectors of the economy. Many nonbiomedical industries have emerged as a result of or been enhanced by biomedical discoveries. For example, freeze-drying, which was developed to concentrate and preserve laboratory samples, is now widely used in the food industry. As another example, basic studies of digestive enzymes led to food industry improvements including meat tenderizers, bread dough conditioners, milk coagulants for cheese production, and preservatives for juices.

### **Summary of NIH Activities**

As noted above, the impact of any single basic research discovery may be quite wide, bearing on multiple other fields. Research on neuronal receptors is perfectly likely to inform understanding of viral receptors. The inherent unpredictability to basic research means that it is not easily compartmentalized. The examples below reflect the breadth and diversity of the basic research pursued by NIH—research that touches on the mission of every IC, and every disease, condition, and effort to improve health.

One critical area of basic research that aims to understand how genes turn off or on or malfunction is epigenetics. In epigenetics research, investigators focus on factors that affect genes at the molecular level but do not change the sequence of the basic building blocks of DNA. Because epigenetics is concerned with factors unrelated to DNA sequence, these efforts differ from conventional genomics and genetics. Factors that cause epigenetic changes can come from the environment or may be in the diet, or related to other influences. Moreover, they are linked to a broad range of illnesses. A recently developed NIH program, the [Genes, Environment and Health Initiative](#), supports research to understand how environmental exposures might induce epigenetic changes, particularly in critical periods such as during pregnancy, early life, and puberty. Related NIH-supported research aims at understanding how epigenetic changes and variations occur at the molecular level. (Also see Chapter 1 for description of the Roadmap 1.5 Epigenetics/Epigenomics initiative, in the section titled “Roadmap 1.5 and the Common Fund Strategic Initiative Process.”)

Another example of NIH-supported basic molecular research is the [Molecular Libraries Roadmap Initiative](#). This program, established in 2006, offers public-sector researchers access to

tens of thousands of small (that is, low in molecular weight) chemical compounds to probe the functions of genes, cells, and biological pathways and their impact on health and disease. Already investigators have used this resource to explore a wide variety of biological activities specifically related to normal processes and disease, including inflammatory pathways, previously unknown signaling proteins, and changes in cellular phenotypes associated with disease. Other investigators are gaining leads for drug discovery through access to these compounds.

The recently established [Nanomedicine Development Centers](#), another component of the NIH Roadmap, takes advantage of technology developments at the nanoscale (on the level of biological molecules and structures inside living cells). The goal of this 10-year program, now involving more than 120 scientists from 30 institutions working at 8 centers, is to understand and control the nanomachinery of life in order to diagnose or treat and prevent diseases and repair injured tissues.

Some molecular-level research focuses on how pain signals are transmitted. For instance, NIH scientists recently learned that a particular protein, cyclin-dependent kinase 5, plays a regulatory role in pain signaling affecting sensory nerves. Their findings suggest that new analgesic drugs that alter this protein's activity could prove beneficial in relieving pain. Separate research on cannabinoids is guiding the design of molecules that block pain more selectively and safely, with minimal side effects and low potential for abuse.

NIH is supporting several molecular-level research programs studying complex carbohydrates, or polysaccharides, which consist of many linked sugars that are attached to the surfaces of proteins and lipids that form the surface of cells. These sugar-containing molecules are involved in diverse cellular activities, including signaling, recognition, adherence, and motility. They also play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. The detection and analysis of such carbohydrates are considered critical for basic and clinical research but are widely regarded as a very difficult challenge.

Some NIH-sponsored molecular-level research explores fundamental physiological processes. For instance, NIH-supported scientists recently identified a protein, PKD1L3, in sensory cells that plays a key role in forming channels specifically for detecting sour tastes. This advance may help scientists treat taste impairments and could lead to the development of better salt and sugar substitutes for the millions of Americans on restricted diets that help to control high blood pressure, diabetes, and obesity.

Other NIH-supported scientists recently found that patients with chronic periodontitis, or gum disease, overproduce a signaling protein known as SHIP, which plays an important regulatory role in immune cells, inducing them to tolerate instead of react against an endotoxin, whose presence is associated with chronic periodontitis and tooth loss. Yet other NIH-supported scientists are studying a molecular byproduct, called resolvin E1 (RvE1), that derives from omega-3 fatty acids. RvE1 dramatically alters the progress of microorganism-initiated periodontitis and other diseases that arise through overly active inflammatory responses.

Some basic molecular-level research entails studying changes in molecules that disrupt cells and thus lead to specific diseases. For instance, misfolded proteins in brain cells are implicated in several neurodegenerative diseases, including Huntington's, Alzheimer's, and Parkinson's. Misfolded proteins can, in turn, disrupt other normal proteins in brain cells, leading to their death. NIH-supported scientists now surmise that learning how to bolster cell-repair mechanisms could provide an approach for treating some of these degenerative diseases.

In addition to proteins, damage also can occur to DNA molecules in cells when they are exposed to factors such as ultraviolet light or environmental toxins, sometimes leading to cancer or other serious clinical problems. NIH-supported scientists recently identified a protein that triggers a "lock-down" response to double-stranded DNA breaks, and helps to explain how cells ordinarily maintain their genetic material but sometimes lose that control in the case of cancer. More broadly, the NIH Tumor Biology and Metastasis Program supports research to delineate molecular mechanisms and signaling pathways involved in tumor progression, cell migration and invasion, angiogenesis (the process by which new blood vessels are formed), and metastasis.

NIH supports a range of basic research projects exploring cells, which are the basic membrane-bound units that make up organisms, and investigating biological systems, meaning the interactions among several or many biological components within organisms that lead to complex effects and integrated behaviors, including at the metabolic, cellular, and organ levels.

For example, many basic research projects focus on embryonic and adult stem cells, with some emphasizing genetic approaches and others analyzing critical events in early human development. NIH-funded researchers recently discovered a genetic switch that enables embryonic stem cells to develop into recognizable cell types; this and similar critical insights are expected to advance research on regenerative medicine and may lead to new treatments for many conditions, including, potentially, Parkinson's disease and spinal cord injuries.

Another example of an NIH-supported effort focused on cellular development is the [Beta Cell Biology Consortium](#), which is conducting research relevant to the development of therapies for type 1 and type 2 diabetes. The consortium is studying how insulin-producing beta cells are made, exploring the potential of stem cells as a source for making insulin-producing islet cells, and determining the mechanisms underlying beta cell regeneration.

Some cell-based research focuses on the thousands of different microbial species that naturally associate with particular anatomic sites within or outside the human body, including in the intestinal tract and on the skin. These studies will help differentiate microorganisms that help to maintain health from others that can cause disease. The studies also are advancing understanding of how environmental factors affect such microorganisms and whether environmental factors affect host susceptibility to or severity of diseases that occur at those and other anatomic sites.

Of course, some microorganisms such as the influenza virus are well known to be pathogenic. The threat of the H5N1 influenza virus, which has been circulating in Asia and elsewhere, is of particular concern because this strain of virus, while not readily transmissible between humans, is highly lethal to those who become infected. As part of a broad-based effort to track and analyze this emerging viral threat, NIH established the [Influenza Virus Resource](#), which includes

a database containing sequence information for more than 40,000 influenza sequences including the sequences of more than [2,500 whole influenza genomes](#). Moreover, in 2007 NIH established six [Centers of Excellence for Influenza Research and Surveillance](#) to conduct research on both animal and human influenza viruses. These efforts will assist investigators in understanding the basic mechanisms by which influenza virus replicates and spreads, which ultimately could lead to better treatments or vaccines.

Research on the activity of influenza viruses is one among several basic science efforts that address the complexities of the human immune system. Another example is the [Immune Tolerance Network](#), a consortium of more than 80 investigators who share the long-term goal of learning how to eliminate harmful immune responses, such as graft rejection, while preserving protective immunity against infectious agents and other disease threats. Similarly, the NIH Consortium of Food Allergy Research is using a mouse model to study how modified forms of peanut allergens protect against peanut-induced anaphylaxis and is conducting an observational study to examine immune mechanisms, genetic factors, and environmental factors associated with the development of new food allergy to peanut and the loss of egg allergy in high-risk young children. In addition, the six centers of the [Cooperative Study Group for Autoimmune Disease Prevention](#) are devoted to understanding immune homeostasis (physiological balance or equilibrium), a concept fundamental to preventing autoimmune diseases, with one emphasis being type 1 diabetes. In yet another effort that began in FY 2005, NIH supports research to better understand the underlying biological and physiological factors involved in asthma exacerbations. These insights ultimately could lead to the development of more effective treatments for this immune system-related condition.

Beyond the immune system, NIH is supporting systems biology research that is driven by both basic experimental and computational approaches. For instance, NIH sponsors efforts at seven interdisciplinary centers to develop predictive computer models for use in analyzing drug metabolism, host-pathogen interactions, organism development, and cell signaling. Similarly, the [Integrative Cancer Biology Program](#) is focusing on networks and systems genetic research to develop a more basic understanding of cancer through multidisciplinary research.

Genetics provides yet another systems approach to studying particular diseases or wider physiological systems. For instance, the [Gene Expression Nervous System Atlas](#), or GENSAT, is a comprehensive effort to analyze where and when during development genes are active within the mouse nervous system. In addition, the genetically engineered mice used to generate the atlas are also proving to be a valuable resource. For example, researchers recently used mice from the GENSAT project to study mechanisms that kill nerve cells in patients with Parkinson's disease. Meanwhile, other genetics efforts in basic research are aimed at uncovering the cause of hereditary hearing loss and stuttering, identifying the genes involved in regulating sensitivity to alcohol, and analyzing the 400 or more genes involved in vision loss.

NIH supports the development or identification of many different animal models for use in studying a broad range of diseases and conditions. In mice alone, this ranges from the development of a genetically engineered mouse for studying several diseases affecting the surface of the eye to the use of aged and obese mice in studying the mechanisms controlling the lifespan.



Several basic research programs focus on angiogenesis, the process whereby new vessels form to supply specific tissues and organs with blood, as well as other disorders affecting blood vessels. For example, NIH-supported research in animal models showed that dietary omega-3 polyunsaturated fatty acids reduce harmful angiogenesis in the retina. In a separate effort, investigators are using mouse models to study the biological and chemical properties of the drug losartan, which is widely used to control hypertension, to determine whether it might also be useful for preventing life-threatening aortic aneurysms, which occur often among individuals with Marfan syndrome. Yet other NIH-sponsored basic research aims at developing novel synthetic replacements for damaged or diseased blood vessels. Further, NIH is sponsoring basic research into the lymphatic system and its function in health and disease; such research might lead to the development of new diagnostic methods and treatment interventions.

The NIH also supports basic research in neuroscience at the molecular, cellular, systems, and cognitive and behavioral levels to understand the development and function of the nervous system (also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2). This research in people and in animal models includes studies of the neurobiological mechanisms underlying pain, sensory perception, learning, and addiction, among other nervous system functions. One project in the neurosciences is developing a set of standardized measures of cognitive, emotional, sensory, and motor function that will help researchers compare and integrate data collected across different studies. Basic research in the neurosciences also includes efforts to develop tools to monitor or probe discrete brain systems. For example, NIH-supported investigators recently genetically engineered neurons in mice and worms to express light-sensitive genes from algae and bacteria, allowing for rapid and precise control over neuronal circuit activity with pulses of light. NIH also invests in research in the behavioral and social sciences, with a goal to better understand social and cultural factors affecting health and illness.

Complementing these efforts, NIH supports a substantial portfolio of multidisciplinary research on mind-body interventions, such as meditation and Tai Chi Chuan, including basic research to understand the biological response to such interventions. Other projects involving complementary and alternative medicine focus on Alzheimer's disease and dementia, and include evaluations of the biological and biochemical consequences of the use of natural products such as an omega-3 fatty acid, *Ginkgo biloba*, and a component of pine trees. Still other projects are elucidating the fundamental mechanisms of turmeric extracts and green tea, used for treating conditions such as rheumatoid arthritis and obesity-associated insulin resistance, respectively. These basic research studies in animal models provide the foundation for future translational and clinical research.

## Notable Examples of NIH Activity

### Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

### Basic Research at the Molecular Level

**Promising Approaches to Treating Chronic Pain:** Opioid analgesics are the most powerful pain medications currently available; unfortunately they can produce drug dependence. Thus, an area of enormous need is the development of potent non-opioid analgesics. In recognition of this, NIH has implemented an aggressive and multidisciplinary research program. Many of these initiatives are yielding tangible results that stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to selectively activate the CB system to provide analgesia with minimal or no psychotropic side effects or abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different receptors, the targeting of which could provide a vastly expanded range of pharmacotherapeutic effects. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on a non-neuronal brain cell type, glia, has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their proinflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of analgesic drugs. At the brain circuit level, a new approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects "learn" how to regulate pain by viewing and then controlling images of their own brains in real time.

- For more information, see <http://www.nida.nih.gov/whatsnew/meetings/painopioides/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDA, NINDS)

**Environmental Influences on Epigenetic Regulation:** The field of epigenetics (gene expression and heritability unrelated to DNA sequence) is uniquely related to environmental health sciences. Almost all known factors causing epigenetic change are from the environment, diet, or supplements. Epigenetic mechanisms are being linked to multiple illnesses, including cancer, cognitive dysfunction, and respiratory, cardiovascular, reproductive, autoimmune, and neurobehavioral diseases. Recently, NIH developed a program in epigenetics that supports research to understand how the epigenome is affected by environmental exposures and how this affects human health. This field promises to shed light on how early life exposures can lead to disease later in life. One purpose of this program is to identify critical windows of susceptibility to epigenetic changes, particularly during pregnancy, early life, and puberty; this will help us develop biomarkers of early exposure, as well as identify possible therapeutic strategies to prevent later disease. Projects currently being supported by this program include epigenetic modulation of DNA repair during breast carcinogenesis and progression, gene silencing in

mammalian cells induced by environmental exposure, impact of nongenetic factors on breast cancer susceptibility gene functions, and epigenetics of human cancer from chronic radiation exposure.

- For more information, see <http://grants1.nih.gov/grants/guide/rfa-files/RFA-ES-05-007.html>
- For more information, see <http://grants2.nih.gov/grants/guide/rfa-files/RFA-ES-05-007.html>
- (E) (NIEHS)

**The Tumor Biology and Metastasis Program:** This program supports research to delineate the molecular mechanisms and signaling pathways involved in tumor progression, cell migration and invasion, angiogenesis, lymphangiogenesis, and metastasis. Research indicates that the progression of cancer depends on the co-evolution of carcinoma cells in their immediate microenvironment. In 2006, NIH launched the Tumor Microenvironment Network (TMEN), to investigate the composition of the stroma in normal tissues, with the goal of delineating the mechanisms of tumor-stromal interactions in human cancer.

- For more information, see <http://tmen.nci.nih.gov/>
- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI)

**Glycomics Technology Development, Basic Research, and Translation into the Clinic:**

Complex carbohydrates are ubiquitous, found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules is thus critical for basic and clinical research across the spectrum of health and disease, but is widely regarded as one of the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- ▷ Biomedical Technology Research Resources are developing and sharing cutting-edge technologies for analysis of carbohydrates in complex biological systems.
  - ▷ Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
  - ▷ Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
  - ▷ A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.
- For more information, see [www.ncrr.nih.gov/glycomics](http://www.ncrr.nih.gov/glycomics)
  - For more information, see [www.functionalglycomics.org](http://www.functionalglycomics.org)
  - This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*.
  - (E) (NCRR, NCI, NHLBI, NIGMS, NINDS)

**Shared Instrumentation Grant and High-End Instrumentation Programs:** The goal of the NIH instrumentation programs is to provide new generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the \$100,000-\$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the \$750,000-\$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located on core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2006 and 2007 the SIG program funded a total of 264 grants for \$95.2 million; the HEI funded a total of 39 awards for \$55.9 million.

- For more information, see [www.ncrr.nih.gov/biomedical\\_technology/shared\\_instrumentation](http://www.ncrr.nih.gov/biomedical_technology/shared_instrumentation)
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*.
- (E) (NCRR)

**ENCODE:** The ENCyclopedia Of DNA Elements (ENCODE) is an international research consortium organized by NIH that seeks to identify all functional elements in the human genome. The initial 4-year pilot phase has just been completed, and the consortium has published a series of papers describing an intricate network in which genes and other regulatory mechanisms interact in complex ways. Other insights include the discovery that the majority of DNA in the human genome is transcribed into functional molecules, called RNA, and that these transcripts extensively overlap one another. These findings challenge long-held beliefs that the genome has small sets of genes and vast amounts of “junk” or untranscribed DNA. Until now, most studies have concentrated on the functional elements of specific genes, and have not provided information about functional elements in the vast majority of the genome that does not contain genes. ENCODE’s exciting discoveries may well reshape the way scientists think about the genome and pave the way for more effective approaches to both understanding and improving human health.

- [The ENCODE Project Consortium, et al. Nature. 2007;447:799-816](http://www.nature.com/447799a), PMID: 17571346
- For more information, see <http://www.genome.gov/10005107>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E) (NHGRI)

**Large-Scale Sequencing Program:** NIH’s Large-scale Sequencing Program funds three major research centers in the United States to conduct genetic sequencing. During and since the completion of the Human Genome Project, NIH-funded centers have used their industrial-scale enterprises to improve DNA sequencing methods, thereby substantially decreasing costs and increasing capacity. For many years, the Program has achieved twofold decreases in cost approximately every 20 months. One of the main projects now under way is the sequencing of the genomes of other primates, such as orangutan, baboon, gibbon, and marmoset (in addition to chimpanzee and macaque, which are complete). By comparing the human genome to that of other primates, researchers can find important information about both health and abilities that are

uniquely human and those shared with other species. The Program also supports the genomic sequencing of human pathogens (organisms that cause disease in humans) and their vectors, the organisms that carry those pathogens. For other relevant NIH programs, see previous section, Microbial Genomics. Also, many mammals are being sequenced to identify elements that are functionally important to human biology. These studies will undoubtedly unveil new biological insights to increase our understanding of how the human genome works.

- [Rhesus Macaque Genome Sequencing and Analysis Consortium, et al. \*Science\*. 2007;316:222-34, PMID: 17431167](#)
- For more information, see <http://www.genome.gov/10001691>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E) (NHGRI)

**Nanomedicine Development Centers (NDC):** The structures inside living cells operate at the nanoscale (about 1/10,000 the thickness of human hair). Recent advances in nanotechnology, which refers to the understanding and control of materials at the nanoscale, have yielded new tools to probe and manipulate objects at the nanoscale. These tools, as well as a variety of newly engineered nanostructures, are starting to be used in biomedical research. Nanomedicine, an offshoot of nanotechnology, is a rapidly emerging, multidisciplinary field that was identified as one of the nine initial NIH Roadmap initiatives. In late 2006, NIH completed the establishment of a national network of eight NDCs after an intensive 2-year planning and application process that involved extramural stakeholders from scientifically and medically diverse fields. The overarching goal of these centers is to understand and control the nanomachinery inside living cells in order to diagnose or treat disease and repair tissue. The work at these centers, which involve over 120 biomedical researchers located in 30 institutions, 12 States, and 6 countries, is geared toward understanding the fundamental properties of intracellular structures with great precision so that highly specific treatment or possibly even replacement of these structures can be achieved with few or no side effects. Unlike traditional, translational research targeting a specific medical problem, these centers are beginning with basic science studies and, over a 10-year period, will apply their tools, technologies, and newly developed structures to a variety of disease or wound conditions that will be identified in parallel with, and as a consequence of, the technological developments. It is expected that this novel approach will stimulate the emergence of nanomedicine as a major contributor to improving human health in a variety of medical specialties.

- For more information, see <http://nihroadmap.nih.gov/nanomedicine/index.asp>
- This example also appears in Chapter 3: *Technology Development*.
- (E) (Roadmap—all ICs participate)

**Developmental Epigenetics:** This rapidly evolving area of research examines how nonstructural changes in gene expression during normal developmental processes can influence health outcomes across the generations. NIH is expanding its research in this area to help scientists learn how typical epigenetic changes and variations occur at the molecular level, starting well before birth. Understanding these epigenetic changes—how they are inherited and passed onto subsequent generations and what factors influence them—could hold the scientific key to

understanding and modifying certain factors that lead to a number of diseases or conditions, from obesity to heart disease.

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (I) (NICHD)

**Researchers Report Chemical Rescue of Cleft Palate in Mice:** A growing understanding of the multiple roles played by the enzyme GSK3 has enabled scientists to realize that this protein molecule has a role in determining the developmental fates of certain undifferentiated cells in the embryo. A few years ago, this realization led a team of scientists to develop a technique that prompts small molecules directly to turn GSK3 on and/or off with a high degree of precision at different stages of fetal development. In the March 1 issue of the journal *Nature*, NIH-supported scientists and their colleagues reported using this on-off technique to determine, in mice, the critical developmental period of the palate, or roof of the mouth. Remarkably, the researchers showed that by turning GSK3 back on in pregnant mice during this key developmental window, their embryos in most cases corrected their developing cleft palates. As they reported, five of nine mouse pups had complete reversal of the developing cleft, while another newborn had a partial rescue of the cleft. As the authors noted: “New approaches to rescuing selected developmental defects require detailed knowledge of timing and levels of protein expression; our studies provide an improved method for defining these experimental conditions in vivo.”

- [Liu KJ, et al. \*Nature\* 2007;446:79-82](#), PMID: 17293880
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDCR)

**Study on Forefronts of Science at the Interface of Physical and Life Sciences:** In FY 2006, NIH cofunded a study by the National Academies to identify research Frontiers of Science at the Interface of Physical and Life Sciences. This study, to be completed in 2008, will identify and prioritize well-defined, large-scale, complex problems or grand challenges at the interface of the life and physical sciences and engineering that will drive research and nucleate the broad scientific community. It will also examine appropriate mechanisms for long-term high-risk research as well as approaches to catalyze greater cross-disciplinary collaborations. This study builds upon prior studies and conferences in this area led by Federal agencies and other National Academies efforts.

- (E) (NIBIB, NIGMS)

**How We Detect Taste at the Molecular Level:** Taste is critical for discriminating between nutritious and spoiled foods. Taste disorders can lead to reduced appetite and poor nutrition. Scientists are trying to increase their understanding by identifying proteins that we produce to help detect taste. Taste cells are clustered in taste buds on the tongue and palate. NIH-supported scientists have identified a new protein, PKD1L3, found specifically in taste cells. The PKD1L3 protein forms a channel that allows tastants, such as sodium ions or protons, to enter through taste cell membranes so that tastes can be detected. Another group of NIH-supported scientists determined that the protein is located in taste pores and is activated by acids (sour) but not other tastants. A third group of NIH-supported scientists reports that mice lacking PKD2L1-expressing cells cannot detect sour tastants but can detect all others. Together, these three reports suggest



that PKD1L3 channels detect sour tastants in food. Scientists can now explain how humans detect the flavors sweet, sour, bitter, and umami, or savory, at the cellular level. This advance in understanding taste may help scientists treat taste impairments, and could also lead to the development of better salt and sugar substitutes for the millions of Americans on restricted diets to control high blood pressure, diabetes, and obesity.

- [LopezJimenez ND, et al. \*J Neurochem.\* 2006;98:68-77](#), PMID: 16805797
- [Ishimaru Y, et al. \*Proc Natl Acad Sci U S A.\* 2006;103:12569-74](#), PMID: 16891422
- [Huang AL, et al. \*Nature.\* 2006;442:934-8](#), PMID: 16929298
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E/I) (NIDCD)

### **Anti-inflammation/Resolution Regulator May Be Involved in a Wide Range of Human**

**Diseases:** Resolvin E1 (RvE1) is a new family of bioactive products of omega-3 fatty acid. Using periodontitis as a model disease, a team of NIH-funded researchers recently reported that RvE1 can dramatically alter the progression of microbe-initiated local inflammatory disease. RvE1 therapy demonstrates greater efficacy without the side effects of chronic antibiotic usage. The results of their study provide new directions for treatment of localized aggressive periodontitis and other inflammation-related bone disorders. In many chronic disorders similar to periodontitis, prolonged and unresolved inflammation contributes to pathogenesis. It is now clear that several endogenous biochemical pathways activated in the host during defense reactions can counterregulate inflammation. This study provides evidence for the role of RvE1 as an endogenous anti-inflammation/resolution regulator that may be involved in the pathogenesis of a wide range of human diseases.

- [Hasturk H, et al. \*FASEB J\* 2006;20:401-3](#), PMID: 16373400
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E) (NIDCR)

**Discovering the Molecular Mechanisms of Pain:** Nociception, the sensory component of pain, depends in part on the intricate network of sensory transmission within our bodies, stretching from our extremities to the spinal cord and onward to the brain. But on its most fundamental level, nociception involves molecules and chemical mechanisms. NIH scientists have reported progress in understanding precisely how individual molecules in our nerve cells generate, transmit, and sustain sensory signals. They discovered that a much-studied protein called cyclin-dependent kinase 5 (Cdk5) plays a regulatory role in pain signaling between sensory nerves in the spinal cord and nerve ganglia. Their paper offers the first direct evidence of this regulatory role for Cdk5. The authors also reported the first evidence from animal studies of the importance of Cdk5 activity in inflammation. These findings point the way for additional research, suggesting that new analgesic drugs that alter Cdk5 activity one day may be beneficial in treating pain.

- [Pareek TK, Kulkarni AB. \*Cell Cycle\* 2006;5:585-8](#), PMID: 16552189
- [Pareek TK, et al. \*Proc Natl Acad Sci U S A\* 2006;103:791-6](#), PMID: 16407116
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (I) (NIDCR)

**New Molecular Targets to Halt Periodontal Bone Loss:** Around 80 percent of American adults have some form of periodontal disease. Chronic periodontitis erodes supporting structures of the tooth, leading to tooth loss. The risk of periodontal diseases is higher in smokers and individuals with diabetes; 20.8 million Americans suffer from diabetes and related complications, including increased incidence and severity of periodontitis: (1) This higher incidence and severity are associated with increased cell death in bone and tissue-forming cells called osteoblasts and fibroblasts. The loss of these cells results in decreased capacity to repair tissue and bone. NIH-supported investigators published two separate papers describing the mechanisms by which the diabetic state enhances cell death. The papers suggest that diabetes-induced cell death and compromised tissue repair are mediated by the TNF- $\alpha$  pro-apoptotic pathway, with the major effector being caspase-3. Inhibition of TNF- $\alpha$  or caspase-3 activity rescues cell death and restores repair capacity. (2) Discrimination between harmful microbes and commensal species is a critical property of the mucosal immune system, essential for maintaining health. Host immune cells have surface receptors that recognize bacterial species such as those known to be associated with periodontitis. Host immune cells can selectively learn to respond strongly or to tolerate endotoxin produced by recognized bacteria. NIH-supported scientists found that patients with chronic periodontitis overproduce a molecule known as SHIP, which plays an important regulatory role in signaling immune cells to tolerate endotoxin. Implication: data from these studies suggest possible targets for developing new ways to treat or prevent chronic periodontitis.

- [Al-Mashat HA, et al. \*Diabetes\* 2006;55:487-95](#), PMID: 16443785
- [Liu R, et al. \*Am J Pathol\* 2006;168:757-64](#), PMID: 16507891
- [Muthukuru M, Cutler CW. \*Infect Immun\* 2006;74:1431-5](#), PMID: 16428799
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDCR)

**Regulating Tumor Formation:** Cells contain tiny pieces of RNA, DNA's chemical cousin, that were once thought to be no more than cellular junk. It is now clear that these microRNAs are important in regulating the activity of many genes in the cell. Two groups of NIH-funded scientists have found correlations between specific microRNAs and the ability of cells to form tumors. One group found that a specific family of microRNAs seems to help prevent cellular problems that can lead to cancer. The other group of researchers discovered that a particular chromosomal change—one that is found in human tumors—can disrupt the function of a certain microRNA. Specifically, the genetic change prevents the microRNA from keeping tight control over the activity of a tumor-promoting gene. This suggests that the loss of control is probably a critical step in tumor formation. A better understanding of the role that microRNAs play with respect to cancer may lead to new ways to prevent the development or spread of the disease.

- [Mayr C, et al. \*Science\*. 2007;315:1576-9](#), PMID: 17322030
- [He L, et al. \*Nature\*. 2007;447:1130-4](#), PMID: 17554337
- (E) (NIGMS)

**Responding to Damaged DNA:** Many factors can damage DNA, including ultraviolet light, environmental toxins, and cellular mistakes. When they divide, damaged cells can pass their faulty DNA to new cells. If the process continues, damaged DNA can build up inside the body,

potentially causing cancer or other serious problems. To prevent this, the body uses powerful controls that lock down damaged cells, preventing them from dividing until their DNA is repaired. Recently, NIH-supported scientists identified a protein that triggers this lock-down in response to a specific type of DNA damage (double-stranded DNA breaks). These studies provide crucial insights into how cells maintain the accuracy of their genetic material and how they lose this control in cancer cells.

- [Kumagai A, et al. \*Cell\*. 2006;124:943-55](#), PMID: 16530042
- [Yoo HY, et al. \*J Biol Chem\*. 2007;282:17501-6](#), PMID: 17446169
- (E) (NIGMS)

**Understanding How Protein Aggregation Causes Cell Death:** Several neurodegenerative diseases—Huntington’s, Alzheimer’s, and Parkinson’s—are characterized by clumps of misfolded proteins in the brain cells of patients. Normally, the body is very good at repairing or eliminating misfolded proteins, so it is not clear what goes wrong in these diseases. By studying the problem in roundworms, NIH-supported researchers learned that the abnormal protein found in Huntington’s disease effectively jams the repair system. As a result, normal cellular proteins that misfold are not repaired. These misfolded, nonfunctional proteins accumulate, which triggers the aggregation of the disease protein. It is likely that the loss of these normal proteins, rather than the clumping of disease protein, is responsible for the death of brain cells. This research suggests that bolstering cellular repair mechanisms could be a promising therapeutic approach to these diseases.

- [Gidalevitz T, et al. \*Science\*. 2006;311:1471-4](#), PMID: 16469881
- (E) (NIGMS)

**The Molecular Libraries Roadmap Initiative:** The Molecular Libraries Roadmap Initiative, part of the NIH Roadmap, offers public-sector researchers access to high-throughput screening of libraries of small organic compounds that can be used as chemical probes to study the functions of genes, cells, and biological pathways. This powerful technology provides novel approaches to explore the functions of major cellular components in health and disease. The initiative is composed of several major components: The establishment of the Molecular Libraries Screening Centers Network (MLSCN), the Molecular Libraries Small Molecule Repository (MLSMR), a public Cheminformatics database (PubChem), and a series of technology development initiatives. In its second year, investigators within the Screening Center Network published several new screening approaches, including several that allow the chemical dissection of inflammatory pathways, one that has successfully identified multiple families of previously unknown signaling proteins, one that examines changes in cellular phenotype associated with disease using automated microscopy, and one that allows a range of compound doses to be screened at once. Each of these is expected to facilitate identification of compounds to probe biological activities and disease processes and identify leads for drug discovery. By December 2007, the 10 centers in the Molecular Libraries Screening Centers Network have entered screening data from more than 400 assays in the PubChem database at the National Library of Medicine.

- [Rosen H, et al. \*Trends Immunol\*. 2007;28:102-7](#), PMID: 17276731
- [Inglese J, et al. \*Nat Chem Biol\*. 2007;3:466-79](#), PMID: 17637779

- [Zheng W, et al. \*Proc Natl Acad Sci U S A\*. 2007;104:13192-7, PMID: 17670938](#)
- [Bologa CG, et al. \*Nat Chem Biol\*. 2006;2:207-12, PMID: 16520733](#)
- [Edwards BS, et al. \*Nat Protoc\*. 2006;1:59-66, PMID: 17406212](#)
- [Ramesh C, et al. \*J Am Chem Soc\*. 2006;128:14476-7, PMID: 17090028](#)
- For more information, see <http://nihroadmap.nih.gov/molecularlibraries/>
- For more information, see <http://mli.nih.gov/mlscn/>
- (E) (Roadmap—all ICs participate)

## Basic Research at the Cellular and Systems Levels

**Innovative Technologies for Engineering Small Blood Vessels:** NIH has initiated a program of basic research studies to enlighten future development of replacements for damaged or diseased small blood vessels. Thousands of patients each year could benefit from small blood vessel substitutes (e.g., to bypass coronary artery or peripheral vascular occlusions or to establish arteriovenous shunts for hemodialysis), but currently available replacement grafts have a high failure rate. Recent advances in materials science, bioengineering, and tissue engineering, as well as the availability of better computational tools, are providing opportunities for the development of replacement blood vessels with properties that closely match those of natural blood vessels.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Technology Development*.
- (E) (NHLBI)

**The Immune Tolerance Network:** In 2007, NIH renewed support for the Immune Tolerance Network (ITN), a consortium of over 80 investigators in the United States, Canada, Europe, and Australia. The ITN studies and tests new drugs and therapies for autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based on stimulating immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to “reeducate” the immune system to eliminate harmful immune responses and graft rejection while preserving protective immunity against infectious agents. The ITN has established state-of-the-art core laboratory facilities to study the underlying mechanisms of candidate therapies and to monitor tolerance. In 2006, the ITN reported that a novel DNA-based ragweed allergy therapy could achieve long-lasting symptom reduction after only 6 weeks of therapy, compared to current methods that require years of biweekly injections. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse progression of autoimmune diseases; approaches to treat and prevent asthma and allergic disorders such as food allergy; and therapies to prevent liver and kidney transplant rejection without causing harmful suppression of immunity.

- For more information, see <http://www.immunetolerance.org/>
- For more information, see <http://content.nejm.org/cgi/content/abstract/355/14/1445>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIAID)

**Craniofacial Birth Defects or Syndromes:** Craniofacial defects are among the most common of all birth defects. Birth defects and developmental disorders can be isolated or may be part of complex hereditary diseases or syndromes. Cleft lip and cleft palate are among the more

common birth defects in the United States, occurring in about 1 to 2 of 1,000 births. Numerous other disorders with oral and craniofacial manifestations such as ectodermal dysplasias, Treacher Collins syndrome, and Apert's syndrome, while considerably more rare than cleft lip/cleft palate, also have serious lifetime functional, esthetic, and social consequences. These disorders are often devastating to parents and children alike. Surgery, dental care, psychological counseling, and rehabilitation may help ameliorate the problems, but often at a great cost and over many years. In fact, the lifetime cost of treating the children born each year with cleft lip or cleft palate is estimated to be \$697 million. NIH is actively pursuing knowledge to prevent future defects as well as treat those currently affected. Exciting advances in genetic studies are shedding light on genes that are important in forming the head and face, how these genes function and how they interact with environmental, nutritional, and behavioral factors. Such information may ultimately provide the information necessary for prenatal diagnosis, the development of methods to prevent craniofacial birth defects, and the basis for developing better treatments. The development of biocompatible naturally derived materials and biodegradable scaffolds offer new hope for the treatment of defects resulting from craniofacial birth defects or syndromes.

- For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/00038946.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E/I) (NIDCR, NIEHS)

**Engineering Stem Cells to Repair or Replace Damaged Tissues:** Guiding a person's own stem cells to repair or replace damaged tissues with healthy tissue is the goal of multiple NIH-supported tissue engineering projects. For example, one team previously reported success creating three-dimensional mandibular (jaw) joints using rodent tissue; their continuing work on the project addresses pragmatic questions that must be answered in order to create functional human joints. Other teams are working on regeneration of the temporomandibular disk, which acts as a "cushion" between the bony components of the jaw joint and on the tissue engineering of skeletal muscle. Tissue engineering holds great promise for regeneration or replacement of dental, oral, and craniofacial structures lost due to trauma, disease, or congenital anomalies. The progress seen in this area will also inform tissue engineering solutions for degeneration in other articular surfaces such as knee, hip, and shoulder joints.

- [Mao JJ, et al. \*J Dent Res\*. 2006; 85:966-79](#), PMID: 17062735
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDCR)

**GENSAT—Gene Expression Nervous System Atlas:** Knowing where and when genes are active is a key to understanding how the nervous system develops, how the normal brain works, and what goes wrong in disease. More than half of all genes are active at some point in the brain, yet only a small fraction of these have been well characterized. To systematically address this issue, NIH initiated the GENSAT project. The project prescreens the activity of many genes at four developmental timepoints in several parts of the brain and spinal cord and, for genes of high interest, generates strains of mice in which a visible marker is turned on wherever and whenever the gene of interest is active. In addition to the value of the publicly accessible GENSAT database, the mice are useful for research on normal development and function and diseases. For example, researchers used GENSAT mice to discover that one of two previously



indistinguishable types of nerve cells is selectively vulnerable in Parkinson's disease. By revealing the molecular mechanism that kills the cells, these experiments also identified a new potential drug target. GENSAT is now a resource within the NIH Neuroscience Blueprint and will expand to include nerve cells in the eye, ear, and pain pathways.

- [Day M, et al. \*Nat Neurosci.\* 2006;9:251-9](#), PMID: 16415865
- For more information, see <http://www.gensat.org/index.html>
- For more information, see <http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&db=gensat>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NINDS, NCCAM, NCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

**The Dog Genome and Human Cancer:** Cancer is the number one killer of dogs, and studying the major cancers in dogs provides a remarkably valuable approach for developing a better understanding of the development of cancer in humans. The clinical presentation, histology, and biology of many canine cancers very closely parallel those of human malignancies, so comparative studies of canine and human cancer genetics should be of significant clinical benefit to both. Furthermore, information gained from studying the genetic variant involved in dog size can provide important information for studying cell growth in humans and has the potential to be a useful tool in cancer research. A 2007 article by NIH's Dr. Elaine Ostrander et al. reported a genetic variant that is a major contributor to small size in dogs. In the following month, Dr. Ostrander and colleagues published a study reporting that a mutation in a gene that codes for a muscle protein can increase muscle mass and enhance racing performance in dogs.

- [Sutter NB, et al. \*Science.\* 2007;316:112-5](#), PMID: 17412960
- [Mosher DS, et al. \*PLoS Genet\* 2007;3:e79](#), PMID: 17530926
- For more information, see <http://www.genome.gov/25520294>
- For more information, see <http://www.genome.gov/15515061>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Genomics*.
- (I) (NHGRI)

**Asthma Exacerbations – Biology and Disease Progression:** In FY 2005, NIH began a basic and clinical research initiative to improve understanding of the causes of asthma exacerbations and to facilitate the development of more effective treatments to control symptoms. Twelve projects have been funded under this initiative. As part of NIH GPRA reporting activity, NIH is assessing the progress of the initiative through an ongoing GPRA goal, “to identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating exacerbations, by 2014.”

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-029.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NHLBI, NIAID) (GPRA Goal)

**Interventions Testing Program:** In a recent study, scientists demonstrated in aged obese mice that resveratrol, an activator of a family of enzymes called sirtuins, had better health and survival than untreated aged overweight mice. Future research will assess the safety and effectiveness of resveratrol-related drugs in humans. To further these and other investigations, NIH has undertaken a multi-institutional study to investigate a variety of agents with the potential to



extend lifespan and delay disease and dysfunction in mouse models. This program is the centerpiece for a new NIH GPRA goal to “identify, by 2012, at least one candidate intervention that extends median lifespan in an animal model.”

- For more information, see <http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20061101Resveratrol.htm>
- For more information, see <http://www.nia.nih.gov/ResearchInformation/ScientificResources/InterventionsTestingProgram.htm>
- (E/I) (NIA) (GPRA Goal)

**The Collaborative Study on the Genetics of Alcoholism (COGA):** In its 18th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) who are densely affected by alcoholism. Several genes have been identified including GABRA2, ADH4, ADH5, and CHRM2, which influence the risk for alcoholism and related behaviors such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes influencing vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

- For more information, see <http://zork.wustl.edu/niaaa/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Genomics*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIAAA) (GPRA Goal)

**Systems Biology and Systems Genetics:** NIH launched the Integrative Cancer Biology Program to focus on networks that can be measured, modeled, and manipulated rather than individual components. Multi-disciplinary teams are critical to integrating the disciplines of biology, medicine, engineering, mathematics, and computer science (e.g., computational biology). Equally important to our understanding of cancer is *systems genetic research* (systems biology + genetics). Networks of genes can be found and their associations tested and quantified, with parallel association studies on relevant human populations.

- For more information, visit <http://icbp.nci.nih.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*.
- (E) (NCI)

**Biomedical Technology Research Resources (BTRRs):** The BTRRs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the

Resources and through intensive collaborations with other leading laboratories. The BTRRs are used annually by nearly 5,000 scientists from across the United States and beyond, representing over \$700 million of NIH funding for 22 institutes and centers. As an example, optical technologies enable researchers to:

- ▷ Harness the power of light to “see” biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- ▷ Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.
  - For more information, see [www.ncrr.nih.gov/biomedical\\_technology](http://www.ncrr.nih.gov/biomedical_technology)
  - This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*.
  - (E) (NCRR)

**National Ophthalmic Disease Genotyping Network (eyeGENE™):** More than 400 genes are known to contribute to vision loss. New understanding of disease-related genes is leading to the next generation of vision care. With the remarkable opportunity afforded by gene therapy and other new treatment advances comes the challenge of identifying individuals who could benefit from these treatments. However, DNA testing remains expensive, time-consuming, and not widely available. To address this need, NEI created a partnership of laboratories across the vision research community and established eyeGENE to broaden accessibility of diagnostic genetic testing. These laboratories will facilitate research on genetic causes of eye disease; provide genotyping for patients in a centralized, secure, and certified process; and will provide a research repository of genetic material and diagnostic information. Currently, eyeGENE provides diagnostic testing for over 40 disease genes.

- For more information, see <http://www.nei.nih.gov/resources/eyegene.asp>
- (E/I) (NEI)

**Lymphatic System in Health and Disease:** NIH recently announced two funding opportunities for research to increase understanding about the lymphatic system and its function in health and disease. The lymphatic system plays a critical role in the well-being of many other systems in the body. When it is not working properly, a broad array of diseases and disorders can result, including lymphedema (characterized by accumulation of lymph fluid that often results in swelling of the arms or legs), inflammation and infections, cancer, and metabolic disorders. In July 2007, NIH issued the program announcement (PA) entitled *Lymphatic Biology in Health and Disease* to encourage research on the biology of the lymphatic system and potential new therapeutic approaches. In addition, in December 2006, NIH re-issued the PA entitled *Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases* to stimulate research on

the lymphatic system and lymphatic dysfunction and related diseases, as well as to develop new diagnostic methods and treatment interventions.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-420.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-165.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NHLBI, NCCAM, NCI, NIAMS, NIBIB, NICHD, NIDDK, NINR)

**Understanding the Mechanisms of Alcohol-Induced Tissue Injury:** Virtually every organ system of the body is impacted by heavy alcohol use (the most vulnerable being the brain and liver) and the resulting pathological conditions contribute to increased mortality and morbidity among all age and racial/ethnic groups and genders. NIH is especially interested in elucidating mechanisms of injury common to multiple body and organ systems. A number of PAs and RFAs have been issued to support research to increase our understanding of the underlying cellular and molecular mechanisms of tissue injury caused by alcohol consumption, including alcohol's genetic, epigenetic and metabolic effects. Long-term goals of these initiatives are to identify biomarkers for alcohol exposure and for the early detection of alcohol-induced tissue injury, and to develop new therapeutics that control or modify outcomes of chronic alcohol use.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-065.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-360.html> (R01)
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-361.html> (R21)
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-004.html> (R01)
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-005.html> (R21)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NIAAA)

**Centers of Excellence for Influenza Research and Surveillance:** Six Centers of Excellence for Influenza Research and Surveillance, established in 2007, significantly expand the ability of NIH to conduct research on different strains of animal and human influenza viruses, collected internationally or in the United States. The centers will lay the groundwork for the development of new and improved control measures for emerging and reemerging influenza viruses, help determine the prevalence of avian influenza viruses in animals in close contact with humans, and extend understanding of how influenza viruses evolve, adapt, and are transmitted. The centers will also bolster research on questions such as how influenza viruses cause disease and how the human immune system responds to infection and will inform public health strategies to control and minimize the impact of seasonal and pandemic influenza.

- For more information, see <http://www3.niaid.nih.gov/research/resources/ceirs/>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIAID)

**Developing New Adjuvants to Boost Vaccine Effectiveness:** The NIH Innate Immune Receptors and Adjuvant Discovery initiative encourages the discovery of novel adjuvants to meet the growing need to boost the effectiveness of vaccines against potential agents of bioterrorism and emerging infectious diseases. Adjuvants activate the body's innate immune

system—microbe-engulfing phagocytes and soluble immune stimulators—leading to effective adaptive immune responses by B cells, which produce antibodies, and T cells, which can directly kill infected cells. Using high-throughput screening, several groups of researchers have identified, optimized, and developed adjuvants now in preclinical development.

- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIAID)

**The Cooperative Study Group for Autoimmune Disease Prevention:** In 2006, NIH renewed the Cooperative Study Group for Autoimmune Disease Prevention, which was established in 2001. This collaborative network is devoted to understanding immune homeostasis in both health and autoimmune diseases and to developing interventions to prevent autoimmune disease. The six participating centers support preclinical research, innovative pilot projects, and non-interventional clinical studies, with an emphasis on type 1 diabetes. By the end of 2006, grantees had published 109 original research papers, and 5 of 48 pilot projects had matured into investigator-initiated grants. Of note, the centers are collaborating on the “Roadmap to Inflammation in the NOD (non-obese diabetic) Mouse” project, which will identify and characterize genes and proteins involved in the development of diabetes, and study the mechanisms by which diabetes develops.

- For more information, see [http://fathmanlab.stanford.edu/roadmap\\_study\\_design.html](http://fathmanlab.stanford.edu/roadmap_study_design.html)
- This example also appears in Chapter 2: *Autoimmune Diseases*.
- (E) (NIAID, NIDDK)

**NIH Stem Cell Task Force:** In 2002, NIH established a Stem Cell Task Force to continually monitor the state of this rapidly evolving area of science. The purpose of the Task Force is to enable and accelerate the pace of stem cell research by identifying rate-limiting resources and developing initiatives to overcome these barriers to progress. The Task Force seeks the advice of scientific leaders in stem cell research about moving the stem cell research agenda forward and exploring strategies to address the needs of the scientific community. Over the past 5 years, under the leadership of the Task Force, NIH has supported a wide array of scientific programs designed to foster research on all types of stem cells, including human embryonic stem cells (hESCs), and is actively working to fund research in this blossoming field. For example, the Task Force has stimulated NIH-supported research by initiating Infrastructure grants to scale up and characterize hESCs eligible for Federal funding, developed training courses to teach stem cell culture techniques, established a National Stem Cell Bank to make hESC lines that are eligible for Federal funding readily available, and encouraged new investigator-initiated research through various means. The Task Force is also responsible for implementing Executive Order 13435, which encourages research on the isolation, derivation, production, and testing of stem cells that are capable of producing all or almost all of the cell types of the developing body and may result in improved understanding of or treatments for diseases or other adverse health conditions, but are derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus.

- For more information, see <http://stemcells.nih.gov/policy/taskforce/>
- (E/I) (NIDCD, NINDS, NCI, NCRR, NHLBI, NICHD, NIDCR, NIDDK, NIGMS, OD/OER, OD/OSP, OTT)

**Beta Cell Biology Consortium (BCBC):** The BCBC is collaboratively pursuing key challenges relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development to understand how insulin-producing beta cells are made, exploring the potential of stem cells as a source for making islets, and determining the mechanisms underlying beta cell regeneration. The BCBC has generated key research resources, such as animal models, microarrays, and antibodies, which are available to the scientific community.

- For more information, see <http://www.betacell.org>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK)

**Basic Research on Human Embryonic Stem Cells:** Research on human embryonic stem cells (hESC) promises to illuminate critical events in early human development and, in the future, may revolutionize regenerative medicine. In FY 2003, NIH funded the first of six Exploratory Centers for hESC research involving stem cell lines listed on the Human Embryonic Stem Cell Registry. Meetings at NIH in 2005 and 2007 highlighted the significant progress being made in this area by NIH-funded researchers. In FY 2007, NIH continued its support of research into the fundamental properties of hESC by funding two Program Project grants.

- For more information, see <http://www.nigms.nih.gov/Initiatives/StemCells/>
- (E) (NIGMS)

**National Centers for Systems Biology:** Systems biology is a new research field that integrates approaches from experimental and computational biology. Currently, NIH-funded researchers at seven interdisciplinary centers are developing predictive computer models to study areas such as drug metabolism, host-pathogen interactions, organism development, and cell signaling. These centers are both advancing their research fields and training the next generation of scientists.

- For more information, see <http://www.nigms.nih.gov/Initiatives/SysBio/>
- (E) (NIGMS)

**Influenza Virus Resource:** This database of more than 40,000 influenza virus sequences allows researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic, and vaccine targets. The resource was developed by NCBI using data obtained from NCBI's Influenza Virus Sequence Database and from NIAID's Influenza Genome Sequencing Project, which has contributed sequences of the complete genomes from over 2,500 influenza samples. In FY 2006 more than 11,000 influenza virus sequences were entered into the database, and new search and annotation tools were added to assist researchers in their analyses.

- [Wolf YI, et al. \*Biol Direct\* 2006;1:34](#), PMID: 17067369
- [Chang S, et al. \*Nucleic Acids Res\* 2007;35:D376-80](#), PMID: 17065465
- For more information, see <http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>
- For more information, see <http://www.niaid.nih.gov/dmid/genomes/mcscs/influenza.htm>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Science*, Chapter 3: *Genomics*, and Chapter 2: *Infectious Diseases and Biodefense*.
- (I) (NLM)

**The Biomarkers Consortium:** Launched through the NIH Program on Public-Private Partnerships in October 2006, the Biomarkers Consortium (BC) is a public-private partnership including NIH; the U.S. Food and Drug Administration; the Centers for Medicare & Medicaid Services; the pharmaceutical, biotechnology, diagnostics, and medical device industries; nonprofit organizations and associations; and advocacy groups. The BC is managed by the Foundation for the NIH. The BC will search for and validate new biological markers – biomarkers – in order to accelerate the delivery of successful new technologies, medicines, and therapies for prevention, early detection, diagnosis, and treatment of disease. Biomarkers are objective measures of risk, disease status, and/or health outcomes and include, for example, cholesterol and blood pressure as well known biomarkers of cardiovascular health. The BC structure will accommodate a number of discrete projects, each devoted to biomarker discovery, qualification, or use in targeted areas of disease-related biomedical and clinical science, with the ultimate aim to improve the public health. Projects will be proposed by members of the BC, academics, patient advocates, and the public, and will be developed and implemented according to their scientific merit, public health need and opportunity, and availability of support and funding.

- For more information, see <http://www.biomarkersconsortium.org>
- (E) (OD)

**Animal Model for Corneal Diseases:** NIH scientists have developed a genetically engineered mouse model for studying a number of eye diseases. In this mouse, the *Klf4* gene was deleted in the cornea, the conjunctiva, the eyelids, or the lens, to study the role of this gene in normal development and maintenance of the ocular surface. Deletion of the *Klf4* gene resulted in a reduced number of epithelial cell layers, irregular, defective cells and an absence of certain cell types. These mouse models will be used to study eye diseases and disorders that affect the surface of the eye, including dry eye, Meesmann's dystrophy, and Stevens-Johnson syndrome.

- [Swamynathan SK, et al. \*Mol Cell Biol\* 2007;27:182-94](#), PMID: 17060454
- (I) (NEI)

**Dietary Control of Angiogenesis in the Eye:** The growth of new blood vessels, angiogenesis, can be a double-edged sword: while necessary for the normal development of tissues, uncontrolled angiogenesis can cause blindness in retinopathy of prematurity or diabetic retinopathy, or promote tumor growth in cancer. NIH-supported research in animal models showed that increased dietary intake of omega-3 polyunsaturated fatty acids reduces harmful angiogenesis in the retina. These findings suggest diet may provide a cost-effective method to prevent or ameliorate retinal vascular diseases.

- [Connor KM, et al. \*Nat Med.\* 2007;13:868-73](#), PMID: 17589522
- (E) (NEI)

**Losartan Offers Promise for the Treatment of Marfan Syndrome:** New research offers hope that losartan, a drug commonly prescribed to treat hypertension, might also be used to treat Marfan syndrome, a genetic disorder that often causes life-threatening aortic aneurysms. After discovering that Marfan syndrome is associated with a mutation in the gene encoding fibrillin-1, researchers tried for many years, without success, to develop treatment strategies that involved



repair or replacement of fibrillin-1. A major breakthrough occurred when NIH-funded researchers discovered that one of the functions of fibrillin-1 is to bind to another protein, TGF-beta, and regulate its effects. After careful analyses revealed aberrant TGF-beta activity in patients with Marfan syndrome, researchers began to concentrate on treating the disease by normalizing the activity of TGF-beta. Losartan, which is known to affect TGF-beta activity, was tested in a mouse model of Marfan syndrome. The results showed that the drug blocked the development of aortic aneurysms as well as lung defects associated with the disease. Based on the promising results, the NHLBI Pediatric Heart Network, in partnership with the National Marfan Foundation, began a clinical trial in 2007 to assess losartan therapy in patients with Marfan syndrome.

- [Habashi JP, et al. \*Science\*. 2006;312:117-21](#), PMID: 16601194
- For more information, see <http://clinicaltrials.gov/show/NCT00429364>
- For more information, see <http://www.pediatricheartnetwork.org/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NHLBI)

**Genes Involved in the Regulation of Sensitivity to Alcohol:** Low doses of alcohol are stimulating in both humans and animals while higher doses have sedating effects. Sensitivity to alcohol, however, varies across individuals and low sensitivity to alcohol is a risk factor for the development of alcohol dependence in humans. Recent animal studies have identified several genes that alter sensitivity to alcohol and may provide targets for medications development.

- ▷ Researchers have discovered a genetic mutation that disrupts the function of the fruit fly gene RhoGAP18B, causing the flies to be much more resistant to alcohol sedation. Other variants of the same gene, each of which has a distinctly different effect on the response to alcohol, were subsequently identified.
  - ▷ Another fruit fly gene, Homer, has been shown to be required for normal sensitivity and tolerance to alcohol. This study shows that ethanol sensitivity and tolerance co-map to the same population of neurons, suggesting that the neuronal circuits controlling these two behaviors, known to contribute to alcohol dependence, are shared.
- [Rothenfluh A, et al. \*Cell\* 2006;127:199-211](#), PMID: 17018286
  - [Urizar NL, et al. \*J Neuroscience\* 2007;27:4541-51](#), PMID: 17460067
  - This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
  - (E) (NIAAA)

**Increased Endocannabinoid Signaling Increases Ethanol Consumption and Decreases Acute Ethanol Intoxication:** Endocannabinoids, the naturally occurring substances in the brain that act on the same receptors as the active ingredients of marijuana, have been discovered to play a role in regulating appetite for alcohol. NIH-supported scientists discovered that mice lacking expression of fatty acid amidohydrolase (FAAH), the main endocannabinoid-degrading enzyme, showed an increased appetite for ethanol, decreased sensitivity to ethanol-induced sedation and faster recovery from ethanol-induced motor incoordination. These results show that impaired FAAH function leads to increased voluntary alcohol intake and point to a FAAH both as a potential susceptibility factor and as a therapeutic target for excessive alcohol consumption.

- [Hansson AC, et al. \*Neuropsychopharmacology\* 2007;32:117-26](#), PMID: 16482090
- [Blednov YA, et al. \*Neuropsychopharmacology\* 2007;32:1570-82](#), PMID: 17164820
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NIAAA)

**Hereditary Hearing Loss:** NIH recognizes that one of the most rapidly developing areas of research is functional genomics, which involves determining the identity, structure, and function of genes. Hereditary or genetic causes account for approximately 50-60 percent of the severe to profound cases of childhood hearing loss. NIH-supported scientists are working to understand the normal function of these genes and how they are altered in individuals with hereditary hearing loss. At present, over 70 genes causing nonsyndromic hereditary hearing impairment have been mapped to intervals on particular chromosomes; many of these efforts were the result of collaborations involving NIH-supported scientists. In collaborative efforts with scientists in Columbia, India, Indonesia, Israel, Lebanon, Mexico, Newfoundland, Pakistan, Tunisia, Puerto Rico, and the United States, NIH is accelerating this gene discovery effort. These research investments to understand the genetic basis of communication disorders will help scientists develop diagnostic tests and better treatments for the millions of Americans with hereditary hearing impairment.

- [Morton CC, Nance WE. \*N Engl J Med.\* 2006;354:2151-64](#), PMID: 16707752
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NIDCD)

**Stuttering:** Stuttering is a communication disorder with notable physical and emotional challenges to the speaker and sometimes to the listener. It is estimated that approximately 3 million Americans stutter. Stuttering affects individuals of all ages but occurs most frequently in young children between the ages of 2 and 6 who are developing speech and language. Boys are three times more likely to stutter than girls. Most children, however, outgrow their stuttering. It is estimated that less than 1 percent of adults stutter. NIH-supported scientists identified a specific location for a gene on chromosome 12 that seems to be an important contributor to stuttering in a series of 40 highly inbred families of Pakistani origin. Determining the underlying molecular causes of stuttering may lead to improved diagnosis and treatment of stuttering.

- [Riaz N, et al. \*Am J Hum Genet.\* 2005;76:647-51](#), PMID: 15714404
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDCD)

**Discovering the Causes of Nonsyndromic Cleft Lip and Cleft Palate:** For nearly 60 years, NIH has supported scientific investigation of causes and interventions for cleft lip and cleft palate, which are among the most common birth defects. In recent years, advances in technology made it possible for scientists to directly sequence genes they suspected of contributing to cleft lip and/or palate. NIH grantees and their associates have used this approach to identify genetic mutations accounting for up to 13 percent of cleft lip and/or palate cases. One of the most recent advances occurred in March 2007, when the scientists reported sequencing the coding regions of 12 members of the fibroblast growth factor (FGF) and FGF receptor gene families and finding seven mutations that may contribute to as much as 5 percent of nonsyndromic cleft lip and/or palate. The group followed up by generating three-dimensional computer models of the FGF

proteins that predicted how the altered amino acids would affect their normal shape and function. In a separate finding, NIH-supported scientists reported that women who carry a fetus whose DNA lacks both copies of a gene involved in detoxifying cigarette smoke substantially increase their baby's chances of being born with a cleft lip and/or palate if they smoke. About a quarter of babies of European ancestry and up to 60 percent of those of Asian ancestry lack both copies of the gene called GSTT1. The scientists calculated that if a pregnant woman smokes 15 cigarettes or more per day, the chances of her GSTT1-lacking fetus developing a cleft increase nearly twentyfold. Globally, about 12 million women each year smoke through their pregnancies. This finding provides additional motivation for expectant mothers to follow existing advice not to smoke.

- [Riley BM, et al. \*Proc Natl Acad Sci U S A\* 2007;104:4512-7](#), PMID: 17360555
- [Shi M, et al. \*Am J Hum Genet\* 2006;80:76-90](#), PMID: 17160896
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDCR)

### **Understanding the Causes and Conceiving New Treatments for Craniosynostosis:**

Craniosynostosis arises when one or more of the fibrous sutures between the six cranial bones prematurely fuse and lock sections of the skull tightly into place. Because the brain continues to grow during early childhood, if left untreated, craniosynostosis can distort the shape of the skull and portions of the face as well as cause hearing loss, blindness, and/or mental retardation. To better understand the causes of craniosynostosis, a team of NIH-supported researchers study the fusion of cranial sutures in mice. They suspect the premature fusion involves alterations in the normal biochemical interplay between embryonic tissue called mesenchyme, from which the cranial sutures form, and a thin fibrous layer of tissue called the dura mater that lies beneath it. The scientists also have found that different regions of the dura mater send different developmental signals to the overlying mesenchyme. Defining in fine detail the signals between the mesenchyme and dura mater could provide the intellectual basis for discovering and developing noninvasive biological approaches to control craniosynostosis. NIH-supported researchers have made an important step in this direction. They isolated mesenchymal cells derived from cranial sutures in two different areas of the skull, cultured each group of cells separately, and later analyzed their gene expression patterns. The scientists found clear differences in the patterns of genes expressed among the two populations of mesenchymal cells. To their knowledge, this marks the first glimpse of the genetic programs wired into mesenchymal cells derived from cranial sutures. This line of research potentially opens a new chapter in understanding the causes and conceiving new treatments for cranial synostosis.

- [Xu Y, et al. \*Plast Reconstr Surg\* 2007;119:819-29](#), PMID: 17312483
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDCR)

**Life on Humans:** A large number of microorganisms exist in us and on us, and some are crucial for our survival. Understanding their roles in health and disease is an important goal. Advances in molecular biology have made it possible to obtain a more comprehensive catalogue of the microbes that are present in environments such as the gastrointestinal tract or skin. NIH-supported researchers who examined microbes on the arms of six healthy subjects found that, although some microbes were common to all subjects, there was substantial diversity between

individuals. Furthermore, the population of microbes present on a single individual changed over time, indicating that human skin supports a few “resident” microbes and many “transients.” These studies are advancing the understanding of how environmental factors such as humidity, light exposure, and cosmetic use may affect microbes, and whether changes in these factors affect the susceptibility to or severity of skin diseases.

- [Gao Z, et al. \*Proc Natl Acad Sci U S A\*. 2007;104:2927-32](#), PMID: 17293459
- (E) (NIGMS)

**Understanding Gene Regulation in Stem Cells:** Stem cells are uniquely capable of being maintained indefinitely in an unspecialized state and of growing into specific cell types like muscle, blood, or nerve cells. Scientists hope to coax stem cells into specific cells that can treat diabetes, Parkinson’s disease, spinal cord injuries, or other conditions in which specific cell types are not functioning properly. Recently, NIH-funded researchers discovered the genetic switch that enables embryonic stem cells to develop into recognizable cell types. This discovery addresses a fundamental question about the early development of mammals. It also brings researchers a step closer to the goal of using stem cells to treat a host of diseases.

- [Lee TI, et al. \*Cell\*. 2006;125:301-13](#), PMID: 16630818
- [Boyer LA, et al. \*Nature\*. 2006;441:349-53](#), PMID: 16625203
- (E) (NIGMS)

**Understanding How Prefrontal Cortex Affects Cognitive Function:** In FY 2008, NIH will support an RFA to stimulate research on how a brain region called the prefrontal cortex interacts with other parts of the brain to give rise to sophisticated behavior and cognitive function. Abnormal functioning of the prefrontal cortex is associated with mental disorders such as schizophrenia and depression.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-110.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NIMH)

**Visual Processing in Neuroscience Blueprint:** Much of the cerebral cortex of the brain is devoted to processing the images that flood our eyes. The visual cortex also connects with many regions of the brain that govern memory, language, movement, and a myriad of other cognitive abilities. NIH’s visual processing research portfolio prioritizes understanding of how the brain processes visual information, how brain activity results in visual perception, and how the visual system interacts with other cognitive systems.

- For more information, see <http://www.neuroscienceblueprint.nih.gov>
- For more information, see [www.nei.nih.gov/funding/app.asp#1b](http://www.nei.nih.gov/funding/app.asp#1b)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NEI)

**Link between Eye Movement and Reward:** Dopamine is vital to motor behaviors, but neurons that release dopamine carry signals related to rewards, not body movements. As a solution to this puzzle, recent theories propose that the reward-related dopamine signals are used for learning of motor behaviors. However, it is unknown how dopamine neurons acquire the reward-related

signals. NIH scientists have shown that a small brain area called the lateral habenula controls dopamine neurons by inhibiting them and thereby suppressing less rewarding eye movements. This discovery opens up new research connecting emotion and motivation to motor behaviors.

- [Matsumoto M, Hikosaka O. \*Nature\* 2007;447:1111-5](#), PMID: 17522629
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (NEI)

**Powerful New Technique Reveals How Brain Cells Wire Together:** In order to understand how the brain processes visual information and performs other tasks, researchers have wanted to construct a “wiring diagram” of the billions of neurons connected in precise, identifiable circuits. A breakthrough technology has helped clear this major hurdle by revealing all the connections made by a single nerve cell. The new tool uses a modified rabies virus, which can spread indefinitely through the nervous system by jumping between communicating nerve cells. However, scientists modified the virus so that it jumps once and then leaves a fluorescent tag in the neurons connected to a single cell. This permits visualization of functional processing circuits in living brains. It can also be used in transgenic mice to deactivate targeted classes of neurons expressing specific genes, revealing changes in brain function, including behavior.

- [Wickersham IR, et al. \*Neuron\* 2007;53:639-47](#), PMID: 17329205
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NEI)

## Basic Research in the Behavioral Sciences and in Complementary and Alternative Medicine

**Tools to Reveal the Mechanisms Governing Behavior:** Newly acquired but rapidly evolving tools and techniques that monitor or probe discrete brain systems have allowed NIH-supported researchers to begin filling in the information gap between molecular or cellular events and behavioral outcomes. A notable preclinical example of this trend is the development of a genetically engineered method to turn the electrical impulses of brain cells on and off with pulses of light—in synch with the split-second pace of real-time neuronal activity. The novel technique borrows genes from light-responsive algae and bacteria to unravel the intricate workings of brain circuits with extreme precision. This powerful new tool could be used to assess the role of neuronal activity in regulating normal behavior and disease processes. On the clinical side, an array of brain imaging devices has produced much information on how neural circuits develop and process information under normal conditions, and how they become impaired by a disease like addiction. These advances have led to the fertile concept that the transition from abuse to addiction is not a switch but a gradual degradation of the ability of different circuits to “talk” to each other as they attempt to compensate for their deficiencies. Interestingly, these studies are also showing significant overlap in the circuits involved in drug abuse and the circuits underlying compulsive overeating and obesity. Moreover, in preclinical studies, compounds that interfere with food consumption in animal models of compulsive eating also interfere with drug administration.

- For more information, see <http://www.nimh.nih.gov/press/lightswitchneurons.cfm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*.
- (E) (NIDA, NIMH)



**Centers of Excellence for Research on CAM (CERC), Developmental Centers for Research on CAM (DCRCs), and International Centers for Research on CAM:** These Centers bring cutting-edge scientific technology to programs of research on the usefulness, safety, and mechanisms of action of various CAM interventions. Based in collaborations between established biomedical research scientists and experts in CAM or traditional medicine, these programs are also aimed at enhancing the global state of research capacity on CAM. For example, the CERCs are led by scientists with outstanding research records who direct teams of investigators with both CAM and conventional scientific expertise. During the first 3 years of the CERC program, awardees have made sentinel advances in our understanding of the scientific basis for the effects of acupuncture through the use of modern brain imaging, and they have explored innovative approaches to the treatment of asthma with antioxidants and approaches based on traditional Chinese medicine (TCM). Other CERCs are focusing on (1) the study of acupuncture and TCM herbal treatments of arthritis, (2) the effects of mindfulness meditation on the progression of HIV/AIDS, and (3) the mechanisms of action of millimeter wave therapy (use of low-intensity millimeter wavelength electromagnetic waves) for a variety of chronic conditions. NIH will fund additional CERCs in late FY 2007.

- For more information, see <http://nccam.nih.gov/training/centers/>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**Basic Research on CAM:** In addition to its focus on clinical investigation of complementary and alternative medicine interventions, NIH places a high priority on basic research aimed at filling important gaps in our knowledge about the mechanisms by which they may exert their effects. Recently released initiatives target this area of research. Examples include the following:

- ▷ “Omics and Variable Responses to CAM” utilizes genomic, proteomic, and metabolomic technologies to examine potential causes for variation in individual responses to CAM interventions (PAR-07-377).
- ▷ “Mechanistic Research on CAM Modalities Purported to Enhance Immune Function” examines the scientific basis for a common but generally unsubstantiated claim made on behalf of a number of CAM modalities (RFA-AT-06-004, RFA-AT-06-005).
- ▷ “Research on the Biomechanical, Immunological, Endocrinological, and/or Neurophysiological Mechanisms and Consequences of Manual Therapies” applies state-of-the-art science to investigating the biological basis for CAM interventions, such as spinal manipulation and massage. (PAR-06-312)

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

**Basic Behavior in Animal Models:** This program supports collaboration between behavioral scientists and molecular biologists to study basic mechanisms of behavior using animal models. The program also supports the development and enhancement of animal models to study normal or abnormal human behavior.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-096.html>
- (E) (NIGMS)



**Methodology and Measurement in the Behavioral and Social Sciences:** This program supports basic and applied research to improve the quality and scientific power of data collected in the behavioral and social sciences. Among the FY 2006 and 2007 awards are projects developing improved measures of pain, physical, social, cognitive and neurocognitive functioning, quality of life, coping, and cultural and linguistic competence.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-060.html>
- For more information, see [http://obssr.od.nih.gov/Content/Research/Program\\_Announcements\\_%28PAs%29/Announcements.htm](http://obssr.od.nih.gov/Content/Research/Program_Announcements_%28PAs%29/Announcements.htm)
- (E) (OBSSR, NCCAM, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIEHS, NIMH, NINDS, NINR, ODS)

**Social and Cultural Dimensions of Health:** This program supports research that elucidates social and cultural constructs and processes. This knowledge can be used to clarify the role of social and cultural factors in the etiology and consequences of health and illness, to link basic research to practice for improving prevention, treatment, health services, and dissemination, and to explore ethical issues in social and cultural research related to health. The currently funded projects examine multiple racial, ethnic, and other groups, and are investigating basic research topics such as discrimination, neighborhood design, stigma, socioeconomic status, physician decision-making, religiosity/spirituality, risk communication and sleep as they relate to behaviors, quality of life, palliative care, disparities, and other aspects of health.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-045.html>
- (E) (OBSSR, NCCAM, NCI, NHGRI, NHLBI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIMH, NINR)

**The NIH Toolbox for Assessment of Neurological and Behavioral Function:** The NIH Blueprint for Neuroscience Research supports this contract awarded to the Evanston Northwestern Healthcare Research Institute. The project entails development of a set of standardized neurological and behavioral measures of cognition, emotion, sensation, and motor function. The toolbox will foster uniformity among the basic measures used and allow comparisons or data compilations across multiple studies. This innovative approach to measurement will be responsive to the needs of researchers in a variety of settings, with a particular emphasis on measuring outcomes in clinical trials and functional status in large cohort studies, e.g., epidemiological studies and longitudinal studies.

- For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-AG-06-008.html>
- For more information, see <http://www.enh.org/aboutus/press/article.aspx?id=4358>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (OBSSR, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR)

**Mechanisms of Action of CAM:** Important and potentially promising findings from recently reported research aimed at elucidating the fundamental mechanisms of various complementary and alternative medicine interventions include:

- ▷ Extracts of turmeric (a common component of Ayurvedic traditional Indian medicines and ingredient in Indian cuisine) containing compounds known as curcuminoids prevent experimental rheumatoid arthritis in an animal model.
- ▷ Green tea is widely promoted for a variety of health-related benefits. It contains a group of chemicals called catechins, one of which is known as epigallocatechin gallate (EGCG). Investigators recently reported that an EGCG-enriched extract of green tea significantly improves glucose and lipid metabolism in an animal model of obesity/insulin resistance/metabolic syndrome.
  - [Funk JL, et al., \*J Nat Prod.\* 2006;69:351-5](#), PMID: 16562833
  - [Li RW, et al., \*J Ethnopharmacol.\* 2006;104:24-31](#), PMID: 16202550
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
  - (E) (NCCAM)

**Mind-Body Medicine:** NIH supports a substantial portfolio of multidisciplinary clinical, translational, and basic research on mind-body interventions, such as meditation and Tai Chi Chuan. This effort is based on (1) promising findings from preliminary controlled clinical investigations and (2) laboratory evidence suggesting that these interventions often involve or invoke well-known biological mechanisms known to play key roles in the cause of and recovery from illness, and in the preservation of health and wellness. For example:

- ▷ Investigators recently demonstrated that patients who practiced Tai Chi Chuan, a form of moving meditation based in traditional Chinese medicine, experienced significant augmentation in levels of immunity to the virus that causes shingles following vaccination against the virus. Other investigators have demonstrated that patients with chronic heart failure show improvements in quality of life, exercise ability, and biomarkers of cardiac health when Tai Chi Chuan is added to conventional medical care.
  - [Irwin MR, et al. \*J Am Geriatr Soc.\* 2007;55:511-7](#), PMID: 17397428
  - [Yeh GY, et al. \*Am J Med.\* 2004;117:541-8](#), PMID: 15465501
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
  - (E) (NCCAM)

**Preclinical Efficacy of Ginkgo Biloba in Alzheimer's Disease:** NIH-supported investigators recently published results showing that *Ginkgo biloba*, studied in an animal model of Alzheimer's disease, reduces both the formation of the specific brain abnormalities seen in humans, and the resulting paralysis seen in the animals. These experiments lend additional support to the hypothesis that *Ginkgo biloba* may be useful in slowing the progression of Alzheimer's disease. That hypothesis is being tested in the largest clinical trial to date of *Ginkgo biloba* for the prevention of dementia, supported by NIH.

- [Wu Y, et al. \*J Neurosci.\* 2006;26:13102-13](#), PMID: 17167099
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NCCAM)



## CLINICAL AND TRANSLATIONAL RESEARCH

*Decades ago, population studies established that, while most human papillomavirus (HPV) infections clear up on their own, virtually all cases of cervical cancer were caused by HPV infection. National Cancer Institute (NCI) scientists Douglas Lowy, M.D., and John Schiller, Ph.D., saw this discovery as an opportunity to develop a vaccine to prevent cervical cancer. The NCI researchers used genetic engineering technology to isolate a single HPV protein and create virus-like spheres that were able to trigger an antibody response capable of protecting the body from the targeted types of HPV. After subsequent development and clinical trials, the unprecedented result is two FDA-approved vaccines that block infection by the major cervical cancer causing types of HPV. These vaccines have the potential to save thousands of women's lives annually in the United States and several hundred thousand more each year worldwide.*

### Introduction

Delivering new and effective treatments and disease prevention approaches to improve health depends on a research continuum that translates basic biomedical research findings into clinical practice and health care decision-making as rapidly as possible (Figure 1) (see also the section on *Molecular Biology and Basic Sciences* in Chapter 3). In this report, clinical and translational research are considered together because the two areas overlap, with translational efforts often focusing on overcoming barriers that impede the progress of clinical research.

**Clinical research** encompasses human subjects research (studies that involve direct interaction between investigators and human subjects or use of material of human origin, such as tissues, specimens, and data that retain information that would allow the investigator to readily ascertain the identity of the subject), epidemiologic (see section on *Epidemiological and Longitudinal Studies* in Chapter 3) and behavioral studies, and outcomes and health services research. Examples of clinical research include studies of mechanisms of human disease, clinical trials, and development of new technologies. Excluded from the umbrella of clinical research, however, are investigations that use anonymous specimens or data from human subjects; such studies would likely fall into the categories of basic or translational research.

**Clinical trials**, a subset of clinical research, often are considered the best method of determining whether interventions are safe and effective in people, including assessing the risks of adverse side effects and other complications. They are designed to answer specific research questions about a biomedical or behavioral intervention. For example, treatment trials test experimental drugs or devices, new combinations of drugs, or new approaches to surgery or radiation therapy.

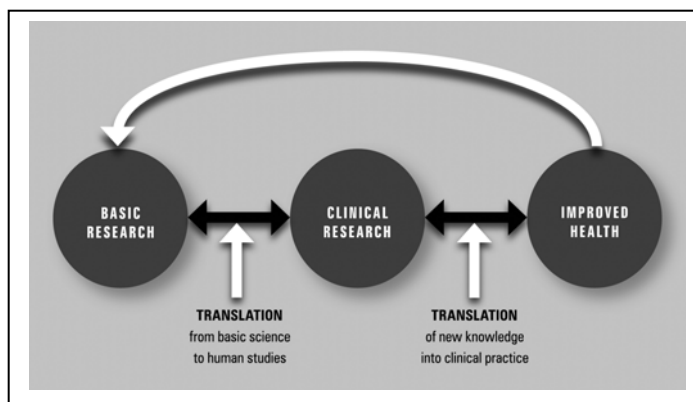


Figure 1. The continuum of biomedical research. Adapted from *JAMA*, March 12, 2003, 289:1278-1287. Copyright © 2003, American Medical Association. All rights reserved.

Prevention trials seek better ways to prevent a disease or to keep a disease from returning. Screening and diagnostic trials are conducted to find better ways to detect or diagnose diseases or health conditions. Finally, quality-of-life trials (or supportive care trials) explore ways to improve comfort and functioning for individuals with chronic illnesses or approaching the end of life.

Although other entities (e.g., pharmaceutical companies, nonprofit organizations) sponsor a sizeable body of clinical and translational research, the Federal Government plays a critical role in focusing on gaps that otherwise would remain unaddressed. NIH supports clinical and translational investigations unlikely to garner significant investment by other sources because of lack of financial incentives, for example, studies that address rare diseases, involve high costs and high risk, or are based on behavioral changes rather than drugs or devices.

NIH's ICs oversee a broad clinical and translational research portfolio that encompasses intramural and extramural programs. Nearly every NIH component supports clinical and translational research in strategic ways related to its mission. A highlight of the intramural program is the [NIH Clinical Center](#), the Nation's largest hospital devoted entirely to clinical research. The Clinical Center logs more than 7,000 inpatient admissions and 100,000 outpatient visits annually. In order to be seen at the Clinical Center, individuals need to meet the eligibility criteria for a research protocol and agree to participate. The NIH extramural program, in addition to supporting both investigator- and NIH-initiated clinical and translational research, fosters collaborations among institutions, industry (e.g., pharmaceutical companies), and local communities; sets up innovative centers of clinical and translational research; underwrites animal and other preclinical studies; and develops new resources and tools for research. Moreover, the NIH extramural program supports important programs to expand capacity for clinical and translational research. A significant dimension of this capacity building is establishing and enhancing clinical research networks. Other vital aspects of this capacity building are training and career development initiatives to ensure that diverse pools of highly trained clinical and translational scientists are available in adequate numbers and in appropriate research areas to carry out the Nation's biomedical and behavioral research agendas (see the section on *Research Training* in Chapter 3). To accelerate and strengthen the clinical research process, a set of NIH Roadmap initiatives and follow-on programs are improving the clinical research enterprise. These include infrastructure for clinical research networks, outcome assessment tools, core services and resources, policy enhancement and harmonization, and a program of [Clinical and Translational Science Awards](#) (CTSAs). Thanks to such programs, a transformation of the clinical research enterprise is under way to speed new discoveries from bench to bedside to community.

**Translational research** drives progress along the research continuum and encompasses two separate stages. The first translational stage involves applying discoveries generated during research in the laboratory to the development of studies in humans. Such preclinical translational investigations often are carried out using animal models, cultures, samples of human or animal cells, or experimental systems. The second translational stage takes results from studies in humans and applies them to research on enhancing the adoption of best practices in the community.

Although sometimes referred to as bench-to-bedside research, translational research really is a two-way street. Basic research scientists provide clinicians with new tools for use with patients, and clinical researchers make new observations about the nature and progression of disease that often stimulate basic investigations. Research on new outreach approaches and the cost-effectiveness and real-world feasibility of prevention and treatment strategies are important aspects of this endeavor, as they provide the feedback necessary to ensure the practicality of interventions.

A special aspect of the scope of NIH activities in translational research is its collaboration with NIH's sister HHS agencies. Most ICs are engaged in such collaborations, which involve almost every other HHS agency. The collaborations include working groups and committees such as the Biomedical Imaging in Oncology Forum, the Joint Working Group on Telehealth, and the Health Literacy Workgroup; a wide range of translational research such as projects on vaccine safety, child abuse and neglect, Diabetes Prevention Program Outcome Study, and Native American Research Centers for Health; database development and management such as the Stem Cell Therapeutics Outcomes Database; and health surveys such as the National Health and Nutrition Examination Survey (NHANES).

### **Summary of NIH Activities**

NIH nurtures strategies for bringing basic research discoveries to human studies, optimizing the conduct of clinical research, facilitating the transfer of new knowledge gained through research into clinical practice, and aligning and reinforcing the entire continuum. The following sections delineate some specific strategies employed by the ICs to drive research along the research continuum and highlight a few examples from NIH's robust portfolio of clinical and translational research.

### **Preclinical Research: Translating Basic Science Discoveries to Human Studies**

Before investigators can conduct human studies, much preliminary (basic and preclinical research) work must be done, and a supportive infrastructure must be in place. NIH equips preclinical translational scientists with research tools, enhances opportunities for collaborative research, and provides resources for developing and testing new drugs before progressing to human studies.

#### ***Research Tools and Resources***

Among the research tools that NIH provides to promote preclinical translational studies are its myriad biosample and data repositories. A central repository allows additional studies on human samples and data collected during clinical studies, enhancing the value of each study and making optimal use of samples and data. It also ensures that samples are stored under uniform conditions and simplifies access to samples by the scientific community. Samples and data are labeled with codes, keeping the study subjects' information confidential. A notable example of such a repository was established through the [\*Genetics of Kidneys in Diabetes\*](#) (GoKinD) study. It facilitates investigator-driven research into the genetic basis of diabetic kidney disease by collecting, storing, and distributing genetic samples from patients with type 1 diabetes and



diabetic nephropathy and from control type 1 diabetes patients without kidney disease. By gathering information and samples of the kind, quality, and quantity that individual researchers would be unable to collect on their own, GoKinD facilitates research on the genetics of diabetic kidney disease. (See also the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3).

Animal models are critical components of translational research. They enable discoveries that are directly related to human health and are used in preclinical research to test therapies and vaccines. [Resource Centers](#) funded by NIH provide investigators with the animals, reagents, and information needed to develop animal models to uncover clues about the effects of specific genes on human health and disease and to gain insights into, for example, basic cellular processes. Additionally, NIH is establishing a new informatics resource to help researchers analyze preclinical research results of diverse studies involving animal models to determine whether a given new scientific discovery merits future development as a potential therapeutic approach (see also the section on *Technology Development* in Chapter 3).

Several preclinical cancer researchers are identifying and developing new biomarkers, which are physical, functional, or biochemical indicators of physiologic or disease processes. Some biomarkers play important roles in disease diagnosis, identifying patient populations that could benefit from particular therapies and monitoring treatment effectiveness. Through such programs as the [Early Detection Research Network](#) and the [Strategic Partnering to Evaluate Cancer Signatures](#) initiative, NIH brings together interdisciplinary teams at dozens of institutions to discover, develop, and test biomarkers and provide advanced analysis and tools that can be used to characterize an individual's disease or tumor so that personalized medical strategies can be developed.

Other translational research at NIH capitalizes on the intricate and interconnected pathways that link and enable communication among genes, molecules, and cells. These molecular pathways work together in a feat of biological teamwork to promote normal development and sustain health. Many NIH-sponsored studies entail research into such pathways to determine how disturbances in them can lead to disease and to develop new therapies targeted at restoring normal function in disease-disrupted pathways. For example, one NIH initiative—[Asthma Exacerbations: Biology and Disease Progression](#)—was designed to improve understanding of what happens in the body at a molecular level to cause asthma flare-ups. The program could help identify and characterize molecular pathways that might provide a rational basis to develop new medications for preventing or treating such episodes.

### ***Collaborative Science***

Oftentimes, translational research can be streamlined or conducted more economically when scientists within NIH, private industry, academia, private practices, or other institutions work in partnership to complement each other's strengths and share costly resources or infrastructure. For this reason, NIH launched its [Centers of Research Translation](#) to unite basic and clinical research in a way that translates basic discoveries into diagnostic approaches and treatments through robust collaborative efforts. The first set of centers focuses on lupus, orthopedic trauma care, scleroderma, and a genetic form of rickets. In addition to these centers, various ICs also

have entered into numerous public-private partnerships. One such public-private partnership is conducting animal studies to test promising compounds for treating fragile X syndrome (FXS), the most common cause of inherited mental impairment. By combining samples and data to increase their collective statistical power, collaborating scientists can conduct studies of rare diseases, such as FXS, more quickly than would be possible if they were working on their own.

### ***Resources for Developing and Testing Investigational Drugs***

NIH helps bridge the gap between drug discovery and clinical testing of promising new agents. Translating promising compounds into drugs for human use is an exacting task that requires very specific, interrelated activities. NIH provides state-of-the-science preclinical drug development resources. Specifically, NIH helps investigators by screening investigational drugs for possible activity against human disease, manufacturing them on a large scale, and clarifying regulatory issues so that FDA requirements are likely to be satisfied when the new investigational drugs are ready for testing in the clinic. One aspect of the [NCI Experimental Therapeutics Program](#) (NExT), for example, safely shortens the timeline for taking anticancer drugs from the laboratory to the clinic by combining NIH's expertise in drug development with that found in excellent research facilities.

Similarly, to move basic research on [Alzheimer's disease into translational research](#) and drug testing in clinical trials, NIH provides drug development and toxicology services to academic and small-business investigators who lack the resources needed to perform the required preclinical studies on promising therapeutic compounds. In addition, an entire menu of preclinical drug development contract resources is available through one of NIH's Roadmap initiatives, the [Rapid Access to Intervention Development \(RAID\)](#) programs. The [Type 1 Diabetes RAID program](#) is designed to facilitate translation to the clinic of novel therapeutic interventions for type 1 diabetes and its complications. Another RAID program is in place for [investigational cancer therapeutics](#).

### **Clinical Research: Learning Which Interventions Work**

Clinical research helps scientists develop and test interventions and new treatments. There are many types of clinical research. For example, some observational clinical research studies involve following a group of patients with a condition and determining their symptoms and responses to treatment in order to try and refine medical practice. Some studies help researchers and clinicians determine whether dosing schedules, behavioral changes, and other elements of a treatment plan are realistic and appropriate. Clinical research sometimes overlaps with the category of epidemiological studies, which is described earlier in this chapter. These research studies can help researchers develop new interventions that can later be evaluated in clinical trials.

Generally, clinical trials, particularly those evaluating drugs or medical devices, are conducted in phases, each of which helps scientists answer different questions. In Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. Phase II trials involve a larger group of people (100-300) to evaluate the safety and effectiveness of the study

drug or treatment. In Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely. Phase IV, or postmarketing, studies are conducted to gather information associated with long-term use in various populations.

The randomized clinical trial has long been considered the gold standard for evaluating the effectiveness of investigational treatments. “Randomization” means that subjects are assigned by chance to either the investigational intervention or the control group. The control group might include interventions such as usual care; best proven care; if known, or no treatment. The specific clinical trial design, including the types and number of intervention and control groups, is dependent upon the medical questions being posed. In addition to the use of control groups, clinical trials often use “blinded” or “masked” study designs, in which subjects are purposely not told whether they are in the intervention or the control group. If feasible, clinical trials are often “double-blinded” or “double-masked” so that the subjects as well as those conducting the study are unable to distinguish between the intervention and control groups.

Participation in clinical trials gives people an opportunity to contribute to the research effort and potentially gain early access to experimental treatments that might prove effective. For some research subjects, participating in a study can provide them with expert medical care at a leading health care facility. To help people access information about clinical trials for which they may be eligible, a Web site (<http://www.clinicaltrials.gov>) offers general information about clinical trials and provides a searchable database of specific studies around the world.<sup>9</sup> Research risks and potential benefits are carefully balanced and the burdens and benefits of participating are shared equally by appropriately including both sexes, people of all races/ethnicities (see Appendix E), and children. Balanced inclusion in trials allows investigators to know whether an intervention works equally well, or not, in all populations. NIH supports outreach efforts to recruit and retain children, women, minorities, and their subpopulations in clinical studies. In addition, NIH holds training events designed to help the research community better understand and be equipped to implement inclusion policy requirements. In 2006, in collaboration with FDA, NIH developed a [Web-based course](#) to create a strong foundation for implementation of the requirements for inclusion of minorities and women. The course addresses the scientific basis of known sex and gender differences and explores the influence of sex and gender differences on health outcomes and illness. Recognizing the importance of developing sound scientific bases for pediatric care while protecting children adequately in research settings, NIH policy requires that children (i.e., individuals younger than age 21) be included in human subjects research conducted or supported by the NIH, unless there are sound scientific and/or ethical reasons for excluding them.

In keeping with ethical mandates, NIH clinical research encompasses the principles of respect for persons, beneficence, and justice. Various NIH initiatives and programs seek to harmonize regulatory aspects governing the conduct of clinical research to ensure that studies are conducted with scientific rigor, with minimal burdens on research subjects and investigators, and with utmost consideration for the safety of subjects. In addition, NIH seeks to bolster participation in clinical trials by providing [clinical trial educational materials](#), such as those targeted to cancer

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<sup>9</sup> As required by the NIH Reform Act of 2006, NIH provides an annual report to the U.S. Food and Drug Administration identifying all trials registered in [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

patients, health care professionals, and the general public to increase awareness of cancer clinical trials.

### ***Fostering Collaborative NIH Clinical Research***

NIH's efforts to bolster activities along the research continuum are enriching the pipeline of biomedical discoveries. To test investigational therapeutic and preventive strategies in the most expeditious way and hasten their entry into the clinic, NIH is supporting a wide variety of collaborations, research centers, and networks to conduct efficient clinical trials.

Collaborations can consist of scientists at several institutions working together, or they may be intradepartmental or interagency government projects. As an example of such collaboration, NIH and the Centers for Medicare & Medicaid Services, which has an interest in developing an evidence base for Medicare coverage decisions, launched the largest ever randomized clinical trial of the effectiveness and safety of [long-term home oxygen therapy](#) for patients with chronic obstructive pulmonary disease.

NIH funnels the majority of its clinical trials funding to its extramural partners, which operate at the regional, State, and local levels. Many studies are conducted not just at one institution, but at many. Such multisite clinical trials help investigators quickly recruit enough subjects for studies; give the public the widest possible access to clinical studies; and address the special health concerns of high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. This approach was used in several practical clinical trials, the primary and secondary phases of which were recently completed. These studies examined treatment effectiveness for such mental disorders as [schizophrenia](#), [bipolar disorder](#), and [depression](#), involving more than 10,000 subjects at more than 200 sites. The infrastructure developed for each of these trials forged collaborative relationships among scientists and clinicians around the country. The platform developed for the trials will serve as a critical foundation for supporting subject enrollment, facilitating communication among trial sites, maintaining up-to-date training in diagnosis and treatment, and providing needed administrative organization for future studies.

Large studies conducted at multiple sites often are best conducted through networks of investigators who are equipped with tools to facilitate collaboration and information sharing. NIH supports many clinical research networks by funding ongoing infrastructure that provides means of standardizing data reporting to enable seamless data- and sample-sharing across studies. Through NIH-funded informatics and other technologies, researchers are better able to broaden the scope of their research and avoid duplicating research efforts, thereby freeing time and funds to address additional research questions. Among the numerous networks established by NIH that have generated significant findings are the [Maternal and Fetal Medicine Units Network](#), [Neonatal Research Network](#), [Obstetric Pharmacology Research Network](#), [Collaborative Pediatric Critical Care Research Network](#), [Pelvic Floor Disorders Network](#), [Traumatic Brain Injury Clinical Trials Network](#), and [Global Network for Women's and Children's Health Research](#). Additionally, the [Community Cancer Centers Program](#), a 3-year pilot program to improve delivery of cancer care, builds upon the exemplary and long-lived Community Clinical Oncology Program, a network established in 1983 for conducting cancer

prevention and treatment clinical trials. It has enrolled more than 200,000 people in treatment and prevention trials.

The [Diabetic Retinopathy Clinical Research Network](#) is a collaborative, nationwide public-private network of eye doctors and investigators at 165 clinical sites conducting clinical research on diabetes-induced retinal disorders with the aim of evaluating promising new therapies. This model network provides the infrastructure to facilitate clinical trials of innovative therapies, rapidly develop and initiate new protocols, and interact with industry partners while ensuring scientific rigor and high ethical standards.

### ***Addressing Gaps in Research***

In terms of clinical evaluation of drugs, there is no clear line where NIH work stops and the pharmaceutical industry picks up. Every drug candidate presents its own profile of financial risk and benefit and potential for gains in public health. NIH's aim is to be sure that all important leads are followed until they are mature enough to attract private-sector interest or until they reach a dead end. About half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed by NIH. Cisplatin for treating testicular, ovarian, and lung cancer, and paclitaxel (Taxol) and fludarabine phosphate for treating several cancers and lymphoma, respectively, are examples where NIH involvement in early-stage drug development resulted in products that eventually were licensed to commercial organizations and reached the market. Recently, large-scale clinical trials of compounds that may prevent substance-abuse relapse demonstrated that the compounds were effective according to scientifically valid criteria accepted by FDA. If their efficacy is confirmed in NIH-sponsored trials, these drugs will be the first generation of medications for treating stimulant dependence. In addition, NIH involvement has been central in developing effective interventions for diagnosis, management, or monitoring of HIV/AIDS, tuberculosis, arthritis, malaria, and many other conditions.

Because behavioral interventions generally do not involve marketable products or services, NIH has a special role to play in research on how changes in behavior can improve health. For example, the objective of [Look AHEAD](#) (Action for Health in Diabetes) is to examine cardiovascular outcomes in people with type 2 diabetes using the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. This multicenter, randomized clinical trial involves several ICs as well as the Centers for Disease Control and Prevention. A second example is the landmark NIH [Diabetes Prevention Program](#) clinical trial, which showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk for the disease. Researchers in a follow-on study found that study subjects benefited from healthy lifestyle changes regardless of their genetic disposition for developing the disease.

As noted earlier, government-funded research is particularly vital for the study of rare diseases. Not only do affected individuals benefit from new treatments that industry does not have the incentive to bring to market, but insights gained from such research often provide knowledge relevant to understanding more common diseases. For these reasons, NIH-funded investigators are studying an inherited retinal degenerative disease called Leber's congenital amaurosis



(LCA), which causes severe vision loss in infancy or early childhood. Translational studies showed that vision could be restored in dogs with LCA using gene therapy to replace defective copies of the retinal gene *RPE65*. Phase I clinical trials of this type of gene therapy are now under way to determine whether this approach can help people with the condition.

## **Putting Clinical Research Results into Practice**

Throughout this report are descriptions of important studies that are changing the way health care is practiced in this country, improving public health and enhancing well-being. To fully realize the potential of new interventions, research results must be disseminated and put into widespread use. NIH investigates strategies for adoption of new evidence at the community level, trains health care providers in best practices, carries out effectiveness research (head-to-head trials of known interventions), disseminates information to providers and the public based on the latest research findings, and sponsors research to learn about the most effective ways to disseminate such findings.

### ***Changing Clinical Practice***

It is not enough merely to have the infrastructure needed to address the ambitious goal of implementing science-based interventions and practices into community settings. In partnership with the Substance Abuse and Mental Health Services Administration and with researchers, clinicians, practitioners, and State alcohol and drug abuse directors, NIH is sharing strategies for incorporating research-based treatment findings into community settings. To accelerate the translation of research into practice in the case of addiction research, NIH embarked on the landmark [Blending Initiative](#). This initiative takes what we know from science, identifies needed products, and disseminates them to providers of drug abuse and addiction treatment programs. The Blending Initiative also includes training components for addiction treatment practitioners.

The largest dataset ever assembled containing information about people with bipolar disorder has produced results with important implications for the way the condition is treated. NIH has taken important steps to ensure that findings from the [Systematic Treatment Enhancement Program for Bipolar Disorder](#) (STEP-BD) are translated into clinical practice. For the study, 4,360 individuals with bipolar disorder received best-practice treatments and were monitored throughout their participation in the study. As a critical translational step, participating doctors received expert training and became STEP-BD-certified in the best treatments for bipolar disorder. Among the consequential outcomes of the research was the finding that patients taking medications to treat bipolar disorder are more likely to get well faster and stay well if they also receive intensive psychotherapy.

NIH studies have transformed the management of antiretroviral therapy (ART) by directly comparing therapy regimens and determining which best extends survival of adults and children with HIV/AIDS. Results from the [SMART study](#), one of the largest HIV/AIDS treatment trials ever conducted, showed that continuous ART is better than periodic therapy for treatment-experienced patients. Deliberately interrupting ART more than doubles the risk of developing AIDS or dying from any cause. The results of these studies stimulated immediate and significant changes in HIV treatment.



### ***Disseminating Research Findings***

NIH is taking the lead in identifying the best ways to inform the public and health care practitioners about research results with the potential to improve the Nation's health (see the section on *Health Communications* in Chapter 3). For example, several large studies of type 1 and 2 diabetes established the importance of patients carefully maintaining blood-sugar control as a way to dramatically reduce the devastating complications of diabetes. Unfortunately, the therapies proven to delay or prevent complications in these studies are not widely incorporated into health care practice. Therefore, NIH is supporting projects exploring ways to disseminate knowledge from successful clinical research into medical practice and community settings. Many of these studies focus on minority populations disproportionately burdened by [type 2 diabetes and obesity](#).

NIH continues to support research designed to strengthen the dissemination and implementation of evidence-based medicine. One example of many such initiatives is improving mental health practices by encouraging transdisciplinary teams to identify and overcome barriers to the adoption of evidence-based interventions. For example, a [recent study](#) reported that providing a minimal level of enhanced care for employees' depression would result in significant savings to employers.

NIH also promotes the fruits of its research by cataloging and disseminating data. For example, NIH leads the [National Toxicology Program](#), an interagency initiative that produces the biennial *Report on Carcinogens*. Under this program, NIH staff members organize and publish data gleaned from numerous sources on some of the more than 80,000 chemicals registered for use in the United States. The 11th edition of the report identifies and discusses agents, mixtures, or exposure circumstances that could pose a health hazard because of carcinogenicity. It includes data on the carcinogenicity, genotoxicity, and biologic mechanisms of the listed substances in humans and/or animals; the potential for human exposure to these substances; and Federal regulations to limit exposures.

In its quest to help clinicians and patients make appropriate decisions about health care, NIH periodically convenes expert panels that review the cumulative research and publish clinical practice guidelines that describe a range of generally accepted approaches for the diagnosis, management, or prevention of specific diseases or conditions. The guidelines, which address such topics as asthma, cholesterol management, overweight and obesity, and HIV management, provide recommendations that patients and their doctors can use to develop individual treatment plans tailored to the specific needs and circumstances of the patient.

Located in the NIH Office of the Director, the [Office of Medical Applications of Research](#) (OMAR) works closely with ICs to assess, translate, and disseminate the results of biomedical research that can be used in the delivery of health services. OMAR coordinates periodic consensus conferences with the goal of reviewing areas of NIH-supported research where there may be a gap between research accomplishments and clinical care. The consensus statements that result from these conferences are shared widely with health care providers, policymakers, patients, and the media. Recent statements have addressed such topics as tobacco use, management of chronic insomnia, and multivitamin/mineral supplements.

## **Bolstering the Research Continuum**

NIH is committed to reengineering the clinical research enterprise, a key objective of the NIH [Roadmap for Medical Research](#). Three critical components of the Roadmap are capacity building, developing a multidisciplinary scientific workforce dedicated to a new discipline of clinical and translational research to implement the Nation's research agenda, and harmonizing, streamlining, and optimizing policies and requirements concerning the conduct and oversight of clinical research.

### ***Building Capacity for Clinical and Translational Research***

NIH supports capacity building for clinical and translational research. Drawing on the momentum of the NIH Roadmap and extensive community input, the [Clinical and Translational Science Award](#) program is creating academic homes for the discipline of clinical and translational science at institutions across the country. Beginning with 12 academic health centers located throughout the Nation, the [consortium](#) will eventually link about 60 institutions. The program encourages the development of novel methods and approaches to clinical and translational research, enhances informatics and technology resources, and improves training and mentoring to ensure that new investigators can navigate the increasingly complex research system. The consortium of research institutions is radically changing how clinical and translational research is conducted and ultimately will enable researchers to provide new treatments more quickly to patients.

Researchers are increasingly conducting studies in community clinics, doctors' offices, and other health care facilities as innovative means of building capacity across the Nation and ensuring that diverse populations are involved in research. For example, NIH fosters scientifically rigorous research in oral health care in [three networks](#) of private dental practices to address the longstanding lack of high-quality research data to guide treatment decisions in the dentist's office. Each network is a grassroots effort, involving 100 or more community dentists and hygienists undertaking short-term clinical studies to compare the benefits of different dental procedures, dental materials, and prevention strategies.

Also, NIH is committed to expanding research capacity in the area of complementary and alternative medicine (CAM). By establishing various [Centers of Research](#), both in the United States and abroad, based on collaborations between established biomedical research scientists and experts in CAM or traditional medicine, NIH has made significant advances in our understanding of the scientific basis for the effects of several CAM treatment approaches.

### ***Developing the Research Teams of the Future***

NIH is anticipating and preparing to meet the need for a multidisciplinary, well-trained cadre of researchers at every point in the research continuum through its career development initiatives (see section on Research Training in Chapter 3). For example, a key component of the CTSA program is the creation of one or more graduate degree-granting and postgraduate programs in clinical and translational science, which will provide an enriched environment for educating and retaining the next generation of clinical and translational researchers.

A **Research Centers in Minority Institutions Translational Research Network (RCMInet)** will be a cooperative research network that will facilitate clinical research in health disparity areas. This Network will consist of a consortium of clinical investigators from the RCMI, RCMI Clinical Research Infrastructure Initiative (RCRII), and [Clinical Research Education and Career Development \(CRECD\)](#) programs; other NIH-supported Clinical Research Centers; relevant organizations, including community health centers, with an interest in health disparity areas; and a Data and Technology Coordinating Center (DTCC).

To respond to the identified need for more veterinarians in the field of biomedical research, NIH funds [career development programs for veterinarians](#) and veterinary studies, which are an important link between the use of animal models and their application to problems involving human health and disease.

## **Optimizing Policy**

The NIH [Clinical Research Policy Analysis and Coordination \(CRpac\)](#) program serves as a focal point for the ongoing harmonization, streamlining, and optimization of policies and requirements concerning the conduct and oversight of clinical research. It is widely recognized that the efficiency and effectiveness of the clinical research enterprise is hampered by variability in regulations and policies that pertain to the conduct and oversight of clinical research. The CRpac program reflects NIH's sense of responsibility, as the lead Federal agency supporting clinical research, to promote the efficiency and effectiveness of the clinical research enterprise by facilitating compliance and oversight. Its objective is to develop and implement coordinated policies and practices reflective of the needs and points of view of NIH's varied stakeholders. The CRpac program works on an array of issues and activities usually in close collaboration with other Federal agencies and offices that have responsibilities concerning the oversight of clinical research. CRpac's current focus includes issues related to Federal adverse event reporting requirements; clinical research review and oversight mechanisms; clinical trial monitoring; Federal regulations and policies governing research with human specimens and data; informed consent; and clinical trial design.

## **Conclusions**

NIH's expanded commitment to optimizing the continuum spanning basic, translational, and clinical research by applying a new multidisciplinary approach to clinical and translational science marks a real turning point. Scientists will have more freedom to engage in productive collaborations with experts in different fields and follow creative approaches that will better serve human health as new treatments and prevention strategies are developed, tested, and brought more rapidly into practice. The results of NIH's commitment to clinical and translational science are apparent in the following section, which highlights a few of the myriad accomplishments and ongoing initiatives in this rapidly developing area of research.

## Notable Examples of NIH Activity

### Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

### Preclinical Research: Translating Basic Science Discoveries to Human Studies

**Rodent Model Resources for Translational Research:** Mouse and rat models are the primary testbed for preclinical research and have played a vital role in most medical advances in the last century. Rodent models comprise about 90 percent of all animal studies enabling a wide range of genetic and physiological research on human disease. NIH plays a major role in supporting the availability of normal and mutant mice and rats for translational research. Recent accomplishments include:

- ▷ Knockout Mouse Project (KOMP): A trans-NIH initiative to individually inactivate each protein-coding mouse gene to better understand the genetic functions of the estimated 22,000 mouse genes, which are, in many cases, very similar to human genes.
- ▷ KOMP Repository: Established in FY 2007 to acquire and distribute the mouse models produced by the KOMP.
- ▷ Mutant Mouse Regional Resource Centers: Distribution of genetically engineered mice increased by 50 percent in FY 2006 because of increased demand.
- ▷ Rat Resource and Research Center: Acquisition and distribution of rat models increased by 50 percent in FY 2006 because of increased demand.
  - For more information, see [ncrr.nih.gov/comparative%5Fmedicine/resource\\_directory/rodents.asp](http://ncrr.nih.gov/comparative%5Fmedicine/resource_directory/rodents.asp)
  - For more information, see <http://www.genome.gov/17515708>
  - For more information, see <http://www.genome.gov/25521840>
  - For more information, see <http://www.mmrc.org/>
  - For more information, see <http://www.nrrrc.missouri.edu/>
  - This example also appears in Chapter 3: *Genomics*.
  - (E) (NCRR)

**Advances in Treatment Development:** NIH continues to fund research into the development of new, targeted medications and treatments for mental disorders.

- ▷ Drug development for cognitive impairments in schizophrenia: The Treatment Unit for Research on Neurocognition in Schizophrenia program is a network that is testing the safety and efficacy of new therapeutic compounds for treating the cognitive deficits of schizophrenia. (E) (NIMH)
- ▷ Studies of Fragile X syndrome (FXS): NIH has entered into a public-private partnership to study and test possible medications for treating FXS, the most common cause of inherited mental impairment. FXS is caused by a single gene mutation, ultimately resulting in exaggerated activity of a brain protein called mGluR5. Researchers will study, in animals, the

safety of chemical compounds known to block mGluR5 activity. If this phase goes well, researchers will move forward with clinical studies. (E) (NIMH, NINDS, NICHD)

- ▷ **Faster-acting depression treatments:** A recent NIH-funded study found that persons with treatment-resistant depression experienced relief in as little as 2 hours following a single intravenous dose of ketamine, a medication usually used in higher doses as an anesthetic. Used in very low doses, ketamine is important for depression research but at higher doses could have side effects that may limit its clinical use. Nevertheless, this research could inform development of faster and longer acting medications for treating depression.

- For more information, see <http://www.nimh.nih.gov/press/ketamine.cfm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (I) (NIMH)

**Engineering Stem Cells to Repair or Replace Damaged Tissues:** Guiding a person's own stem cells to repair or replace damaged tissues with healthy tissue is the goal of multiple NIH-supported tissue engineering projects. For example, one team previously reported success creating three-dimensional mandibular (jaw) joints using rodent tissue; their continuing work on the project addresses pragmatic questions that must be answered in order to create functional human joints. Other teams are working on regeneration of the temporomandibular disk, which acts as a "cushion" between the bony components of the jaw joint and on the tissue engineering of skeletal muscle. Tissue engineering holds great promise for regeneration or replacement of dental, oral, and craniofacial structures lost as a result of trauma, disease, or congenital anomalies. The progress seen in this area will also inform tissue engineering solutions for degeneration in other articular surfaces such as knee, hip, and shoulder joints.

- [Mao JJ, et al. \*J Dent Res\*. 2006; 85:966-79](#), PMID: 17062735
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)

**Molecular Profiling of Cancer:** The underlying cause of each patient's disease is typically unique to the individual. Because each tumor has its own biological properties, molecular profiling provides advanced analysis and tools to characterize each individual's disease or tumor so that tailored medical strategies can be applied. Several notable examples include:

- ▷ *The Early Detection Research Network (EDRN)* brings together dozens of institutions to help detect cancer in its earliest stages. EDRN was formed to bring a collaborative approach to the discovery, development, and validation of early detection markers by accelerating the translation of biomarker information into clinical applications.
- ▷ *The Strategic Partnering to Evaluate Cancer Signatures (SPECS) Program* establishes strategic partnerships to bring together interdisciplinary teams to evaluate the clinical utility of molecular signatures. SPECS focuses on confirming, evaluating, and refining signatures/profiles derived from molecular analysis of tumors (i.e., biomarkers detection) to improve patient management and outcomes.

- For more information, see <http://cancerdiagnosis.nci.nih.gov/specs/index.html>
- For more information, see <http://edrn.nci.nih.gov/>
- This example also appears in Chapter 2: *Cancer*.

- (E/I) (NCI)

**Monitoring Organ Rejection Using MRI:** Organ transplants give patients a new lease on life. However, preventing their immune systems from rejecting the transplanted organ sometimes presents a challenge. Physicians must strike a balance between suppressing the immune system so that it does not reject the organ and maintaining enough immune activity to ward off infections. Tracking how the body accepts the new organ is critical to this process. The current “gold standard” for monitoring organ rejection is tissue biopsy, an invasive procedure in which a physician removes a small sample of the transplanted organ for testing. Biopsy has two drawbacks: patient discomfort (the physician must perform the procedure multiple times) and poor selectivity (biopsy removes tissue only from a limited number of sites and can miss rejection starting elsewhere in the organ). To overcome these limitations, NIH-supported researchers are developing a new method to monitor organ rejection using magnetic resonance imaging (MRI). They label macrophages (immune cells) with polymer-coated micron-size iron oxide particles. These magnetic particles allow the migration of the macrophages to rejection sites in the transplanted organ to be clearly tracked by MRI. At the present time this work is being performed on rats, but the investigators are extending it to large animals and humans. If successful, the approach could be used to optimize the administration of immunosuppressant drugs in clinical situations.

- [Wu YL, et al. \*Proc Natl Acad Sci U S A\*. 2006;103:1852-7, PMID: 16443687](#)
- For more information, see <http://www.nibib.nih.gov/HealthEdu/PubsFeatures/eAdvances/25Sep06>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIBIB)

**Basic Research on CAM:** In addition to its focus on clinical investigation of complementary and alternative medicine interventions, NIH places a high priority on basic research aimed at filling important gaps in our knowledge about the mechanisms by which they may exert their effects. Recently released initiatives target this area of research. Examples include the following:

- ▷ “Omics and Variable Responses to CAM” utilizes genomic, proteomic, and metabolomic technologies to examine potential causes for variation in individual responses to CAM interventions (PAR-07-377).
  - ▷ “Mechanistic Research on CAM Modalities Purported to Enhance Immune Function” examines the scientific basis for a common but generally unsubstantiated claim made on behalf of a number of CAM modalities (RFA-AT-06-004, RFA-AT-06-005).
  - ▷ “Research on the Biomechanical, Immunological, Endocrinological, and/or Neurophysiological Mechanisms and Consequences of Manual Therapies” applies state-of-the-art science to investigate the biological basis for CAM interventions, such as spinal manipulation and massage. (PAR-06-312)
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
  - (E) (NCCAM)

**NCI Experimental Therapeutics Program (NExT):** The NExT program safely shortens the timeline for taking anticancer drugs from the laboratory to the clinic by combining NIH’s



expertise in drug development with state-of-the art research facilities. The program also utilizes new FDA guidelines that allow early Phase I clinical trials to proceed before certain time-consuming and expensive drug development steps occur. The first such study passed the initial stage of clinical examination, demonstrating that this new type of trial can reduce the number of patients required for an early clinical study, and the time necessary to gather critical drug development information.

- For more information, see <http://dctd.cancer.gov/MajorInitiatives/02NExT.htm>
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NCI)

**The NCI Alliance for Nanotechnology in Cancer:** This is a comprehensive, systematized initiative encompassing the public and private sectors, designed to accelerate the application of the best capabilities of nanotechnology to cancer. The program supports research on novel nanodevices that may detect and pinpoint the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real time if these drugs are effective in killing malignant cells. Nanotechnology will likely change the very foundations of cancer diagnosis, treatment, and prevention.

- For more information, visit <http://nano.cancer.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*.
- (E/I) (NCI)

**Biomedical Technology Research Resources (BTRRs):** The BTRRs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Resources and through intensive collaborations with other leading laboratories. The BTRRs are used annually by nearly 5,000 scientists from across the United States and beyond, representing over \$700 million of NIH funding for 22 institutes and centers. As an example, optical technologies enable researchers to:

- ▷ Harness the power of light to “see” biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- ▷ Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margins of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

- For more information, see [www.ncrr.nih.gov/biomedical\\_technology](http://www.ncrr.nih.gov/biomedical_technology)
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NCRR)

**Glycomics Technology Development, Basic Research, and Translation into the Clinic:** Complex carbohydrates are ubiquitous, found on the surfaces of cells and secreted proteins.

Glycan binding proteins mediate cell signaling, recognition, adherence, and motility and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules are thus critical for basic and clinical research across the spectrum of health and disease but are widely regarded as among the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- ▷ Biomedical Technology Research Resources are developing and sharing cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- ▷ Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
- ▷ Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- ▷ A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.
  - For more information, see [www.ncrr.nih.gov/glycomics](http://www.ncrr.nih.gov/glycomics)
  - For more information, see [www.functionalglycomics.org](http://www.functionalglycomics.org)
  - This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
  - (E) (NCRR, NCI, NHLBI, NIGMS, NINDS)

**Preclinical Disease Models Informatics:** Preclinical research results derived from animal models are an essential element in the decisional process to determine whether a basic science discovery should be considered as a potential therapeutic approach worthy of future development. However, more effective integration of the growing number of disparate data sources is urgently needed. NIH is developing a new resource to assimilate information from diverse disease-model data repositories and to disseminate innovative and novel interpretations of these data. This will help researchers minimize the time required to search multiple data sources, while optimizing the quality and relevance of the results. Activities in this area include:

- ▷ Determined community-defined needs and next steps during a workshop held in FY 2006.
- ▷ Issued request for proposals (fall 2007) that will address the need for an electronic directory of models resources.
- ▷ Forming critical inter/intra-agency and public-private partnerships to (1) address the need for and development of extensible prototypes and (2) ensure this resource remains broadly informed and grows coincidental with relevant technology.
  - For more information, see [www.esi-bethesda.com/ncrrworkshops/navigating/index.aspx](http://www.esi-bethesda.com/ncrrworkshops/navigating/index.aspx)
  - (E) (NCRR)

**Translational Research at Primate Research Centers:** Non-human primates (NHPs) are critical components for translational research because of their close physiological similarities to humans. NHPs are widely used for both hypothesis-based and applied research directly related to

human health, such as the development and testing of vaccines and therapies. The NIH-supported National Primate Research Centers and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using NHPs. In FY 2007, more than 1,000 research projects used NHPs from these resources. Highlights of research activities include:

- ▷ Use of the simian immunodeficiency virus for AIDS-related research, including development of novel microbicides to prevent infection by the AIDS virus and testing of AIDS vaccines
- ▷ Identification of the central role of specific genes and molecules in drug addiction and neurological conditions and diseases, studies of the biochemistry and physiology of drug and alcohol addiction, and development of stem cell-based therapies for neurodegenerative diseases.
- ▷ Sponsored scientific workshops in FY 2006 and 2007 that further defined the genetic tools necessary for translational research using NHPs.
  - For more information, see [ncrr.nih.gov/comparative%5Fmedicine/resource\\_directory/primates.asp](http://ncrr.nih.gov/comparative%5Fmedicine/resource_directory/primates.asp)
  - This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
  - (E) (NCRR)

**Medical Countermeasures Against Nuclear and Radiological Threats:** NIH is leading the HHS effort to sponsor and coordinate research to develop means to counter detrimental effects of a range of radiological threats. Most medical countermeasures to treat radiation injury are still in the early stages of development but are progressing. NIH-funded researchers recently (1) screened more than 40,000 candidate compounds and identified 52 candidates for evaluation as protective agents against the toxic effects of ionizing radiation, (2) developed improved forms of the chelating agent diethylenetriaminepentaacetic acid (DTPA), which animal testing data suggest can effectively clear the radionuclide Americium-241 from the blood, and (3) studied 29 candidate drugs that are active against a broad range of radionuclides and might be useful in treating victims of radiological dispersion devices (“dirty bombs”).

- For more information, see <http://www3.niaid.nih.gov/research/topics/radnuc/>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIAID)

**Centers of Research Translation (CORT):** NIH launched its CORT program to unite basic and clinical research in a way that translates basic discoveries into diagnostic approaches and treatments. The first set of centers, focusing on lupus, orthopaedic trauma care, scleroderma, and a genetic form of rickets (a childhood disorder characterized by a softening and weakening of bones), began in FY 2006 and are funded through FY 2011.

- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Press\\_Releases/2006/11\\_08.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/11_08.asp)
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIAMS)

**Quantum Program:** The NIH Quantum Grants Program has been developed to make a profound (quantum level) advance in health care by funding research, over two phases, on targeted projects that will develop new technologies for the diagnosis, treatment, or prevention of

a major disease or national public health problem. The first of the Quantum Grants was to engineer stem cell-based neurovascular regenerative units in a laboratory environment, which can then be implanted into the damaged cortex of stroke patients to provide a source of neural and vascular cells that will continue to develop and differentiate and lead to the first true treatment for stroke, one of the most common causes of disability, severely affecting quality of life of patients throughout the world. Another Phase I Quantum competition was completed in September 2007, with four additional grants awarded. The Phase II Quantum competition will begin in FY 2009.

- For more information, see <http://www.nibib.nih.gov/Research/QuantumGrants>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIBIB)

**Genetics of Kidneys in Diabetes (GoKinD):** This program facilitates investigator-driven research into the genetic basis of diabetic kidney disease through a biospecimen repository. Individuals with type 1 diabetes were screened to identify two subsets, one with clear-cut kidney disease and another with normal kidney function despite long-term diabetes. Nearly 10,000 DNA, serum, plasma, and urine samples—plus genetic and clinical data—from more than 1,700 adults with diabetes have been collected. The entire GoKinD collection is being genotyped for whole genome association studies as part of the Genetic Association Information Network (GAIN), a public-private partnership between NIH and industry.

- [Mueller PW et al. \*J Am Soc Nephrol\*. 2006;17:1782-90, PMID: 16775037](#)
- For more information, see [http://www.jdrf.org/index.cfm?fuseaction=home.viewPage&page\\_id=B9C33021-1321-C834-0382E079E7865807](http://www.jdrf.org/index.cfm?fuseaction=home.viewPage&page_id=B9C33021-1321-C834-0382E079E7865807)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (NIDDK)

**Type 1 Diabetes–Rapid Access to Intervention Development (T1D-RAID):** Many investigators who have discovered promising therapeutic agents in the laboratory do not have the resources to ready the agents for use in human clinical trials. Therefore, NIH supports the T1D-RAID program to provide resources for preclinical development of agents to test in clinical trials. For example, the drug lisofylline, prepared and tested by T1D-RAID, will be studied in an upcoming pancreatic islet transplantation clinical trial.

- For more information, see <http://www.t1diabetes.nih.gov/T1D-RAID/index.shtml>
- This example also appears in Chapter 2: *Autoimmune Diseases*.
- (E) (NIDDK, NCI)

**Specialized Program of Translational Research in Acute Stroke (SPOTRIAS):** The objective of the SPOTRIAS is to serve as an incubator for translational and early-phase clinical research studies. SPOTRIAS sites are located at medical centers where staff members have the capacity to evaluate and treat stroke patients very rapidly after symptom onset. NIH supports seven SPOTRIAS sites, which have made substantial progress, including impressive increases in the use of the “clot buster” tPA (tissue plasminogen activator) to treat acute stroke; the establishment of three interlinked repositories for protein and DNA tissue samples, neuroimages,

and clinical data; enrollment of more than 640 individuals with acute stroke into treatment protocols; the management of 17 early-phase clinical trials; and the training of 25 research fellows.

- For more information, see <http://www.spotrias.com/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NINDS)

**Toward Better Treatment for Muscular Dystrophy:** Activities funded by NIH are pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4). NIH also recently funded two large-scale translational research projects in muscular dystrophy: one to develop small-molecule drugs for Duchenne and potentially other forms of muscular dystrophy and another to develop the optimal vector for vascular delivery of genes. A new NIH Government Performance and Results Act (GPRA) goal aims to advance two emerging strategies for treating muscular dystrophy to clinical trial readiness by 2013. The Muscular Dystrophy Coordinating Committee's *Action Plan for the Muscular Dystrophies* also identified therapy development goals to be pursued by NIH and the committee's partner agencies and organizations. A recent workshop convened by NIH reviewed the status of different therapeutic approaches for muscular dystrophy and discussed ways to move this research forward.

- For more information, see [http://www.ninds.nih.gov/find\\_people/groups/mdcc/MDCC\\_Action\\_Plan.pdf](http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan.pdf)
- For more information, see [www.wellstonemdcenters.nih.gov](http://www.wellstonemdcenters.nih.gov)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (COE) (NINDS, NIAMS, NICHD) (GPRA Goal)

**The SMA Project:** A decade ago, spinal muscular atrophy (SMA) was one of hundreds of poorly understood inherited disorders that affect the nervous system, and the outlook for developing treatments was bleak. The discovery of the gene defect causing SMA dramatically improved prospects, revealing a rational strategy to develop drugs. The SMA Project is a novel approach to pre-clinical drug development and may serve as a model for other disorders. The Project brought together expertise from industry, academia, the FDA, and NIH to generate a detailed drug development plan. A "virtual pharma organization" develops and applies the resources to carry out the plan through subcontracts to companies that serve the pharmaceutical industry. The project created a new drug through extensive modification of indoprofen, a drug with known activity in experimental settings that was not suitable for clinical application. Through repeated modification and evaluation cycles in laboratory tests, the project produced hundreds of chemical compounds related to indoprofen and has made encouraging progress. In 2007, preclinical studies began to evaluate the two best candidates for clinical readiness. The best of these will likely be ready for early stage clinical testing in 2008 or 2009.

In early 2008, the project also began two new drug development projects that could yield additional drug candidates for SMA.

- For more information, see <http://www.smaproject.org/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS)

**Translational Research:** To meet the special needs of translational research across neurological disorders, NINDS developed a program to support pilot projects, full-scale collaborative teams in academia and small businesses, and training efforts. Investigator-initiated proposals are rigorously peer reviewed, with expertise and criteria tailored to translational research objectives. Funding is milestone-driven, and the program fosters collaborative research. Ongoing projects are developing drug, stem cell, or gene therapies for ALS, Batten disease, epilepsy, Huntington's disease, Duchenne and other muscular dystrophies, Parkinson's disease, tuberous sclerosis, and stroke and other disorders. In 2008 the program will expand to include molecular diagnostics, which are critical for catching disease early when intervention is most likely to succeed.

- For more information, see <http://www.ninds.nih.gov/funding/research/translational/index.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NINDS)

**The NIH Rapid Access to Intervention Development (RAID) Pilot Program:** The NIH-RAID Pilot program makes available, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new small-molecule drugs, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving from bench to bedside. Among the projects approved are drugs for hepatic fibrosis, the blood diseases beta thalassemia and sickle cell anemia, brain tumors, and the neurological disorders Friedreich's ataxia and Alzheimer's. The NIH-RAID Pilot is part of the NIH Roadmap for Medical Research.

- For more information, see <http://nihroadmap.nih.gov/raid/index.aspx>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (Roadmap—all ICs participate)

**Translational Research on Alzheimer's Disease (AD):** To move basic research on AD and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. In order to closely monitor the progress of the translational projects, provide guidance, and foster interactions among investigators involved in translational research funded by these programs, NIH staff held the First Annual Investigators Meeting for Translational Research in September 2007.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-07-048.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NIA)



**Potential Therapy for Children Afflicted With Progeria Syndrome:** Hutchinson-Gilford progeria syndrome (HGPS) is a genetic disorder of accelerated aging. In addition to other symptoms of aging, HGPS patients suffer from accelerated cardiovascular disease and often die in their teen or even pre-teen years from heart-related illnesses. No treatments are currently available for HGPS; however, recent work led by NHGRI researchers indicates that farnesyltransferase inhibitors (FTIs), a class of drugs originally developed to treat cancer by blocking the growth of tumor cells, are capable of reversing the effects of the defective HGPS protein, lamin A. Ongoing studies in a mouse model have validated the results of preliminary experiments, and a clinical trial of FTIs in children with progeria began in 2007. In FY 2008, researchers plan on expanding the study to investigate whether FTIs are capable of reversing the detrimental effects after progression of the cardiovascular anomalies that are seen in the mouse model. The development of biological assays to assess the effects of FTI treatment on the patients' cells is in progress to monitor potential beneficial effects of the clinical trial. In addition, it has been demonstrated that the progerin protein is present in small amounts in normal aging tissues. The investigation of this phenomenon is being pursued as a contributory factor to the normal aging process.

- [Cao K, et al. \*Proc Natl Acad Sci U S A\*. 2007;104:4949-54, PMID: 17360355](#)
- [Capell BC, et al., \*Proc Natl Acad Sci U S A\*. 2005;102:12879-84, PMID: 16129833](#)
- For more information, see <http://www.genome.gov/10000608>
- For more information, see <http://www.genome.gov/15515061>
- This example also appears in Chapter 3: *Genomics* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (I) (NHGRI)

**Trans-NIH Initiative for Translational Research in Immunology, Autoimmunity, and Inflammation:** A new, trans-NIH initiative is being developed by the intramural research program to facilitate the translation of advances in basic immunology to improved therapies and clinical care for immune-mediated diseases. The translation of basic immunology to the clinic has been impeded by separations between basic immunologists, physicians, and epidemiologists and by barriers among clinicians who address diseases that share pathophysiologic mechanisms but are historically separated in different specialty practices. The new program will integrate research efforts not only across the basic, clinical, and population sciences but also across conventional medical subspecialties. Research will focus on a variety of autoimmune diseases, congenital and acquired immunodeficiency syndromes, processes in which inflammation or altered immunity has a pathogenic role, and malignant diseases influenced by the immune system. Studies will address the underlying role of the immune system and the similarities and differences of the inflammatory response in many seemingly unrelated immune-mediated diseases. The initiative is expected to advance understanding of the causes of the diseases and to promote the development of new therapies. It also is expected to serve as a model for future trans-NIH translational research efforts to facilitate more rapid development and testing of new therapies and enhance interdisciplinary training.

- This example also appears in Chapter 2: *Autoimmune Diseases*.
- (I) (NHLBI, NIAID, NIAMS, NIDDK)

## Clinical Research: Learning Which Interventions Work

**New Medical Adhesive Boasts Unique Wet-Dry Abilities:** One day, tissue engineering will make it possible to regenerate lost facial components. Until then, victims of massive craniofacial trauma or extensive surgeries due to cancer often must depend on maxillofacial prosthetics to provide the form and function needed to resume their day-to-day lives. Current adhesives are not always retentive over long periods or changing conditions. The loss of retention can result in visible margins or even dislodgement of the prosthesis. Now NIH-supported scientists report they have merged two of nature's most elegant strategies for wet and dry adhesion. As reported in *Nature*, the scientists designed a synthetic material that starts with the dry adhesive properties of the gecko lizard and supplements it with the underwater adhesive properties of a mussel. The hybrid material, which they call a geckel nanoadhesive, proved in initial testing to be adherent under dry and wet conditions, and also adhered much longer under both extremes than previous gecko-based synthetic adhesives, a major issue in this area of research. According to the authors, their findings mark the first time that two polar opposite adhesion strategies in nature have been merged into a man-made reversible adhesive. It is envisioned that the new adhesive will be used for many medical applications including enhancing the retention of oral/maxillofacial prosthetics.

- [Lee H. et al. \*Nature\* 2007;448:338-41](#), PMID: 17637666
- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2007/PR07182007.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*.
- (E) (NIDCR)

**Diabetes Prevention Program Outcomes Study (DPPOS):** The landmark NIH Diabetes Prevention Program clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk. The DPPOS is a long-term followup study of the DPP subjects that is determining the durability of the interventions in preventing disease. DPP researchers recently confirmed that a variant in a gene predisposes people to type 2 diabetes. DPP subjects at highest genetic risk benefited from healthy lifestyle changes as much or more than those who did not inherit the variant. Participants over 60 years of age responded especially well to the lifestyle intervention, showing a 71 percent risk reduction in the incidence of diabetes, as compared to groups treated with metformin or standard medical advice. The lifestyle intervention had greater impact with increasing age (from age 25 to over 60) while the metformin treatment had progressively less impact with increasing age.

- [Florez JC. et al. \*N Engl J Med.\* 2006;355:241-50](#), PMID: 16855264
- For more information, see <http://tinyurl.com/24okog>
- For more information, see <http://tinyurl.com/295h4l>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK, CDC, IHS, NCMHD, NEI, NHLBI, NIA, NICHD, ORWH)

**Clinical Research and Trials in Neurological Disease:** NINDS provides extramural funding for more than 1,000 clinical research studies. Nearly 1 million people participate in these projects, and it is essential to assess the return on this investment in improving quality of life. NINDS contracted an independent evaluation of the costs and benefits of its Phase III clinical trials. Investigators found that while the total cost of clinical trials in the study was \$335 million, the cumulative benefits over a 10-year period exceeded \$15 billion and added 470,000 healthy years of life to people in the United States. NINDS is extending this evaluation approach by developing a computer model that will estimate the public health impact of any given clinical trial in neurology or neurosurgery. This model will be publicly available for use by researchers and the Institute to facilitate decision-making. NINDS is also assessing ways to further improve its trials. To this end, the Institute has funded a Neurological Emergencies Treatment Trials (NETT) Network to facilitate high-quality clinical trials in acute neurological disorders and accelerate the implementation of new therapies into practice in emergency departments.

- [Johnston SC, et al. \*Lancet\* 2006;367:1319-27](#), PMID: 16631910
- For more information, see <http://www.nett.umich.edu/nett/welcome>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NINDS)

**Multiple Sclerosis (MS):** While the exact cause of MS is unknown, research suggests a strong genetic component. NIH funds a number of studies to determine the underlying genetic causes of MS, including a project to identify regions of the genome containing MS susceptibility genes using a large familial dataset and genomic analysis tools. NIH also funds clinical trials to test therapies for MS, including the CombiRx trial, a randomized, controlled clinical trial comparing the efficacy of treatment combining interferon-beta (IFN) and glatiramer acetate (GA) versus treatment with a single agent for relapsing forms of MS. A study conducted in conjunction with CombiRx by NIH intramural researchers (BioMS) is assessing MS biomarkers using genomic and proteomic technology and relating the information obtained back to clinical and MRI data generated by the CombiRx clinical trial.

- [Gregory SG, et al. \*Nat Genet.\* 2007;39:1083-91](#), PMID: 17660817
- [International Multiple Sclerosis Genetics Consortium, et al. \*N Engl J Med.\* 2007;357:851-62](#), PMID: 17660530
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NINDS)

**Toward Better Treatment for Muscular Dystrophy:** Activities funded by NIH are pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4). NIH also recently funded two large-scale translational research projects in MD: one to develop small molecule drugs for Duchenne and potentially other forms of MD and another to develop the optimal vector for vascular delivery of genes. A new NIH GPRA goal aims to advance two emerging strategies for treating MD to clinical trial readiness by 2013. The Muscular Dystrophy Coordinating Committee's (MDCC) *Action Plan for the Muscular Dystrophies* also identified therapy development goals to be pursued by NIH and its MDCC partner agencies and

organizations. A recent workshop convened by NIH reviewed the status of different therapeutic approaches for MD and discussed ways to move this research forward.

- For more information, see [http://www.ninds.nih.gov/find\\_people/groups/mdcc/MDCC\\_Action\\_Plan.pdf](http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan.pdf)
- For more information, see [www.wellstonemdcenters.nih.gov](http://www.wellstonemdcenters.nih.gov)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS, NIAMS, NICHD)

**Practical Clinical Trials:** NIH has completed primary and secondary phases of several practical clinical trials that have examined treatment effectiveness for mental disorders such as schizophrenia, bipolar disorder, and depression. The infrastructure developed for each of these large multi-site trials—involving over 10,000 subjects at over 200 sites—has forged efficient, effective, and collaborative relationships between scientists and clinicians throughout the country. In order to capitalize on the national networks established for the trials, NIH will fund infrastructure-only support for the platform of clinical sites and an administrative core. It is anticipated that the platform will serve as a critical foundation for supporting subject enrollment, facilitating communication between trial sites, maintaining up-to-date training in diagnosis and treatment, and providing needed administrative organization.

- For more information, see <http://www.nimh.nih.gov/healthinformation/catie.cfm>
- For more information, see <http://www.nimh.nih.gov/healthinformation/stard.cfm>
- For more information, see <http://www.nimh.nih.gov/healthinformation/stepbd.cfm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIMH)

**Scientific Basis of the Placebo Effect:** The placebo effect can be defined as the measurable, observable, or felt changes that occur during but are not directly attributable to a specific health intervention. It is a ubiquitous and frequently powerful phenomenon that operates in all forms of medicine, so good clinical research is designed to account for its effects as well as those of the intervention under study. Because of the power of the effect, it is equally important to understand the mechanisms by which it operates and to explore how its benefits might be maximized to enhance the quality and effectiveness of all forms of health care. An ongoing NIH initiative is examining multiple aspects of the placebo effect through interdisciplinary investigations employing molecular, physiological, biochemical, immunological, genetic, behavioral, and social science approaches. This work is beginning to shed light on many facets of the effect. For example, one recently published study showed that placebo-associated pain relief was correlated with activation of areas of the brain that are associated with pain relief that occurs through both innate mechanisms and with use of opioid narcotics. Other ongoing studies are examining the role and importance of the effect in the relationship between patient and health care provider.

- [Zubieta JK, et al. \*J Neurosci\* 2005;25:7754-62](#), PMID: 16120776
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NCCAM)

**The Scientific Basis of Acupuncture:** Ongoing research on acupuncture includes a substantial portfolio of basic and translational studies employing state-of-the-art neuroimaging technology. This work is beginning to provide powerful scientific insight into the potential neurobiological mechanisms of action by which acupuncture might work. Clinical trials of acupuncture for a number of medical conditions are also under way, including studies examining (1) the potential role of traditional acupuncture as an additive/alternative treatment for the prevention of acute cardiac events in patients with coronary artery disease, (2) whether manual or electro acupuncture contribute to neurological recovery after spinal cord injury, and (3) the efficacy of acupuncture in relieving post-thoracotomy pain syndrome (severe and persistent aching or burning pain along surgical scars in the chest).

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NCCAM)

**Gene Therapy for Leber’s Congenital Amaurosis (LCA):** LCA is a rare, inherited retinal degenerative disease that causes severe vision loss in infancy and early childhood. Although currently untreatable, NIH-funded investigators have restored vision in dogs with LCA using gene therapy to replace defective copies of the retinal gene *RPE65*. Furthermore, new evidence suggests retinal activity also restores function to the brain’s visual center. Investigators have recently begun to translate this promising therapy to patients with LCA.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NEI)

**Multicenter Uveitis Steroid Treatment (MUST) Trial:** Uveitis, a disease that causes inflammation in middle layers of the eye, is a major cause of blindness in the United States often requiring systemic, long-term treatment with oral corticosteroids and immunosuppressants. Ideally, a local therapy impacting only the eye is preferable to systemic therapy. This comparative effectiveness trial tests a new intraocular implant therapy in severe uveitis.

- For more information, see <http://www.musttrial.org/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NEI)

**Sildenafil for Pulmonary Hypertension in Adult Patients with Sickle Cell Disease:** In 2006, NIH began a new study to evaluate a course of treatment with sildenafil in sickle cell disease patients who have pulmonary hypertension. A randomized, double-blind, placebo-controlled Phase II clinical trial is testing the drug’s safety and its efficacy in improving exercise capacity, symptoms, and measures of circulatory function. The trial involves approximately 180 patients at extramural sites and at the NIH Clinical Center. Because pulmonary hypertension occurs frequently in persons with sickle cell disease and confers a high risk of death, a positive outcome of this trial would represent an important step toward improved patient care.

- For more information, see <http://www.clinicaltrials.gov/ct2/show/NCT00492531?term=sildenafil&rank=7>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (NHLBI)

**Maternal Oral Health and Obstetric Outcomes:** In recent years evidence has suggested that a pregnant woman with periodontal (gum) disease might be at increased risk for premature birth. Two similar but not identical NIH-supported trials evaluate this possibility. Conducting more than one large clinical trial on this important public health question will cast a wide enough investigational net to determine which, if any, women are at risk. One study, called the *Obstetrics and Periodontal Therapy Trial (OPT)* recently concluded that periodontal treatment during pregnancy is safe for mother and baby but does not significantly lower preterm birth risk. The *Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR)* study is ongoing.

- See <http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/PeriodontalPretermBirthRisk.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDCR)

**The PCOS Twin Study:** The PCOS (Polycystic Ovarian Syndrome) Twin Study is sponsored by NIH. NIH researchers are studying polycystic ovary syndrome in twins to find out if it is caused by genetics or the environment or a combination of both. Once scientists know more about the causes of PCOS, then health care professionals can then treat it more effectively or possibly lower the chance that a woman will develop it.

- For more information, see <http://www.niehs.nih.gov/pcos/index.htm>
- (NIEHS)

**Salivary Gene Transfer and Therapeutics:** Gene transfer may be an ideal strategy to boost salivary production for cancer patients whose salivary glands were damaged during radiation therapy. While radiation therapy kills cancerous cells, it frequently also destroys the acinar (fluid-producing) salivary gland cells that lie within the salivary gland in grape-like clusters. Patients are unable to produce adequate saliva and suffer a host of long-term problems such as recurrent oral infections and difficulties with swallowing, speech, and taste. Unlike acinar cells, ductal cells in the salivary gland (which can be thought of as the “stems” on the grapes) often survive irradiation. But they cannot make or secrete saliva. NIH scientists used gene transfer techniques to insert an aquaporin protein gene into the ductal cells; aquaporins are a family of proteins that form pores in cell membranes, through which fluid can pass. Their insertion “plumps up” the stems and allows the flow of fluid into the mouth again. The scientific team has collaboratively and methodically moved this promising idea through the research process, benefiting greatly from the wealth of scientific expertise on the NIH campus. This year, FDA approved the first clinical trial of gene transfer into the salivary glands for cancer patients with dry mouth. Although the outcome of clinical trials is always hard to predict, the preclinical data have been extremely promising.

- This example also appears in Chapter 2: *Cancer*.
- (I) (NIDCR)

**Long-Term Oxygen Treatment Trial (LOTT):** Although oxygen therapy is known to benefit patients who have chronic obstructive pulmonary disease (COPD) and experience severe hypoxemia (low blood oxygen level) when resting, the value of this treatment in patients with



less-serious disease is not known. In November 2006, NIH and the Centers for Medicare and Medicaid Services launched the LOTT, the largest ever randomized clinical trial of the effectiveness and safety of long-term home oxygen therapy for patients with COPD and moderately severe hypoxemia. Results are expected to shed light on the role of oxygen therapy in management of such patients and to provide a basis for Medicare coverage decisions. LOTT is the focus of a new NIH Government Performance and Results Act (GPRA) goal to be included in GPRA reporting in 2007 – “by 2012, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia.”

- For more information, see <http://www.nhlbi.nih.gov/new/press/06-11-20.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NHLBI) (GPRA Goal)

**HIV/AIDS Epidemiological and Long-Term Cohort Studies:** NIH supports epidemiological HIV research through a wide range of cohort studies that contribute to our understanding of risk factors that lead to HIV transmission and disease progression. Established in 2005, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) compiles data from NIH-funded international HIV research to answer population-level questions about HIV variants and resistance, HIV pathogenesis in different settings, success of antiretroviral therapy, treatment history of HIV in different populations, success of prevention strategies, and vaccines. The Pediatric HIV/AIDS Cohort Study (PHACS), established in 2005, addresses two critical pediatric HIV research questions: the long-term safety of fetal and infant exposure to prophylactic antiretroviral chemotherapy and the effects of perinatally acquired HIV infection in adolescents. The Women’s Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) are the two largest observational studies of HIV/AIDS in women and homosexual or bisexual men, respectively, in the United States. These studies exceed standard clinical care diagnostics and laboratory analysis on both HIV-infected, and, importantly, HIV-negative controls, which allows for novel research on how HIV spreads, how the disease progresses, and how it can best be treated. The studies focus on contemporary questions such as the interactions among HIV infection, aging, and long-term treatment; cardiovascular disease; and host genetics and their influence on susceptibility to infection, disease progression, and response to therapy.

- For more information, see <http://www3.niaid.nih.gov/news/newsreleases/2007/ctu07.htm>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID) (GPRA Goal)

**Look AHEAD (Action for Health in Diabetes):** This multicenter NIH-led clinical trial is examining the health effects of an intensive lifestyle intervention designed to achieve and maintain weight loss over the long term, through decreased caloric intake and increased physical activity. The impact of the intervention on the incidence of major cardiovascular events will be evaluated in 5,100 overweight or obese subjects with type 2 diabetes. Look AHEAD is one of four trials that collectively address GPRA Goal SRO-6.2.

- [The Look AHEAD Research Group. \*Diabetes Care\* 2007;30:1374-83](#), PMID: 17363746
- For more information, see <http://tinyurl.com/2xaypk>

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (NIDDK, CDC, NCMHD, NHLBI, NINR, ORWH) (GPRA Goal)

**Interventions and Services for Youth With Mental Illness Who Are Transitioning to Adulthood:** The transition to adulthood for youth with mental illness is often a period in which care is compromised, with a host of negative outcomes. In 2006, NIH launched an initiative to stimulate research on refining and testing interventions in service delivery models for youth transitioning to adulthood. Four applications were funded.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-07-050.html>
- <http://www.nimh.nih.gov/science-news/2007/new-research-to-help-youth-with-mental-disorders-transition-to-adulthood.shtml>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIMH)

**Age-Related Eye Disease Study, Part 2 (AREDS2):** Age-related Macular Degeneration (AMD) is the leading cause of blindness in the elderly in the United States and will be an increasing burden in future years based on demographics. The original AREDS study, completed in 2005, demonstrated that antioxidant vitamin and mineral supplements reduced the progression to advanced AMD by 25 percent. Building on these landmark findings, AREDS2 is assessing additional supplements (lutein, zeaxanthin, and long-chain omega-3 fatty acids) as a treatment for AMD and cataracts. AREDS2 is also evaluating effects of eliminating beta-carotene and/or reducing zinc in the original AREDS formulation on AMD progression. AREDS2 investigators will also explore gene-environment interactions in the development of these conditions, cognitive function, and cardiovascular health.

- For more information, see <http://www.areds2.org/>
- This example also appears in Chapter *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NEI, NIA)

**Improved Management of Antiretroviral Therapy for Adults and Children:** Two recent NIH studies transformed the management of antiretroviral therapy (ART) by extending survival of adults and children with HIV/AIDS. Results from the Strategies for Management of Antiretroviral Therapy (SMART) study, one of the largest HIV/AIDS treatment trials ever conducted, showed that episodic use of ART based on CD4+ cell levels is inferior to use of continuous therapy for treatment-experienced patients and that deliberately interrupting antiretroviral therapy more than doubles the risk of developing AIDS or dying from any cause. The Children with HIV Early Antiretroviral Therapy (CHER) Study examined early ART in South African children. Interim data showed a 96 percent increase in survival among infants who received immediate ART compared to infants who received therapy later.

- [SMART Study Group et al. \*N Engl J Med\* 2006;355:2283-96](#), PMID: 17135583
- For more information, see <http://www3.niaid.nih.gov/news/newsreleases/2006/smart06.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIAID)

**Improving the Lives of Asthmatic Children in the Inner City:** The NIH Inner-City Asthma Consortium (ICAC) evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children, who are disproportionately affected by asthma. An ICAC longitudinal birth cohort study involving 500 inner-city children is investigating the immunologic causes of the development of recurrent wheezing, a surrogate marker for asthma in children under three. The ICAC is also conducting a multicenter trial to evaluate the safety and efficacy of Xolair (omalizumab) in children with moderate to severe allergic asthma whose symptoms are inadequately controlled with inhaled steroids. Finally, researchers are conducting a clinical trial to determine the safety and dosing levels of a potential new allergy immunotherapy for cockroach allergen, which previous ICAC findings showed are a major determinant of asthma severity among inner-city children.

- For more information see [http://www3.niaid.nih.gov/research/topics/allergies/research\\_activities.htm](http://www3.niaid.nih.gov/research/topics/allergies/research_activities.htm)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIAID)

**Therapies to Treat and Prevent Food Allergies:** The NIH Consortium of Food Allergy Research is developing immune-based approaches to treat food allergy, rather than to simply avoid food allergens. Basic studies are ongoing using mouse models to study how modified forms of peanut allergens protect against peanut-induced anaphylaxis. The five clinical sites of the Consortium are developing treatment and prevention strategies for food allergy, and they work to educate parents and health care providers regarding food allergies. An ongoing observational study is examining immune mechanisms, genetic factors, and environmental factors associated with the development of new food allergy to peanut and the loss of egg allergy to high-risk children. An interventional study aims to determine the safety and immunologic effects of giving egg by mouth to egg-allergic children, with the goal of inducing immunological tolerance. Phase I clinical trials are assessing the safety of treating peanut-allergic subjects with either a modified form of peanut allergen or small amounts of peanut allergen under the tongue.

- For more information, see <http://www3.niaid.nih.gov/healthscience/healthtopics/foodAllergy/ReportFoodAllergy.htm>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIAID)

**Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA):** This 5-year clinical study's longitudinal design will greatly accelerate the identification of better treatments to control the pain of temporomandibular joint and muscle (TMJ) disorders. The OPPERA study marks one of the first prospective clinical studies of a chronic pain disorder. A prospective study is the "gold standard" of medical research: it looks forward in time, monitoring the health of those in the study over several years to track the onset or progression of a disease. With the study's 5-year vantage point, investigators will begin identifying individual genetic, physiologic, and psychological factors that cause or contribute to TMJ disorders and advance virtually all aspects of understanding and caring for these disorders.

- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2005/PR12052005.htm>
- See <http://www.nidcr.nih.gov/Research/ResearchResults/InterviewsOHR/TIS012006.htm>

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDCR)

**Longitudinal Assessment of Bariatric Surgery (LABS):** The multicenter NIH-funded LABS consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Because bariatric surgery is also sometimes used in clinical practice as a treatment for severely obese adolescents, NIH is additionally supporting an observational study of teens already scheduled for surgery, Teen-LABS, to collect data to help determine whether it is an appropriate treatment option for extremely obese adolescents.

- For more information, see <http://tinyurl.com/399zmt>
- For more information, see <http://tinyurl.com/yoer3l>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDDK, ORWH)

**Polycystic Kidney Disease (PKD):** The Consortium for Radiologic Imaging Studies of PKD (CRISP) showed that magnetic resonance imaging could accurately track structural changes in the kidneys in people with the more common form of PKD. An extension, CRISP II, will continue to monitor these patients to determine whether these changes in kidney volume predict changes in kidney function. NIH is also conducting two clinical trials of people with the most common form of PKD; one is in patients with early kidney disease and another in patients with more advanced disease. These two trials are the largest multicenter studies of PKD conducted to date, and are collectively termed HALT-PKD. They are testing whether optimum blood pressure management, in combination with medication, will slow the progression of PKD.

- [Grantham JJ, et al. \*N Engl J Med\*. 2006;354:2122-30](#), PMID: 16707749
- For more information, see <http://tinyurl.com/2qu94j>
- For more information, see <http://www.pkd.wustl.edu/pkd-tn/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK)

**Stress Incontinence Surgical Treatment Efficacy (SISTER) Trial:** The first of several studies to be conducted by the NIDDK-funded Urinary Incontinence Treatment Network, the SISTER trial recently showed that the sling surgical procedure helps more women achieve dryness than the Burch surgical technique. Two years after surgery, 66 percent of women who had the sling procedure and 49 percent who had the Burch were continent.

- [Albo ME et al. \*N Engl J Med\*. 2007;356:2143-55](#), PMID: 17517855
- For more information, see <http://www.nih.gov/news/pr/may2007/niddk-21.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK)

**Studies of Diabetes in Youth:** Previously known as a disease of adults, type 2 diabetes is increasingly being observed in youth. The Treatment Options for Type 2 Diabetes in Youth study is comparing three different treatment strategies for children with the disease. The SEARCH for Diabetes in Youth Study is providing key data on childhood diabetes incidence and

prevalence. SEARCH estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. While type 2 diabetes is increasing in children over 10, particularly minorities, type 1 diabetes accounts for most new cases, with an estimated 15,000 youths diagnosed annually.

- For more information, see <http://www.todaystudy.org/index.cgi>
- For more information, see <http://www.searchfordiabetes.org/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Epidemiological and Longitudinal Studies*, and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDDK, CDC)

**Centers on Suicide Prevention:** In response to the 2002 Institute of Medicine Report, “Reducing Suicide: A National Imperative,” NIH issued a request for applications and funded three centers focused on intervention and prevention of suicide. Now in their third year of support, the centers have conducted pilot intervention studies with patients suffering from mental and substance use disorders.

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH, NIAAA, NIDA)

**Prevention of Trauma-Related Mental Disorders in High-Risk Occupations:** NIH is supporting a research initiative to develop and test preemptive interventions to prevent trauma-related disorders, such as posttraumatic stress disorder, among occupational groups at high risk for trauma exposure, such as the military, firefighters, police, and rescue workers.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-010.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH)

**ClinicalTrials.gov:** Established in 2000 in response to congressional mandate (Pub. L. No. 105-115), [ClinicalTrials.gov](http://ClinicalTrials.gov) has grown to become the largest clinical trial registry in the world with information on clinical research studies for hundreds of diseases and conditions conducted in 148 countries. At the end of September 2007, it contained more than 47,000 registered trials—more than double the number of entries 2 years earlier. Legislation enacted in September 2007, the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85), expanded the scope of trials to be registered with [ClinicalTrials.gov](http://ClinicalTrials.gov) and the registration information to be provided. It also mandates the inclusion of specified results information beginning in September 2008.

- [Drazen JM, et al. \*N Engl J Med.\* 2007;356:184-5](#), PMID: 17215537
- [Zarin DA, et al. \*N Engl J Med.\* 2005;353:2779-87](#), PMID: 16382064
- For more information, see <http://clinicaltrials.gov>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (I) (NLM)

**Acupuncture for Osteoarthritis of the Knee:** Clinical trials supported by NIH and others suggest that acupuncture may have a useful role in treating a variety of chronic painful



conditions, hypertension, and obesity. For example, in 2006 NIH-funded investigators reported findings from the longest, largest, randomized, controlled clinical trial of acupuncture ever conducted. The results demonstrated that acupuncture is an effective adjunct to conventional treatment for osteoarthritis, the most common form of arthritis and a major cause of pain, limitation of activity, and health care utilization among the elderly. Study subjects receiving acupuncture had significantly reduced disability and improved quality of life. The innovative trial design resulted from an interdisciplinary collaboration of rheumatologists, licensed acupuncturists, and biostatisticians, ensuring that the research methodology was scientifically sound and accurately reflected acupuncture as traditionally practiced.

- [Manheimer E, et al. \*Acupunct Med\* 2006;24:S7-14](#), PMID: 17308513
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NCCAM)

**Research on Popular Dietary Supplements:** A significant body of research on complementary and alternative medical practices focuses on documenting the safety and efficacy of various widely used dietary supplements. Important recently reported findings include the following:

- ▷ The combination of glucosamine plus chondroitin sulfate did not provide significant relief of pain from osteoarthritis of the knee in the overall study population, although a subset of the study subjects with moderate-to-severe pain showed significant relief with the combined supplements.
  - ▷ The dietary supplement alpha-tocopherol (a form of vitamin E) administered at a high dosage of 1200 IU/day for 2 years had no effect on serum concentrations of total, LDL, or HDL cholesterol.
- [Clegg DO, et al. \*N Engl J Med\*. 2006;354:795-808](#), PMID: 16495392
  - [Singh U, et al. \*Clin Chem\*. 2007;53:525-8](#), PMID: 17234730
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
  - (E) (NCCAM, NIAMS, ODS)

**Losartan Offers Promise for the Treatment of Marfan Syndrome:** New research offers hope that losartan, a drug commonly prescribed to treat hypertension, might also be used to treat Marfan syndrome, a genetic disorder that often causes life-threatening aortic aneurysms. After discovering that Marfan syndrome is associated with a mutation in the gene encoding fibrillin-1, researchers tried for many years, without success, to develop treatment strategies that involved repair or replacement of fibrillin-1. A major breakthrough occurred when NIH-funded researchers discovered that one of the functions of fibrillin-1 is to bind to another protein, TGF-beta, and regulate its effects. After careful analyses revealed aberrant TGF-beta activity in patients with Marfan syndrome, researchers began to concentrate on treating the disease by normalizing the activity of TGF-beta. Losartan, which is known to affect TGF-beta activity, was tested in a mouse model of Marfan syndrome. The results showed that the drug blocked the development of aortic aneurysms as well as lung defects associated with the disease. Based on the promising results, the NHLBI Pediatric Heart Network, in partnership with the National Marfan Foundation, began a clinical trial in 2007 to assess losartan therapy in patients with Marfan syndrome.



- [Habashi JP, et al. \*Science\*. 2006;312:117-21](#), PMID: 16601194
- For more information, see <http://clinicaltrials.gov/show/NCT00429364>
- For more information, see <http://www.pediatricheartnetwork.org/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHLBI)

**Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial:** The HALT-C trial studies whether long-term antiviral therapy can prevent liver disease progression in people with hepatitis C who do not respond to standard, short-term therapy. The trial has advanced understanding of the impact of disease severity and antiviral drug dose on response to long-term therapy, and yielded a new tool to monitor treatment response. These advances can help health care providers determine which patients are unlikely to respond to long-term antiviral therapy, so that those patients can be spared from ineffective treatment and its side effects.

- [Morishima C et al. \*Hepatology\*. 2006;44:360-7](#), PMID: 17241864
- For more information, see <http://www.haltctrial.org/>.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK, NCI, NIAID)

**Compliance With the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research:** NIH works to ensure compliance with the NIH Policy for the Inclusion of Women and Minorities as Subjects in Clinical Research by convening a trans-NIH committee that addresses consistency in inclusion policy implementation and population data reporting. Over the last 2 years, a more streamlined method of reporting minority participation in NIH-funded clinical research has been developed; the most recent Federal standards for reporting race and ethnicity have been clarified; and new methodologies for collecting and reporting more reliable population data from investigators have been implemented. In 2007, ORWH collaborated with OER in providing training sessions for grants management, review, and program staff on implementation of the NIH inclusion policy. These mandatory training sessions, “Sex/Gender, Race and Ethnicity Inclusion in Clinical Research,” were designed to help participants better understand congressionally mandated inclusion policies and how to implement them, reemphasized the vital role and responsibilities of NIH staff members in the management of grants, contracts, and cooperative agreements that involve human subjects research, and also highlighted the role of NIH staff, peer reviewers, and investigators in meeting inclusion policy requirements. In addition to these activities, NIH prepared the annual aggregate comprehensive reports: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research (see Appendix E) as well as the 2007 Biennial Report Certifying IC Compliance with the Inclusion Guidelines based upon IC Advisory Council reviews, as required by statute.

- For more information, see <http://orwh.od.nih.gov/inclusion.html>
- (E, I) (ORWH, OER)

**Developing Pediatric Drug Data:** Clinicians prescribing pharmaceuticals for sick infants and children face major gaps in the scientific data on safety and efficacy of pharmaceuticals for their young patients. Obtaining available data from drug trials in adults is often problematic because of important differences in the ways that drugs act in the bodies of adults and children.

Furthermore, data from adults cannot be used to characterize the effects of drugs on children's development and health over time. To respond to this concern, Congress passed the Best Pharmaceuticals for Children Act (BPCA) to support the additional research needed to test the effect of pharmaceuticals specifically for children. NIH, in collaboration with FDA and private-sector experts and organizations, maintains an extensive program for identifying priority drugs used "off label" in children—that is, prescribed without safety and efficacy data that would be required for FDA to approve or label them for use in children. This program involves requests to industry for needed pediatric research on priority "off-patent" drugs and conducting studies of priority drugs that industry declines to undertake. Under NICHD leadership, NIH Institutes participate in the ongoing BPCA program, including its funding.

- For more information, see <http://bpca.nichd.nih.gov/index.cfm>
- (NICHD)

**Web-Based Instruction on the Science of Sex and Gender in Human Health:** NIH, in collaboration with the Office of Women's Health, U.S. Food and Drug Administration (FDA), developed a Web-based course in 2006 to create a permanent foundation for sex and gender accountability in medical research and treatment. The course provides uniform instruction for physicians and scientists to meet the NIH and FDA requirements for inclusion, and the implications of sex and gender differences for policy, research, and health care. The course addresses the scientific basis of known sex and gender differences and explores the influence of sex and gender differences on health outcomes and illness. Each lesson is interactive and includes seminal references on topics such as developmental biology and pharmacogenomics.

- For more information see <http://sexandgendercourse.od.nih.gov/>
- (E) **ORWH**, NICHD, NHLBI, FDA, AHRQ

## Putting Clinical Research Results Into Practice

**Success in Treating Drug Addiction Internationally:** International efforts to disseminate effective drug abuse treatments have seen success in countries with epidemic opiate addiction/HIV problems. Because of NIH research demonstrating that addiction is a chronic, relapsing disease that can be effectively treated, a culture change is starting to occur in these countries. For example, despite experiencing severe drug problems, Malaysia lagged behind in the treatment of drug addiction and related disorders, even as it coped with having the second highest HIV prevalence rate among adult populations and the highest proportion of HIV cases from injection drug use. Historically, drug abusers were "rehabilitated" involuntarily in correctional facilities. and although 60 percent of prisoners had drug-related offenses, no or minimal treatment was available in prison, and no medications were permitted. This primarily criminal treatment approach had limited effectiveness, which led to widespread public dissatisfaction and the recent introduction of medications for addiction. These include naltrexone (1999), buprenorphine (2001), and methadone (2003). These drug treatment programs, rapidly embraced by the country's medical community, have resulted in tens of thousands of opiate-dependent patients receiving medical treatment. Now the Ministry of Health rather than the Ministry of Security has authority for providing medical treatment for heroin addiction. This shift signals a remarkable change in Malaysian policies and approaches to addiction and an

important opportunity to develop, implement, and disseminate effective treatments. A similar success story is starting to unfold in China as well.

- [Mazlan M, Schottenfeld RS, Chawarski MC. \*Drug Alcohol Rev\* 2006;25:473-8](#), PMID: 16939945
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIDA, NIAID)

**Value of Early HIV Screening, Testing, and Counseling:** HIV/AIDS disproportionately affects several minority groups, particularly African Americans. Although adult and adolescent African Americans make up ~13 percent of the population, they accounted for half of the new HIV/AIDS diagnoses in 2001-2005. This disparity is particularly striking because African Americans do not have higher rates of addiction or intravenous drug use than Whites. One contributing factor is that African Americans are often diagnosed with HIV infection at a later point in the illness, increasing their likelihood of progressing to AIDS and of transmitting the disease. As part of efforts to prevent late diagnosis and HIV spread, NIH is working to identify and address the cultural barriers to making HIV screening more acceptable and to strengthen the link between education, testing and counseling, and treatment within all ethnic groups. Indeed, NIH-supported modeling research has shown that routine HIV screening, even among populations with prevalence rates as low as 1 percent, is as cost-effective as screening for other conditions such as breast cancer and high blood pressure. These findings have important public health implications, recognized by the Centers for Disease Control and Prevention (CDC), which has called for increased HIV screening as part of its recommended guidelines. NIH is eager to advance new HIV rapid-screen technologies and counseling in community drug treatment programs and in criminal justice settings.

- For more information, see <http://www.drugabuse.gov/ResearchReports/hiv/hiv.html>
- For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIDA)

**Diagnostic Genetic Test Translation From the Research Laboratory to the Clinic:** Because the majority of rare diseases are genetic disorders, genetic testing is an essential part of diagnosis and treatment. Few incentives exist for translating research findings into clinical tests that are available to the public. To address this gap, NIH created the Collaboration, Education and Test Translation (CETT) for Rare Genetic Diseases pilot program. The CETT pilot program brings new genetic and diagnostic tests to patients, encourages clinical laboratory and research collaborations, and stimulates dialogue with patient advocacy groups. Goals include developing models for information on clinical uses of the test; how the test results will be interpreted for clinical care providers, patients, and their families; methods to collect and store in publicly accessible databases the clinical information on each sample necessary to interpretation, while at the same time respecting confidentiality; and methods to collect and store test result information in publicly accessible databases. Since February/March 2006, 21 tests have been reviewed and 19 have been approved. The CETT pilot program has seen the successful development of 10 clinical tests for Cornelia de Lange syndrome, Joubert syndrome, cherubism, X-linked chondrodysplasia punctata, Kallmann syndrome, progressive familial intrahepatic cholestasis, Russell Silver syndrome, MPS VI, Niemann Pick disease A/B, and X-linked periventricular

nodular heterotopia. These tests address more than 18 conditions and 13 genes. Tests for primary ciliary dyskinesia, infantile neuroaxonal dystrophy, and arginase deficiency will be released later this year and more tests are under development.

- For more information, see <http://www.cettprogram.org>
- (E/I) (ODP/ORD, NLM)

**Advances in Oral Cancer Detection:** The first product of a current NIH-funded research project to integrate new technologies into a reliable clinical protocol to improve oral cancer detection and survival has reached the market. Researchers report success using a customized optical device that allows dentists to visualize in a completely new way whether a patient might have a developing oral cancer. The simple, handheld device emits a cone of light into the mouth that excites molecules within our cells, causing them to absorb the light energy and re-emit it as visible fluorescence. Remove the light, and the fluorescence disappears. Changes in the natural fluorescence of healthy tissue can indicate light-scattering changes caused by developing tumor cells. Health care providers shine a light onto a suspicious sore in the mouth, look through an attached eyepiece, and check for changes in color. Normal oral tissue emits a pale green fluorescence, while early tumor cells appear dark green to black. The instrument is an effective screening adjunct and is useful for helping surgeons determine how far to extend the surgical borders when removing tissue for biopsies.

- For more information, see <http://clincancerres.aacrjournals.org/cgi/content/full/12/22/6716>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*.
- (E) (NIDCR)

**Head Off Environmental Asthma in Louisiana:** Nearly 20 million people, 6.5 million of them children, suffer from asthma in the United States, and minorities are disproportionately represented. NIEHS with NCMHD and others cofunds the HEAL Project (Head Off Environmental Asthma in Louisiana) to assess the impact on asthma in New Orleans children of environmental health conditions that were caused and exacerbated by Hurricane Katrina, as well as to implement an intervention program to address these problems. The project's three main goals are to conduct an extensive epidemiology study to assess the nature of the environmental and psychological impacts of Hurricane Katrina and subsequent flooding on children in New Orleans; to examine the genetic and environmental risk factors for asthma, including genetic susceptibility to mold toxins, and gene interactions; and to design, implement, and evaluate a case management program to meet the health care needs of children with asthma in a disrupted and highly challenging environment. The project has a clear plan for informing the community of the goals, implementation, and outcome, as well as for receiving input from the community.

- For more information, see <http://www.niehs.nih.gov/heal/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (NIEHS, NCMHD)

**The Report on Carcinogens, Eleventh Edition:** More than 80,000 chemicals are registered for use in the United States. Each year, an estimated 2,000 new ones are introduced for use in such everyday items as foods, personal care products, prescription drugs, and household cleaners. In

response to concerns about the relationship between environment and cancer, the National Toxicology Program (NTP), an interagency program led by NIEHS, produces the Report on Carcinogens (RoC) biennially. The RoC is an informational scientific and public health document that identifies and discusses agents, mixtures, or exposure circumstances that may pose a hazard to health by virtue of their carcinogenicity. It includes data on the carcinogenicity, genotoxicity, and biologic mechanisms of the listed substances in humans and/or animals, the potential for human exposure to these substances, and Federal regulations to limit exposures.

- For more information, see [http://ntp.niehs.nih.gov/files/11thROC\\_factsheet\\_1-31-05.pdf](http://ntp.niehs.nih.gov/files/11thROC_factsheet_1-31-05.pdf)
- For more information, see <http://ntp.niehs.nih.gov/index.cfm?objectid=72016262-BDB7-CEBA-FA60E922B18C2540>
- (NIEHS)

**Blending Initiative: Bench to Bedside to Community:** Efforts to systematically move science-based interventions and practices into community settings are exemplified in the testing of drug abuse treatment approaches directly in the community settings where they will be used by drug treatment professionals trained to implement them. This work is occurring through the National Drug Abuse Treatment Clinical Trials Network (CTN) at NIH, which involves practitioners from community treatment programs (CTPs) not only in formulating research protocols, but also in providing real-world feedback on their success and feasibility. The adoption of the addiction medication buprenorphine by a growing number of CTPs treating patients with opioid addiction is an example of real culture change issuing from NIH clinical research. A similar approach is under way to enhance treatment for drug-addicted individuals involved with the criminal justice system through research supported under the Criminal Justice—Drug Abuse Treatment Studies (CJ-DATS) initiative. It seeks to achieve better integration of drug abuse treatment for criminal offenders with other public health and public safety forums, and is a collaborative effort by NIH and multiple Federal agencies and health and social service professionals. These initiatives are helping to change the culture of how drug abuse treatment is delivered in this country.

- For more information, see <http://www.drugabuse.gov/CTN/>
- For more information, see <http://www.cjdats.org/>
- For more information, see <http://www.drugabuse.gov/Blending/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDA) (GPRA Goal)

**Treatments to Fight Methamphetamine Addiction:** The abuse of methamphetamine—a potent and highly addictive psychostimulant—is a serious problem in the United States. Methamphetamine abuse can have devastating medical, psychological, and social consequences. Adverse health effects include memory loss, aggression, psychotic behavior, heart damage, and abnormal brain function. Methamphetamine abuse also contributes to increased transmission of hepatitis and HIV/AIDS, and can spawn increased crime, unemployment, and other social ills. The good news is that methamphetamine abuse and addiction are treatable, and people do recover. As methamphetamine abuse has increased, so has NIH’s support of research to combat it, including research on genetics, brain development, and translation of findings. This research has led to the development of two effective behavioral therapies for methamphetamine addiction: (1) the Matrix Model, consisting of a 16-week program that includes group and individual



therapy and addresses relapse prevention, behavioral changes, establishment of new drug-free environments, etc. and (2) Motivational Incentives for Enhanced Drug Abuse Recovery, a cost-effective incentive method for cocaine and methamphetamine addiction, shown to sustain abstinence in twice the number of subjects engaged in treatment as usual. Increasingly, community treatment providers nationwide are implementing motivational incentives as part of drug addiction treatment.

- For more information, see <http://www.drugabuse.gov/ResearchReports/Methamph/Methamph.html>
- For more information, see <http://www.drugabuse.gov/Testimony/6-28-06Testimony.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDA)

**Research to Strengthen the Dissemination and Implementation of Evidence-Based Mental Health Interventions:** NIH continues to support research designed to strengthen the dissemination and implementation of evidence-based mental health practices. NIH released a Program Announcement (PAR) to encourage transdisciplinary teams of scientists and practice stakeholders to work together to develop innovative approaches for identifying and overcoming barriers to the adoption of evidence-based interventions. This PAR serves as the basis for a GPRA Goal as well. NIH also supports research designed to enhance implementation by providing evidence of intervention benefits not just to the individual, but to a broader system as well. For example, a recent study reported that providing a minimal level of enhanced care for employees' depression would result in significant savings to employers.

- [Wang PS et al., Arch Gen Psychiatry 2006;63:1345-53](#), PMID: 17146009
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-07-086.html>
- For more information, see <http://www.nimh.nih.gov/press/cost-benefitsimulation.cfm>
- (E/I) (NIMH, NCI, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NINR) (GPRA Goal)

**Science of Dissemination and Implementation:** Relatively little is known about how to ensure that the lessons learned from research inform and improve the quality of health and human services in the population at large. The goals of the program announcement, *Dissemination and Implementation Research in Health*, and conference, *Building the Science of Dissemination and Implementation in the Service of Public Health* (September 2007), are to support innovative approaches to identifying, understanding, and overcoming barriers to the adoption, adaptation, implementation, and maintenance of evidence-based practices by health providers, insurers, policymakers, and the public.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-07-086.html>
- For more information, see <http://obssr.od.nih.gov/di2007/index.html>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NCI, NHLBI, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIMH, NINR, OBSSR, ODS)

**Translational Research for the Prevention and Control of Diabetes and Obesity:** NIH is supporting research projects to explore ways to bring knowledge from successful clinical research into medical practice and community settings. Studies are seeking to develop effective, sustainable, and cost-effective methods to prevent and treat type 1 and type 2 diabetes and



obesity in clinical health care practice and other real world settings. Many of these studies focus on minority populations disproportionately burdened by type 2 diabetes and obesity.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIDDK)

**Comprehensive Review of Meditation Research:** A recent comprehensive literature review on meditation research included over 800 studies of a variety of forms of meditation for a number of chronic conditions, including hypertension, coronary artery disease, and substance abuse. The review concludes that there are promising indications that meditation may have beneficial effects on a variety of outcomes including blood pressure, perceived stress, anxiety, and behavioral modification, but additional and higher quality research is needed.

- For more information, see <http://www.ahrq.gov/clinic/tp/medittp.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NCCAM)

**Spine Patient Outcomes Research Trial (SPORT):** Before SPORT, many patients with back pain were conflicted about whether to undergo surgery. Now, people who have back pain due to a herniated disc can be assured that a surgical procedure called lumbar discectomy is generally effective in relieving pain from herniated discs, but—if their pain is tolerable—their symptoms will likely subside even without surgery, over time. On the other hand, if a patient has spondylolisthesis with stenosis, they are likely to benefit more from decompression and fusion surgery than from nonoperative treatments.

- [Weinstein JN, et al. \*JAMA\*. 2006;296:2441-50](#), PMID: 17119140
- [Weinstein JN, et al. \*JAMA\*. 2006;296:2451-9](#), PMID: 17119141
- [Weinstein JN, et al. \*N Engl J Med\*. 2007;356:2257-70](#), PMID: 17538085
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/backpain\\_surgery.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/backpain_surgery.asp)
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Press\\_Releases/2007/06\\_28.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/06_28.asp)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIAMS, NIOSH, ORWH)

**Neonatal Onset Multisystem Inflammatory Disease (NOMID):** For children and young adults who suffer from a rare and debilitating disorder called NOMID, the arthritis drug anakinra brings marked improvement in both symptoms and the inflammation underlying the disease.

- [Goldbach-Mansky R, et al. \*Arthritis Rheum\*. 2007;56:2099-101; author reply 2101-2](#), PMID: 17530657
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Press\\_Releases/2006/08\\_09.asp](http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/08_09.asp)
- (NIAMS)

## Bolstering the Research Continuum

**Clinical Trials Education:** Materials represent a collection of over 20 resources developed to increase awareness and participation in cancer prevention and treatment clinical trials. These materials include workbooks, a guide for community outreach, a trainer's guide, online courses for health professionals, DVDs, and slide sets to assist in education programs.

- For more information, see <http://cancer.gov/publications>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (NCI)

### **Health Care Delivery Consortia To Facilitate Discovery and Improve Quality of Cancer:**

NIH supports several research consortia that are designed to enhance understanding of cancer control across the continuum of prevention, screening, and treatment within the context of health care delivery.

- ▷ The most comprehensive of these initiatives, the **Cancer Research Network (CRN)**, seeks to improve the effectiveness of preventive, curative, and supportive interventions for major and rare tumors. The CRN consists of the research programs, enrolled populations, and data systems of 13 health maintenance organizations covering care for over 9 million enrollees, or 3 percent of the U.S. population. This initiative uses a consortium of delivery systems to conduct research on cancer prevention, early detection, treatment, long-term care, and surveillance. Given its large and diverse populations, the CRN is uniquely positioned to study the quality of cancer care in community-based settings and to explore rare conditions. Seminal research includes, for example, CRN research documenting specific gaps in implementing effective tobacco cessation services among clinicians, reasons for late diagnosis of breast and cervical cancer, more rapid uptake in the use of aromatase inhibitors in comparison to tamoxifen in treatment for breast cancer, and examination of the role of a number of common drugs and cancer outcomes using its large and automated pharmaceutical databases.
- ▷ In the area of the evaluation of cancer screening in clinical care, the [Breast Cancer Surveillance Consortium \(BCSC\)](#) is a collaborative network of mammography registries linked to tumor and/or pathology registries designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. Because of the vast size and continually updated clinical information in this research initiative, the BCSC is responsible for research that for the first time documented the falling incidence of hormone replacement therapy among screened women, quantified the extent of difference in the association of breast density with breast cancer risk among pre- and postmenopausal women, and identified that although biopsy rates are twice as high in the United States in comparison to the United Kingdom, cancer detection rates are very similar in the two countries.
- ▷ In an effort to address how characteristics of patients, providers, and care delivery systems affect the cancer management and treatment services that patients receive, as well as the relationship between cancer-related clinical practices and outcomes, including patient-centered outcomes, such as symptom control and quality of life, the **Cancer Care and Outcomes Research Surveillance Consortium (CanCORS)** was established. It supports prospective cohort studies on 10,000 patients with newly diagnosed lung or colorectal

cancers across geographically diverse populations and health care systems and examines issues related to health outcomes, costs, and patient-centered issues such as symptom control and quality of life.

- For more information, see <http://crn.cancer.gov/>
- For more information, see <http://breastscreening.cancer.gov>
- For more information, see <http://healthservices.cancer.gov/cancers/>
- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*, and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NCI)

**Clinical and Translational Science Award (CTSA) Program Progress:** Since the inception of the CTSA program, NIH has made significant progress in building a national consortium for clinical and translational research. The first CTSA awards were made in September 2006 to 12 academic health centers (AHCs) throughout the country, along with 52 planning grants to help institutions prepare to join the Consortium in the future. To meet the goal of 60 CTSA sites by 2012, NIH has developed and released annual funding opportunity announcements, which will provide AHCs, including those with General Clinical Research Centers (GCRCs), an opportunity to build on their existing resources and transform into this new integrated program. The CTSA infrastructure will not only enhance the research capacity already developed through the GCRC program, but will also create an integrated home for clinical and translational research and training. During the transition to the CTSA program, NIH is continuing to work closely with GCRCs and is allowing them flexibility on a case-by-case basis to plan and apply for a CTSA award.

- For more information, see <http://www.ctsaweb.org/>
- (E) (NCRR)

**Clinical Research Networks:** Clinical research is essential for translating laboratory findings into evidence-based interventions targeting an array of public health concerns. Many research programs involve collaborative networks, drawing scientists together to bring the benefits of clinical research to high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. Among such networks that have generated significant findings to advance medical practice and improve public health are the Maternal and Fetal Medicine Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, and Global Network for Women's and Children's Health Research.

- For more information, see <http://www.bsc.gwu.edu/mfmu/>, <http://neonatal.rti.org>
- For more information, see <http://www.nichd.nih.gov/about/org/crmc/opp/index.cfm>
- For more information, see <http://www.cpccrn.org/>, <http://www.pfdnetwork.org/>
- For more information, see <http://www.nichd.nih.gov/research/supported/TBI.cfm>
- For more information, see <http://www.nichd.nih.gov/publications/pubs/upload/GlobalNetwork.pdf>
- (E) (NICHD, FIC, NCCAM, NCI, NIDCR, NIDDK, ORWH)

**Centers of Excellence for Research on CAM (CERC), Developmental Centers for Research on CAM (DCRCs), and International Centers for Research on CAM:** These Centers bring cutting-edge scientific technology to programs of research on the usefulness, safety, and

mechanisms of action of various CAM interventions. Based in collaborations between established biomedical research scientists and experts in CAM or traditional medicine, these programs are also aimed at enhancing the global state of research capacity on CAM. For example, the CERCs are led by scientists with outstanding research records who direct teams of investigators with both CAM and conventional scientific expertise. During the first 3 years of the CERC program, awardees have made sentinel advances in our understanding of the scientific basis for the effects of acupuncture through the use of modern brain imaging, and they have explored innovative approaches to the treatment of asthma with antioxidants and approaches based on traditional Chinese medicine (TCM). Other CERCs are focusing on (1) the study of acupuncture and TCM herbal treatments of arthritis, (2) the effects of mindfulness meditation on the progression of HIV/AIDS, and (3) the mechanisms of action of millimeter wave therapy (use of low-intensity millimeter wavelength electromagnetic waves) for a variety of chronic conditions. NIH will fund additional CERCs in late FY 2007.

- For more information, see <http://nccam.nih.gov/training/centers/>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCCAM)

**Resuscitation Outcomes Consortium:** Recognizing the critical importance of early intervention for victims of cardiopulmonary arrest and traumatic injury, in FY 2004 NIH and its U.S. and Canadian partners initiated the Resuscitation Outcomes Consortium, a large-scale network to conduct clinical trials of promising approaches to improving outcomes. During FY 2006-2007, two Consortium clinical trials began enrolling patients—one to compare the efficacy of three fluids for initial resuscitation of hypotensive or brain-injured patients, and the other to test two strategies for increasing blood flow during cardiopulmonary resuscitation. The Consortium also established a pre-hospital Cardiac Arrest and Trauma Registry across the United States and Canada. In addition, emergency medicine fellowship training programs established at several study sites are enhancing training in resuscitation medicine.

- For more information, see <https://roc.uwtc.org/>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NHLBI, NINDS)

**Alzheimer's Disease Cooperative Study (ADCS):** Much of the AD-related clinical research supported by NIH takes place through the ADCS. The study involves a consortium of centers in the United States and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of AD or predict the disease's development in vulnerable people. To date, approximately 4,600 people have participated in the trials. In FY 2007, new studies included a trial to demonstrate whether intravenous immunoglobulin (IVIg) is clinically useful for treating AD and a trial to examine whether treatment with docosahexaenoic acid (DHA), an omega-3 fatty acid, will slow cognitive decline in patients with AD.

- For more information, see <http://www.nia.nih.gov/NewsandEvents/PressReleases/PR20061017ADCS.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIA)

**The Immune Tolerance Network:** In 2007, NIH renewed support for the Immune Tolerance Network (ITN), a consortium of over 80 investigators in the United States, Canada, Europe, and Australia. The ITN studies and tests new drugs and therapies for autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based on stimulating immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to “reeducate” the immune system to eliminate harmful immune responses and graft rejection while preserving protective immunity against infectious agents. The ITN has established state-of-the art core laboratory facilities to study the underlying mechanisms of candidate therapies and to monitor tolerance. In 2006, the ITN reported that a novel DNA-based ragweed allergy therapy could achieve long-lasting symptom reduction after only 6 weeks of therapy, compared to current methods that require years of biweekly injections. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse progression of autoimmune diseases; approaches to treat and prevent asthma and allergic disorders such as food allergy; and therapies to prevent liver and kidney transplant rejection without causing harmful suppression of immunity.

- For more information, see <http://www.immunetolerance.org/>
- For more information, see <http://content.nejm.org/cgi/content/abstract/355/14/1445>
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAID)

**A Multidisciplinary Approach to Nicotine Addiction:** Nicotine addiction is the number one preventable public health threat, with enormous associated morbidity, mortality, and economic costs. NIH-supported research has generated new knowledge to support the development of more effective prevention messages and treatment approaches. Several notable examples characterize NIH’s multidisciplinary approach to targeting the best treatment (or combination of treatments) for nicotine addiction. Genomic studies have recently uncovered a series of genes associated with nicotine addiction that could provide new targets for medications development and for the optimization of treatment selection. Pharmacologic studies, critical to understanding the basis of nicotine’s mode of action, have recently revealed that its addictiveness may hinge upon its ability to slowly shut down or desensitize the brain’s response to nicotine. A recent imaging study indicated that a part of the brain called the insula may play an important role in regulating conscious craving. This exciting finding provides a new target for research into the neurobiology of drug craving and for development of potentially more effective smoking cessation and other addiction treatments. Results of a Phase II clinical trial strongly suggest that a nicotine vaccine, which works by preventing nicotine from ever reaching the brain, may be a particularly useful tool for cessation programs in the not-too-distant future.

- For more information, see <http://www.drugabuse.gov/ResearchReports/Nicotine/Nicotine.html>
- This example also appears in Chapter 3: *Genomics*, Chapter 2: *Cancer*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NIDA, NCI) (GPRA Goal)

**Asthma Exacerbations—Biology and Disease Progression:** In FY 2005, NIH began a basic and clinical research initiative to improve understanding of the causes of asthma exacerbations and to facilitate the development of more effective treatments to control symptoms. Twelve projects have been funded under this initiative. As part of the NIH GPRA reporting activity, NIH

is assessing the progress of the initiative through an ongoing GPRA Goal, “to identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating exacerbations, by 2014.”

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-029.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHLBI, NIAID) (GPRA Goal)

**Programs to Accelerate Medications Development for Alcoholism Treatment:** Alcoholism is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ from one drinker to another. Therefore a diverse repertoire of medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure their interest in taking promising compounds through the final phase clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- ▷ Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies have already produced several targets for human studies that are now under way, such as rimonabant, a cannabinoid CB1 receptor blocker, and antalarmin, a corticotropin-releasing factor receptor blocker.
  - ▷ A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early human trials network.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
  - (E/I) (NIAAA) (GPRA Goal)

**Antimicrobial Resistance Research:** Antimicrobial resistance, caused by factors such as overuse of antibiotics, is severely jeopardizing the utility of many “first line” antimicrobials and has emerged as a major public health threat. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. For example, clinical studies are testing interventions for community-acquired multidrug-resistant *Staphylococcus aureus* (CA-MRSA) infection and to evaluate the efficacy of off-patent antimicrobials. A clinical study is evaluating the efficacy of antimicrobials in young children with acute ear infections through the comparison of symptom resolution in children receiving antimicrobial therapy versus placebo. Research initiatives such as “Sepsis and CAP [Community-Acquired Pneumonia]: Partnerships for Diagnostics Development” and “Partnerships to Improve Diagnosis and Treatment of Selected Drug-Resistant Healthcare-Associated Infections” are supporting the development of new diagnostics to facilitate the optimization of antimicrobial therapy and eliminate the overuse of broad-spectrum



antimicrobials. NIH will continue to address high-priority research questions regarding resistance to help public health officials hold the line against drug-resistant microbes.

- For more information, see <http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm>.
- For more information, see <http://www3.niaid.nih.gov/topics/AntimicrobialResistance/research/default.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E/I) (NIAID) (GPRA Goal)

**Improving Transplantation Outcomes:** Organ transplantation prolongs survival and improves quality of life for children and adults suffering from a wide range of diseases. Yet despite advances in organ transplantation, organ recipients rarely achieve normal life expectancy and health-related quality of life. To improve the outcome of organ transplantation, NIH supports the Clinical Trials in Organ Transplantation (CTOT) initiative, a cooperative, multisite consortium that conducts interventional and observational clinical studies as well as studies of the mechanisms of graft rejection. The consortium includes 34 clinical sites and 30 immunology laboratories at 13 universities. Five clinical trials are currently enrolling individuals undergoing kidney, heart, liver, or lung transplantation.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIAID, NHLBI) (GPRA Goal)

**Clinical, Operational, and Health Services Research Training (noncommunicable diseases):**

To successfully develop and implement health interventions in the developing world, a well-trained cadre of scientists is needed to plan, design, and conduct clinical, operational, health services, and prevention science investigations. NIH funds research training in these disciplines, which supports the development and implementation of evidence-based interventions for non-communicable disorders/diseases in low- to middle-income countries. Projects funded by this program require collaboration between U.S. and foreign institutions and include epidemiology, health services, and genetics research on major psychiatric disorders in India; a study examining the impact of institutionalization on children in Turkey; and multidisciplinary training in substance abuse research in Eastern Europe.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/icohrta/index.htm](http://www.fic.nih.gov/programs/training_grants/icohrta/index.htm)
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (FIC, NIA, NIDA, NIDCR, NIMH, NINDS, ODS)

**HIV Research Training Programs:** The AIDS International Training and Research Program (AITRP) builds institutional, national, and regional HIV research capacity in low- and middle-income countries. Over the past 19 years, this program has been responsible for many of the first generation of research scientists from these countries, with many more in the pipeline. The program offers multidisciplinary biomedical, behavioral, and social science research training to a wide range of professionals. Building on the AITRP, the Clinical, Operational and Health Services Research Training Program for HIV/AIDS and TB (ICOHRTA AIDS/TB) began in 2002 to strengthen the capacity for clinical, operational, and health services research in low- and middle-income countries where AIDS, TB, or both are significant problems. Through training health professionals who reach across the spectrum of clinical and public health research, this program is strengthening the capacity of scientists, program managers and policymakers to

evaluate and better implement large-scale prevention, treatment, and care interventions that are locally relevant and effective. Many local leaders of programs supported by the President's Emergency Plan for AIDS Relief have received or are receiving their research training through the AITRP and the ICOHRTA AIDS/TB programs.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/aitrp/index.htm](http://www.fic.nih.gov/programs/training_grants/aitrp/index.htm)
- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/icohrta/aids\\_tb.htm](http://www.fic.nih.gov/programs/training_grants/icohrta/aids_tb.htm)
- This example also appears in Chapter 3: *Research Training and Career Development* and Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (FIC, NCI, NIAID, NHLBI, NIDA, NIDCR, NIMH, NINDS, NINR, OAR, ORWH)

**Clinical Trials Networks:** These networks are part of the infrastructure that allows patients and community physicians access to national studies, facilitating the ability to put successful regimens into practice:

- ▷ The Community Clinical Oncology Program (CCOP) is a network for conducting cancer prevention and treatment clinical trials. In 23 years of CCOPs, over 200,000 people have enrolled in treatment and prevention trials. An example is the Study of Tamoxifen and Raloxifene trial (STAR), which compares the effectiveness of these two drugs for reducing the incidence of breast cancer in postmenopausal women at increased risk of the disease. Initial results indicate that raloxifene is as effective as tamoxifen with fewer side effects.
- ▷ Cooperative Group Trials consist of researchers, Cancer Centers, and community doctors who investigate new cancer treatment, prevention, early detection, quality of life, and rehabilitation. They involve more than 1,700 institutions, thousands of individual investigators, and more than 22,000 patients each year. These trials are testing therapies that demonstrate improvement to overall patient survival. For example, the Bevacizumab with Platin-Based Chemotherapy study showed that when the monoclonal antibody [bevacizumab](#) is added to a paclitaxel-carboplatin chemotherapy regimen for patients with non-small cell lung cancer (NSCLC), their overall survival, progression-free survival, and response rates significantly increased.
- ▷ The NCI Community Cancer Centers Program (NCCCP) is a 3-year pilot program to test the concept of a national network of community cancer centers to alleviate inadequate care delivery. NCCCP will develop and evaluate programs on community-based cancer care and identify ways to facilitate their broader engagement in cancer research.
  - For more information, see <http://www.cancer.gov/STAR>
  - For more information, see <http://dcp.cancer.gov/programs-resources/programs/ccop>
  - For more information, see <http://ctep.cancer.gov/>
  - For more information, see <http://ncccp.cancer.gov/>
  - This example also appears in Chapter 2: *Cancer*.
  - (E) (NCI)

**The Radiation Research Program (RRP):** The RRP establishes priorities, allocates resources, and evaluates the effectiveness of radiation research and coordinates with other Federal radiation research programs. RRP has established guidelines for studying proton radiation therapy. Major

trials are evaluating radiation dose escalation, as well as novel combinations of chemotherapy with concomitant boost radiation therapy, in non-small cell lung cancer.

- [Bonner JA, et al. \*N Engl J Med.\* 2006;354:567-78](#), PMID: 16467544
- [Bao S, et al. \*Nature.\* 2006;444:756-60](#), PMID: 17051156
- This example also appears in Chapter 2: *Cancer*.
- (I) (NCI)

**The NCI Vaccine Program:** The Vaccine Program develops novel vaccines for cancer immunotherapy and prevention, and HIV. The program encourages collaborations, identifies organizational and reagent needs for the community, and develops the optimal infrastructure for vaccine development and novel clinical trial approaches. Gardasil, the first vaccine to prevent cervical cancer induced by HPV, is now available to potentially save over 5,000 U.S. women's lives each year. This FDA-approved vaccine resulted from the basic research performed at NIH producing a prototype vaccine and the observation that linked the human papillomavirus (HPV) and cervical cancer.

- This example also appears in Chapter 2: *Cancer* and Chapter 2: *Infectious Diseases and Biodefense*.
- (E/I) (NCI)

**Career Development for Veterinarians in Translational Biomedical Research:** Two recent reports from the National Academies, *National Need and Priorities for Veterinarians in Biomedical Research* and *Critical Needs for Research in Veterinary Science*, have confirmed the shortage of veterinarians involved in biomedical research. To address the shortage, NIH provides career development awards in biomedical research specifically for veterinarians and veterinary students. Mentored Career Development Awards to veterinarians serve as a bridge for postdoctoral fellows to become independent investigators. In FY 2006, 25 career development awards were made to young veterinary investigators to increase the number of researchers in this field. Additionally, an initiative that began in FY 2007 encourages the specialization of veterinarians in clinical medicine at NIH-supported primate centers to address the shortage of clinical veterinary support for research primate colonies.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-RR-06-006.html>
- For more information, see [http://www.ncrr.nih.gov/career\\_development\\_opportunities/individual\\_training\\_grants/](http://www.ncrr.nih.gov/career_development_opportunities/individual_training_grants/)
- *National Need and Priorities for Veterinarians in Biomedical Research:* [http://books.nap.edu/catalog.php?record\\_id=10878](http://books.nap.edu/catalog.php?record_id=10878)
- *Critical Needs for Research in Veterinary Science:* [http://books.nap.edu/catalog.php?record\\_id=11366](http://books.nap.edu/catalog.php?record_id=11366)
- (E) (NCRR)

**Collaborative Community-Based Research:** NIH is focusing on strategies and best practices for conducting collaborative community-based clinical and translational research, particularly in minority communities and other medically underserved communities where health disparities persist. The Institutional Development Award (IDeA) and Research Centers in Minority Institutions (RCMI) programs are encouraging efforts to build and strengthen partnerships among Government agencies and academic and private-sector organizations that are also working to improve community health outcomes. Translational, community-based research

funded in several IDeA states and RCMI-supported Centers, in both urban and rural settings. is focusing on:

- ▷ Enhancing recruitment and retention of research subjects through community buy-in
- ▷ Implementing practical and effective research protocols in community health care settings
- ▷ Developing versatile and sustainable core research infrastructure to encourage community participation and leverage existing resources

In addition, in FY 2007 NIH conducted two workshops to gather specific recommendations from the community that will help shape future initiatives to enhance clinical and translational research in minority and other medically underserved communities ([www.esi-bethesda.com/ncrrworkshops/Fostering/index.aspx](http://www.esi-bethesda.com/ncrrworkshops/Fostering/index.aspx)). Workshop subjects included other DHHS-agencies, such as AHRQ, CDC, the Indian Health Service, and HRSA.

- For more information, see [www.ncrr.nih.gov/research\\_infrastructure](http://www.ncrr.nih.gov/research_infrastructure)
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCRR)

**Institutional Development Award (IDeA) Program:** The NIH IDeA program fosters health-related research and improves the competitiveness of investigators in 23 states and Puerto Rico that historically have not received significant levels of competitive research funding from NIH. The IDeA program supports multidisciplinary centers and statewide collaborative partnerships that increase institutions' capacity to conduct cutting-edge biomedical research. IDeA supports faculty development and enhancement of research infrastructure at institutions and also promotes collaborative community-based research, particularly in minority communities and other medically underserved communities where health disparities persist. The IDeA program supports the IDeANet initiative, which is expanding access to high-performance computational resources for data-intensive science applications and providing bioinformatics software tools and training to investigators. IDeANet began with Lariat, a pilot program that has enabled connectivity in six States (Alaska, Hawaii, Idaho, Montana, Nevada, and Wyoming). IDeANet ultimately will enable all institutions in the IDeA program, as well as participants in NIH's Research Centers in Minority Institutions program, to engage in national and international collaborations.

- For more information, see [http://www.ncrr.nih.gov/research\\_infrastructure/institutional\\_development\\_award/](http://www.ncrr.nih.gov/research_infrastructure/institutional_development_award/)
- For more information, see IDeA program evaluation GPRG Goal 8.4.
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCRR) (GPRG Goal)

**Research Centers in Minority Institutions (RCMI):** The Research Centers in Minority Institutions (RCMI) Program began in 1985 in response to congressional report language (House Report 98-911 on the Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill for FY 1985 [July 26, 1984, pages 78-79) directing funds to “establish research centers in those predominantly minority institutions which offer doctoral degrees in the health professions or the sciences related to health.” RCMI support includes funds to recruit established and promising researchers, acquire advanced instrumentation, modify laboratories for competitive research, and fund core research facilities and other research support. Because many

investigators at RCMI institutions study diseases that disproportionately affect minorities, NCCR support serves the dual purpose of bringing more minority scientists into mainstream research and enhancing studies of minority health. The next step in increasing the research capacity of the RCMI is to link each of them together.

- For more information, see [http://www.ncrr.nih.gov/research\\_infrastructure/research\\_centers\\_in\\_minority\\_institutions/](http://www.ncrr.nih.gov/research_infrastructure/research_centers_in_minority_institutions/)
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCRR, NCMHD, NHLBI, NIA, NIAID, NIAMS, NICHD, NIDA, NIDDK, NIMH)

**Shared Instrumentation Grant and High-End Instrumentation Programs:** The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the \$100,000-\$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the \$750,000-\$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located on core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2006 and 2007 the SIG program funded a total of 264 grants for \$95.2 million; the HEI funded a total of 39 awards for \$55.9 million.

- For more information, see [http://www.ncrr.nih.gov/biomedical\\_technology/shared\\_instrumentation/](http://www.ncrr.nih.gov/biomedical_technology/shared_instrumentation/)
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NCRR)

**Diabetic Retinopathy Clinical Research Network (DRCR.net):** Diabetes, a leading cause of blindness in working-age adults, causes blood vessels in the retina to leak and can lead to retinal detachment. Laser treatment is effective but is not optimal. DRCR.net is a collaborative, nationwide public-private network of eye doctors and investigators in 165 clinical sites conducting clinical research of diabetes-induced retinal disorders (diabetic retinopathy, diabetic macular edema) with the aim of evaluating promising new therapies. DRCR.net serves as a model network to provide the infrastructure to facilitate multiple concurrent and consecutive clinical trials of innovative therapies, to rapidly develop and initiate new protocols, and to interact with industry partners while ensuring scientific rigor and high ethical standards.

- For more information, see <http://public.drcr.net>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NEI)

**Retinal Neurodegeneration Program:** This new multidisciplinary intramural research program combines basic, preclinical, and translational research to develop and test therapeutic interventions in several retinal degenerative diseases. These interventions include gene therapy,

small molecules, neurotrophic factors, and cell-based systems, in combination with a variety of treatment delivery technologies.

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (NEI)

**Multiplex Initiative:** With the completion of sequencing of the human genome, genetic susceptibility tests that give “personalized” information about risk for a variety of common health conditions are now being developed and marketed. This genetic information ultimately will improve primary care by enabling more personalized treatment decisions for common diseases like diabetes and heart disease. This information also might motivate patients to change unhealthy behaviors. NIH investigators have teamed with the Group Health Cooperative in Seattle and the Henry Ford Health System in Detroit to launch a study to investigate the interest level of healthy, young adults in receiving genetic testing for eight common conditions. Called the Multiplex Initiative, the study will also look at how people who decide to have the tests interpret and use the results in making health care decisions. One thousand subjects who meet the study’s eligibility requirements will be offered free multiplex genetic testing. The testing is designed to yield information about 15 different genes that play roles in common diseases such as type 2 diabetes and coronary heart disease. Trained research educators will make followup telephone calls to help subjects interpret and understand test results and subjects will receive newsletters to update them on new developments about the tested genes. This research should provide insights into how best to utilize the powerful tools of genomic medicine to improve health.

- For more information, see <http://www.genome.gov/25521052>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (I) (NHGRI)

**Comprehensive Sickle Cell Centers (CSCCs):** The CSCCs were established in 1972, in response to a Presidential initiative and a congressional mandate, to support multidisciplinary research to expedite development and application of new knowledge for improved diagnosis and treatment of sickle cell disease. In addition to basic research, training, and patient services activities, the CSCCs currently support multicenter Phase II trials, neurocognitive and neuroimaging studies, development of a collaborative database, and a study on the epidemiology of priapism (painful, prolonged erection) among sickle cell patients. Ten centers are funded through FY 2007, and the program will be renewed in FY 2008.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-008.html>
- For more information, see <http://www.sicklecell-info.org/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NHLBI)

**Dental Practice-Based Research Networks:** NIH has established three regional dental practice-based research networks (PBRNs) to perform clinical research in areas that are not well suited for the academic or laboratory setting. Each PBRN involves 100 or more research-trained dentists and dental hygienists who will propose and conduct studies across a range of patient and



clinical conditions. The PBRNs also will collect information to generate data on disease, treatment trends, and the prevalence of less common oral conditions. The success of the PBRNs will be rooted in their focus on real-world clinical issues and their ability to generate information that will be of immediate value to practitioners and patients alike. For example, all three networks are collaborating to expand the evidence base on an emerging public health question: a suspected increased risk of a serious condition known as osteonecrosis of the jaw for individuals who have received therapy with a kind of drug known as bisphosphonates. Dental PBRNs have the potential to generate a body of high-quality clinical research data in a relatively short period of time. Most importantly, their research will substantially enhance the evidence base that clinicians use to inform treatment decisions, translate newer information into daily practice, and directly affect and improve care.

- For more information, see <http://www.nidcr.nih.gov/NewsandReports/NewsReleases/NewsRelease03312005.htm>
- (E) (NIDCR)

**Oral Health Disparities Centers Initiative:** In May 2007, NIH announced plans to fund a competing renewal of the *Oral Health Disparities Centers Initiative* due to the promising achievements of currently funded centers, and the magnitude of the need for scientific advancement to eliminate disparities. Despite the remarkable improvement in the Nation's oral health over the years, not all Americans have benefited equally. *Oral, dental, and craniofacial conditions remain among the most common health problems for low-income, disadvantaged, and institutionalized Americans.* Unfortunately, there is no easy, one-size-fits-all solution. Much remains to be learned about the complex array of cultural, economic, genetic, and other contributory factors to these disparities and how best to overcome them. The five currently supported Centers have devised innovative, low-cost approaches to address severe early childhood caries, oral cancer, poor diet, and malocclusion.

- For more information, see <http://grants1.nih.gov/grants/guide/rfa-files/RFA-DE-08-008.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities.*
- (E) (NIDCR)

**Dialysis Access Consortium:** Arteriovenous (AV) fistulas and grafts are the two most common methods of gaining repeated access to the circulation of patients on hemodialysis. The Dialysis Access Consortium (DAC) is conducting two trials to assess the impact of anticlotting reagents in preventing early failure in AV fistulas and AV grafts. The AV Fistula Trial is evaluating the ability of clopidogrel to maintain access patency, while the AV Graft Trial is evaluating the ability of aspirin/extended-release dipyridamole to maintain access patency.

- [Dember LM et al. \*Clin Trials\*. 2005;2:413-22](#), PMID: 16317810
- [Dixon BS et al. \*Clin Trials\*. 2005;2:400-12](#), PMID: 16317809
- For more information, see <http://www.niddk.nih.gov/patient/dac/DAC.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E) (NIDDK)

**Community-Based Participatory Research (CBPR):** CBPR is scientific inquiry conducted in communities and in partnership with researchers. Persons affected by the health condition or issue under study, or other key stakeholders in the community's health, fully participate in each phase of the work. This input offers CBPR the potential to generate better informed hypotheses, develop more effective interventions, and enhance the translation of research results into practice. The Program Announcement *Community Participation in Research* supports CBPR on health promotion, disease prevention, and health disparities. CBPR is also the theme of the annual NIH *Research on Social Work Interventions and Health Summer Institute* (July 2007).

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-283.html>
- For more information, see <http://obssr.od.nih.gov/summerinstitute2007/index.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (OBSSR, AHRQ, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINR, NIOSH)

**Critical Issues in eHealth Research Conference:** Toward Quality Patient Centered Care (September 2006): This second of two eHealth conferences served three purposes: (1) to highlight research methodologies that intersect across information technology, health communications, behavioral science, medical science, and patient care research, (2) to showcase existing and emerging technologies relevant to communications among patients and their health care teams, and (3) to discuss conceptual issues related to patient-centered eHealth research.

- [Atienza AA, et al. Am J Prev Med. 2007;32:S71-4](#), PMID: 17466821
- This example also appears in Chapter 3: *Technology Development*.
- (E) (OBSSR, NCI, ODP/ORD)

**Research on Social Work Practice and Concepts in Health:** Social workers focus on the creation of physical and mental health prevention and treatment interventions in order for individuals to become more productive members of society. As providers of front-line services in such areas as aging, teen pregnancy, child abuse, and substance abuse, particularly in underserved communities, they are in a unique position to provide valuable information on these complex social concerns. This initiative aims to incorporate unique social work concepts and perspectives into the NIH research portfolio and to build the scientific base for use by allied health professionals.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-292.html>
- (E) (OBSSR, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NINR, ODP/ORD, ORWH)

**Understanding and Promoting Health Literacy:** The DHHS Healthy People 2010 initiative established a national health objective to improve health literacy by the decade's end. While many diseases and conditions can be prevented or controlled, too often people with the greatest health burdens have few fact-finding skills, the least access to health information, and least effective communication with health care providers. This program announcement supports research that increases our understanding of the health literacy problem and its relationship to

health disparities as well as the development of interventions to overcome the adverse consequences of low health literacy.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-07-020.html>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses* and Chapter 2: *Minority Health and Health Disparities*
- (E) (OBSSR, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

**SBIR/STTR Management Redesign:** The NIH Small Business Research programs, SBIR and STTR, serve to foster and encourage innovative research with the goal of transferring technologies and processes into commercial applications that will improve the health of the Nation. By March 2007, NIH established a working group (Trans-NIH SBIR/STTR Think Tank Working Group) to develop an agency-wide strategy that aligns the SBIR/STTR program with crosscutting NIH program goals (e.g., the NIH Roadmap for Medical Research) and advances the agency's vision for translating scientific discoveries into commercial products and services by using SBIR/STTR strategically. Future efforts will include the development and implementation of a pilot SBIR/STTR initiative that would meet these objectives, foster effective public-private partnerships, and ensure a stronger, more integrated technology program.

- For more information, see <http://grants.nih.gov/grants/funding/sbir.htm>
- (OD/OER)

**Clinical and Translational Science Award (CTSA) Consortium:** To remove barriers to clinical (including pediatric) research identified by research communities, NIH launched the Clinical and Translational Science Award (CTSA) program in September 2006. The program will more rapidly and efficiently facilitate the transfer of discoveries made in the laboratory into new strategies to prevent or treat disease. Through the CTSA, academic health centers are forming a national consortium with interdisciplinary teams that cover the complete spectrum of biomedical research—from basic molecular biology to clinical medicine. The CTSA Consortium will design clinical research informatics tools, forge new partnerships with private and public health care organizations, expand outreach to minority and medically underserved communities, develop better designs for clinical trials, and train the next generations of clinical and translational researchers. Working together, the Consortium will adopt and disseminate best practices, policies, procedures, and other measures to advance collaborative clinical and translational research. The CTSA Consortium is the primary initiative for addressing the NIH Roadmap for Medical Research theme to Re-Engineer the Clinical Research Enterprise.

- For more information, see <http://www.ctsaweb.org/>
- (E) (Roadmap—all ICs participate)

**Training Activities of the Clinical and Translational Science Award Program:** Comparing new disease treatments and prevention strategies against those in current use requires dedicated clinical and translational research teams that include physicians, basic scientists, statisticians, and informatics experts, among others. Clinical research requires unique skills in addition to those needed to care for patients, so academic health centers must equip promising individuals with the special training they need to succeed in research careers. To address this need, NIH has expanded its clinical research training programs, first through the Roadmap T32 and K12

programs and, more recently, through Clinical and Translational Science Awards (CTSAs). Each program is based on placing the trainees in a mentored environment, where they learn the skills needed to cultivate multidisciplinary research team collaborations and design research projects to successfully compete for funding. The CTSA program will grow through 2012 to serve about 60 academic sites, providing research training and career development opportunities to a combined total of more than 1,200 trainees and new investigators covering multiple individual disciplines.

As mandated in Section 106 of the National Institutes of Health Reform Act (Pub. L. No. 109-482), NIH will conduct an evaluation and comparison of the outcomes and effectiveness of the CTSA training programs. This evaluation will be part of a much larger comprehensive evaluation of the CTSA program as a whole. Each individual CTSA is expected to include their training activities in their own evaluation. To coordinate and share information, including results of training activity evaluations, there is a CTSA Education/Career Development Steering Committee which provides a forum for the advancement of integrated and interdisciplinary education, training, and career development in the clinical and translational sciences and serves as a clearinghouse for clinical research training. Since the CTSA program was only recently initiated (September 2006), significant evidence of the long-term impact of the CTSA program is more likely to be measurable after 7 or more years. However, short-term process milestones and intermediate outcomes are expected in 1 to 7 years.

- For more information, see [nihroadmap.nih.gov/clinicalresearch/overview-training.asp](http://nihroadmap.nih.gov/clinicalresearch/overview-training.asp)
- For more information, see <http://www.ctsaweb.org/>
- This example also appears in Chapter 3: *Research Training and Career Development*
- (E) (Roadmap—all ICs participate)

**Reports of Clinical Trials Working Group (CTWG) and Translational Research Working Group (TRWG):** Recognizing the importance of translational and clinical research, two major reports of comprehensive evaluations were recently released that will lead to more rapid progress in translating important research findings into new, effective interventions. The CTWG and TRWG were constituted as broad and inclusive panels (memberships comprised experts from academia, the pharmaceutical industry, advocacy groups, NIH, and other governmental agencies) to review and evaluate the current portfolio of research being done in that area and identify ways to synergize, integrate, and coordinate efforts.

- For more information, see <http://www.cancer.gov/trwg>
- For more information, see <http://integratedtrials.nci.nih.gov/>
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NCI)

**Clinical and Translational Science Award (CTSA) Program Evaluation:** Given the ambitious goals of the CTSA program to transform the practice of clinical and translational science, NIH recognizes that rigorous attention must be given to evaluate the program's effectiveness in meeting those goals. NIH must ensure that program findings and outcomes are disseminated to stakeholders, including researchers, advocacy groups, Congress, and especially the patients who stand to benefit most from new prevention strategies and treatments reaching them faster. Therefore, NIH has launched a comprehensive evaluation of the CTSA program that will assess the impact of the CTSA Consortium on transforming translational and clinical

research. The CTSA evaluation will proceed at both a national and an institutional level, allowing NIH to assess national, Consortium-wide goals while providing flexibility for the individual CTSA to evaluate components unique to their specific CTSA.

- For more information, see <http://www.ctsaweb.org/>
- (E) (NCRR)

**Mind-Body Medicine:** NIH supports a substantial portfolio of multidisciplinary clinical, translational, and basic research on mind-body interventions, such as meditation and Tai Chi Chuan. This effort is based on (1) promising findings from preliminary controlled clinical investigations and (2) laboratory evidence suggesting that these interventions often involve or invoke well-known biological mechanisms known to play key roles in the cause of and recovery from illness, and in the preservation of health and wellness. For example:

- ▷ Investigators recently demonstrated that patients who practiced Tai Chi Chuan, a form of moving meditation based in traditional Chinese medicine, experienced significant augmentation in levels of immunity to the virus that causes shingles following vaccination against the virus. Other investigators have demonstrated that patients with chronic heart failure show improvements in quality of life, exercise ability, and biomarkers of cardiac health when Tai Chi Chuan is added to conventional medical care.
  - [Irwin MR, et al. \*J Am Geriatr Soc.\* 2007;55:511-7](#), PMID: 17397428
  - [Yeh GY, et al. \*Am J Med.\* 2004;117:541-8](#), PMID: 15465501
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
  - (E) (NCCAM)

## TOOLS AND TRAINING

### DISEASE REGISTRIES, DATABASES, AND BIOMEDICAL INFORMATION SYSTEMS

*The Atlanta physician had never before treated a boy complaining of “numb chin.” He sent the lad to the examining room to undress and quickly turned to his personal computer. He typed in the term “numb chin” and read from the screen a lengthy description of an article on just that subject. This information provided the vital clue the physician needed to diagnose a form of lymphoma. Similar scenes are reenacted thousands of times every day in physicians’ offices, research laboratories, hospital nurses’ stations, and medical schools—in short, wherever health professionals require information. The system this physician tapped into is MEDLINE, just one of the National Library of Medicine’s growing numbers of online databases containing medical references, abstracts, and other essential health information for professionals as well as the general public.*

#### Introduction

From bench to bedside and from database to desktop, *information* itself has become a primary driver of progress in the biomedical and health care enterprise. For example, the volumes of data resulting from sequencing the genomes of thousands of patients have become primary resources for identifying associations between specific genes and diseases. The data that flow from large-scale clinical studies, advanced diagnostic and imaging equipment, and electronic medical records is a key enabler of improvements in clinical practice and individual patient care. Up-to-date information from disease registries has become a critical resource for studying disease incidence and treatment patterns and forms the basis for public health interventions. The availability of this and other health information on the Internet enables consumers to play a more active role in managing their health and further increases demand for reliable and authoritative health information.

The development, deployment, and utilization of disease registries, databases, and other biomedical information systems are essential to managing large amounts of data for improved health. Such systems permit the efficient collection, storage, and accessing of biomedical information. Disease registries collect information about the occurrence of specific diseases, such as cancer and Parkinson’s disease, the kinds of treatment that registered patients receive, and other information that might be relevant to researchers or public health officials. This information can help in identifying causal factors of disease, assessing the effectiveness of various interventions, and identifying questions of concern to researchers, clinical professionals, and policymakers. Biomedical databases serve as repositories for a wide range of information, from the results of scientific or clinical research studies, to genomic information, to standard reference materials (such as genome sequences or anatomical images), to published journal articles and citations to the medical literature. They are widely used by biomedical researchers, as well as a growing number of clinicians, public health officials, and consumers.



Increasingly, biomedical databases serve not only as repositories of information, but also as research tools in and of themselves. Discoveries can be made by examining the information they contain. Scientists can use molecular databases to study the molecular profiles of individual tumors and create small-molecule anticancer agents to target them. They can analyze large-scale databases linking genotype and phenotype information from thousands of individuals to identify the genes associated with particular observable traits (e.g., obesity) or diseases (e.g., diabetes, cancer). In these ways, biomedical information systems are changing the nature of research itself, and promise to change the nature of clinical care and public health.

The utility of biomedical information systems rests on many factors, including the quality of the data they contain, accessibility to the full range of potential users, how easily they can be searched to find relevant and interesting results, and the availability of useful tools for analyzing the information they contain. New data must be added on a regular basis, while existing data are maintained or updated to reflect new findings. Improved search tools are needed to comb through the massive datasets and retrieve relevant results. Standard vocabularies that are used to organize information and ensure accurate retrieval must be updated to accommodate new concepts and relationships. New analytical tools are needed to explore increasingly complex questions, such as how the expression patterns of multiple genes are associated with a particular trait or response. Preserving, protecting, and ensuring the validity and security of information stored in biomedical databases remains of paramount importance.

## **Scope of NIH Activities in Disease Registries, Databases, and Biomedical Information Systems**

Because of the growing importance of information and its management in biomedical science, clinical care, and public health, virtually every NIH IC is engaged in the development, deployment, and use of biomedical information systems that support their mission. Several trans-NIH Roadmap activities also feature the development of significant biomedical information resources, including the tools, infrastructure, and associated research needed to make databases and registries more valuable.

Most evident among NIH's biomedical information resources are major scientific databases such as [GenBank](#) (genomic sequence data), [PubChem](#) (small molecules data), and [dbGaP](#) (database of Genotype and Phenotype). These and many similar databases (NLM alone oversees 36) have become indispensable national and international resources for biomedical and health research and public health. DNA sequence data stored at NIH, for example, allowed rapid identification of the first known polio case in the United States since 1999 and the rapid initiation of treatment.

NIH also houses the leading source of authoritative biomedical literature for professional and lay audiences. NLM's exhaustive Medline/PubMed database, for example, indexes citations to some 5,000 peer-reviewed scientific journals on a regular basis. PubMed Central, its digital archive of full-text articles, provides online access to a growing number of scientific journal articles deposited by publishers and by NIH-funded researchers who are complying with the [NIH Public Access Policy](#). These comprehensive resources are widely used by scientists, health care providers, and consumers who seek peer-reviewed information on biomedical and health topics of interest. As another example, peer-reviewed studies from the [National Toxicology Program](#)

are used by State, local, and Federal health officials to assess the toxicologic potential of environmental compounds to cause adverse health effects such as cancer.

NIH also works with other Federal and private entities to integrate disease registries for national and local use. For example, for 34 years the [Surveillance, Epidemiology, and End Results](#) (SEER) program has collected and published cancer incidence and survival data from cancer registries covering approximately 26 percent of the American population. SEER information has been the foundation for innumerable studies, including recent research into links between hormone therapy and breast cancer. [NIAMS](#) supports a dozen [registries](#) associated with specific diseases, including lupus, muscular dystrophy, and rheumatoid arthritis.

NIH's work on biomedical information systems goes beyond the establishment of databases and registries. NIH is also the largest Federal funder of biomedical informatics research, which aims to advance the applications of computing to biomedicine—for both research and clinical care. Grant programs support research and training in medical informatics and medical librarianship. NIH also leads the government's efforts to develop standardized vocabularies and terminology to support interoperability among biomedical information systems and has developed numerous tools to facilitate data analysis. These efforts aim to create and sustain the biomedical information infrastructure needed for research, clinical care (including electronic health records), and public health.

## **SUMMARY OF NIH ACTIVITIES**

### **Expanding and Enhancing NIH Scientific Databases**

Keeping pace with the expanding biomedical knowledge base is a continuing challenge for scientists; thus, NIH devotes considerable attention and resources to developing, expanding, and maintaining tools and resources for information management. NLM's [Medline/PubMed](#) database of the peer-reviewed bioscience literature, for example, added almost 1.3 million new citations to its archive in fiscal year (FY) 2006-2007 and now contains indexed citations of more than 17 million articles, editorials, comments, and other materials. [PubMed Central](#), NIH's electronic archive of full-text journal articles, passed the 1 million article mark in June 2007. NIH's online registry of clinical trials, [Clinicaltrials.gov](#), added information on more than 23,000 clinical research studies in FY 2006-2007 and by the end of FY 2007 contained information on some 45,000 clinical trials conducted in more than 140 countries. Many other NIH databases have seen similar growth, placing greater demand on NIH's information infrastructure and on the resources needed to input, store, and index information. Ongoing efforts are needed to streamline such processes and boost their productivity.

Increased utilization goes hand in hand with the expanding content of NIH's databases. [Medline](#) alone logged nearly 900 million searches in FY 2006, almost twice the level of FY 2003, and [Clinicaltrials.gov](#) saw some 500 thousand unique visitors in June 2007, double the number 2 years earlier. Some of this increase is attributable to an expanding scope of users—not just biomedical researchers, but also clinicians, consumers, and other practitioners. NIH actively endeavors to make its information resources more accessible to varied types of users, as illustrated by its work on [MedlinePlus](#), NLM's comprehensive health information source for consumers and health professionals, and [WISER](#), the Wireless Information System for

Emergency Responders. WISER makes information available to emergency responders from NIH's [TOXNET](#) databases. TOXNET, is a cluster of 14 large databases covering toxicology, hazardous chemicals, environmental health, and related topics. It has been used by toxicologists for decades, assisting them in locating toxicology data, literature references, and toxic release information on particular chemicals, as well as in identifying chemicals that cause specific health effects. To make these resources more useful to first responders at the scene of a disaster, NIH developed the WISER system, which enables wireless access to a selection of the most relevant data for emergency responders. WISER can be installed on personal digital assistants, providing emergency personnel with access to critical information for identifying and safely cleaning up spilled chemicals, understanding their health effects, treating exposed victims, and assessing environmental impact. A Web-based version of WISER, released in FY 2006, can be accessed from any Web-enabled device. WISER was used to access information on dangerous chemicals to which Hurricane Katrina victims may have been exposed.

## **Genomic Information Systems**

NIH also has made great strides in developing information resources to support genetics research. NIH has long supported genetic information resources through widely used repositories such as [GenBank](#), the NIH genetic sequence database. More recent efforts have aimed to support the analysis of data from genome-wide association studies, which explore the connection between specific genes (genotype information) and phenotype information, such as observable traits (e.g., blood pressure, weight) or a particular disease. NIH's [dbGaP](#) (database of Genotype and Phenotype) was launched in December 2006 to house data from a number of genome-wide association studies. By the end of FY 2007, dbGaP contained more than 12 large datasets, including genetic analyses from the landmark [Framingham Heart Study](#), and studies of age-related eye diseases and Parkinson's disease. The wide availability of information linking genotype to phenotype should help researchers better understand gene-based diseases and speed development of effective therapies.

Several NIH ICs have established genetics repositories to accelerate research and multidisciplinary collaborations in specific disease areas. Programs such as the [NIMH Genetics Repository](#), the NINDS [Human Genetics Repository](#), the NCBI [Influenza Virus Resource](#), the NIA [Genetics of Alzheimer's Disease Data Storage Site](#), and the [National Database for Autism Research](#) give researchers access to vast storehouses of genetic and genomic data, DNA samples, and clinical data, along with informatics tools designed to facilitate their analyses. For example, the Influenza Virus Resource database, comprising information obtained from the NIAID Influenza Genome Sequencing Project and GenBank, contains more than 40,000 influenza virus sequences, including the sequences of more than 2,500 whole influenza genomes. More than 11,000 sequences were added in FY 2006, along with new search and annotation tools. This resource enables scientists to compare influenza virus strains so that emergent variants can be more rapidly identified and vaccines developed accordingly. As the library of viral sequences grows it will be an increasingly important reference to help further understand how avian viruses spread to humans, and how influenza activity spreads throughout the world.

## **Disease Registries and Surveillance Systems**

NIH-supported disease registries have paid many dividends over the years. Recently, for example, with the participation of patients from the [Alopecia Areata Registry](#), NIH-supported scientists discovered four chromosomal locations that appear to be associated with susceptibility to this common autoimmune disease, which is characterized by patchy hair loss. Understanding the mechanisms of the genes found at these locations could lead to the development of an effective treatment for the disease, which is presently untreatable.

Registries also serve as an effective mechanism to gather data on the incidence, prevalence, and natural history of diseases. The NIEHS-supported [California Parkinson's Disease Registry](#), for example, enables researchers to identify the possible environmental and genetic origins of this progressive neurological disorder suffered by an estimated 1.5 million Americans. Data in the registry can help to determine whether race, ethnicity, gender, age, environmental factors, or place of residence influence the likelihood of getting the disease, and can help track incidence and demographic trends.

Registries also are integral elements of more comprehensive NIH programs designed to monitor and analyze disease trends in the United States. For example, the [Surveillance, Epidemiology, and End Results \(SEER\)](#) program has a rich track record of identifying emerging trends, geographic variation, ethnic disparities, and other patterns that have provided new directions for epidemiologic research in cancer etiology and control. SEER data provided critical insight into the relationship between hormone therapy and breast cancer incident rates. Reported incidents of breast cancer in the SEER registry began to decline in mid-2002, shortly after a highly publicized series of reports from the NIH [Women's Health Initiative](#) (WHI) revealed an association between the risk of breast cancer and the use of hormone therapy. By analyzing SEER data on breast cancer incidence rates using several key factors such as the estrogen-receptor status of tumors, WHI researchers demonstrated that the incidence of tumors most likely to be affected by changes in hormone therapy reflected usage patterns, while trends for other tumors did not.

Surveillance and monitoring programs are also crucial sources of information and analysis for policymakers, legislators, public health officials, clinicians, and the public. SEER participates in [Cancer Control P.L.A.N.E.T.](#) (Plan, Link, Act, Network with Evidence-based Tools), a Web portal that provides links to comprehensive cancer control resources and data for public health professionals. NIDA supports several epidemiologic programs designed to gather ongoing data and monitor emerging drug abuse trends in adolescents and other populations, helping to guide national and global prevention efforts, drug control, and public health policy. Among the projects is the [Monitoring the Future \(MTF\) Survey](#), which has been tracking trends in substance use, attitudes, and beliefs among adolescents and young adults in the United States since 1975. Data from the 2007 MTF Survey show good news and continuing areas of concern. For although teen drug use continues to decline—including cigarette smoking, now at the lowest rate in the survey's history—use of prescription-type drugs is still high, with more than 15 percent of 12th graders reporting nonmedical use within the past year.

## **Enhancing the Utility of Data Resources: Tools and Standards**

Other efforts aim to enhance the utility of NIH databases. A key element of this work is to exploit the inherent relationships among information in disparate databases. NIH's [PubChem](#) database, for example, is an integrated hub within the Entrez suite of biomedical information resources. PubChem is the repository for data flowing from the high-throughput bioassay centers that were established with NIH funding under the [Molecular Libraries Initiative](#) of the NIH Roadmap. It provides information about the biological activity of small molecules, organized as three linked databases along with a chemical structure similarity search tool. PubChem's chemical structure and bioassay records are interlinked with the biomedical literature in PubMed and with three-dimensional protein structure records. This integration provides many routes by which biomedical researchers may discover the candidate probes developed by the Molecular Libraries Initiative. A researcher examining a protein sequence record, for example, may see that a particular protein has been screened, view the active compounds, and examine structure-activity relationships using PubChem analysis tools. NLM's Discovery Initiative, launched in FY 2006-2007, aims to take database linking to the next level. The Discovery Initiative will improve the presentation of results from search queries conducted across a range of NIH databases so that users, who often do not go beyond retrieving the basic results of a search query, are more likely to be drawn to related data that could lead to serendipitous discoveries, even if that information resides in another NIH database.

Other efforts relate to the development of standardized nomenclatures and data protocols. Medical terminology can be difficult to remember and can vary from one laboratory or clinical facility to another. Often there are many names for a single concept (e.g., cancer of the colon, colonic neoplasm, colon cancer). Standard vocabularies and ontologies (models of the relationships between concepts) improve information search and retrieval by endowing systems with the ability to automatically perceive and retrieve information about related terms. As expansion of the scientific frontiers produces new concepts, terms, and relationships, standard vocabularies must be regularly revised so that articles and other data can be properly indexed and search engines can find relevant and related terms.

NLM continues to update its Unified Medical Language System (UMLS), which is heavily used in advanced biomedical research and data mining worldwide. NLM and many other institutions apply UMLS resources in a wide variety of [applications](#) including information retrieval, natural language processing, creation of patient and research data, and the development of enterprise-wide vocabulary services. NIH's [ClinicalTrials.gov](#) database now uses the UMLS to improve the system's ability to retrieve information about clinical trials related to a user's interests.

UMLS and related NIH programs also contribute to efforts to national efforts to expand the use of electronic health records to improve the quality and efficiency of health care. Standardized clinical terminology and coding systems facilitate the exchange of information among care providers, insurers, and patients, contributing to implementation of an interoperable health information technology infrastructure. NLM is the government's lead agency for maintaining and disseminating clinical terminology standards. In 2007, NIH helped to establish the International Health Terminology Standards Development Organization, which is globally



distributing SNOMED CT (Systematized Nomenclature of Medicine—Clinical Terms), a comprehensive clinical terminology for electronic health records.

## **Informatics/Computational Biology Initiatives**

NIH also has embarked on a number of large-scale initiatives to develop and deploy infrastructure and tools for storing, sharing, integrating, and analyzing the large volumes of data routinely generated by today's laboratories.

In the area of cancer research, for example, NIH has established the cancer Biomedical Informatics Grid ([caBIG](#)). caBIG is a collaborative information network for all of NCI's advanced technology and program initiatives, connecting scientists, practitioners, and patients and enabling the collection, analysis, and sharing of data and knowledge along the entire research pathway from bench to bedside. Specific biomedical research tools under development by caBIG include clinical trial management systems, tissue repositories and pathology tools, imaging tools, and a rich collection of integrative cancer research applications. Patients benefit from caBIG through systems and services such as [BreastCancerTrials.org](#) (BCT), which was launched in 2006 to match patients' medical case histories to ongoing clinical trials in the greater San Francisco and Sacramento areas. Created by patients for patients, BCT is an online version of a caBIG tool called [caMatch](#), which aims to save patients time and energy, while also giving them greater options in seeking clinical trials that are relevant to their condition.

Other efforts aim to provide the informatics infrastructure to advance basic research and clinical studies across the spectrum of biomedical sciences. NIH's [Biomedical Informatics Research Network](#), for example, is a virtual community of shared informatics resources. It includes a data repository that makes research data freely available for sharing and exchange; data integration tools that allow searching across distributed databases; and tools for data analysis, management, and collaborative research. The [National Electronics Clinical Trials and Research](#) (NECTAR) network, a clinical research "network of networks," is a Roadmap initiative that will provide the informatics infrastructure for interconnected and inter-operable clinical research networks. NECTAR will allow clinical investigators to broaden the scope of their research while enhancing efficiency and reducing duplication of efforts by integrating clinical research networks that currently operate independently of each other. Another Roadmap initiative will create a national software engineering system through Bioinformatics and Computational Biology initiatives. Through a computer-based grid, biologists, chemists, physicists, computer scientists, and physicians anywhere in the country will be able to share and analyze data using a common set of software tools. The National Centers for Biomedical Computing are a central focus of this effort.

## **Biomedical Informatics Research and Training**

Ensuring continued advances in biomedical informatics resources requires active support of fundamental research that seeds the further development of new tools, resources, and approaches. It also is critical to generating a continuous supply of skilled biomedical informatics researchers, information specialists (such as medical librarians), and life sciences researchers trained in bioinformatics. NIH continues to expand its efforts in bioinformatics research and



training in response to the growing importance of informatics in the biomedical and life sciences (see section on *Research Training*).

Several ICs fund informatics research projects within their areas of specialization. However, NLM remains the primary Federal sponsor of biomedical informatics research, and its extramural grants program supports research on the characterization, management, and efficient use of data, information, and knowledge in health care and basic biomedical sciences. Grants funded in FY 2006-2007 explored informatics challenges related to clinical care, biomedical research, genomics, and public health. NLM's long-range plan, *Charting a Course for the 21st Century*, published in September 2006, identifies a number of emerging informatics challenges that will demand continued research and development.

### **Notable Examples of NIH Activity**

#### **Key for Bulleted Items:**

E = Supported through **E**xtramural research

I = Supported through **I**ntramural research

COE = Supported through a congressionally mandated **C**enter of **E**xcellence program

GPRA = Relates to progress toward a goal tracked under the **G**overnment **P**erformance and **R**esults **A**ct

### **Scientific Databases**

**MEDLINE/PubMed and PubMed Central (PMC):** NIH continued to expand MEDLINE/PubMed as a tool for biomedical research, clinical medicine and consumer health. Almost 1.3 million citations were added to MEDLINE/PubMed in FY 2006-2007, a 10 percent increase from the previous two-year period. NIH made significant strides in enhancing PMC, its repository of full-text biomedical journal articles. PMC surpassed the 1 million-articles mark in June 2007, and, to support NIH policy on public access to NIH-funded research, the NIH Manuscript Submission system was developed, enabling NIH grantees to deposit manuscripts into PMC. To foster international cooperation on preservation and access to biomedical literature, NIH made PMC software available to archiving organizations outside the United States and worked with the Wellcome Trust and other major United Kingdom research funders in the to establish a UKPMC service. Five other countries plan to establish PMC sites.

- For more information, see <http://www.pubmed.gov>
- For more information, see <http://www.nihms.nih.gov/>
- For more information, see <http://www.pubmedcentral.nih.gov/about/pmci.html>
- For more information, see <http://ukpmc.ac.uk/>
- (I) (NLM)

**MedlinePlus/MedlinePlus en Español:** NIH employed new methods to increase awareness of its MedlinePlus databases. Weekly podcasts by NLM's Director were initiated to provide timely reports on health news; *NIH MedlinePlus The Magazine* was rolled out at a press event on Capitol Hill attended by members of Congress and guest celebrity Mary Tyler Moore, featured on the cover. The magazine is distributed free of charge to 40,000 physician offices and has covered stories on cancer, diabetes, and heart attack. NIH expanded the content and features of the English and Spanish MedlinePlus Web sites and the associated GoLocal sites that provide

information on local health resources for approximately one-third of the U.S. population. MedlinePlus was one of two U.S. winners of the 2005 Award at the World Summit on the Information Society.

- For more information, see <http://www.medlineplus.gov>
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (I) (NLM)

**TOXicology Data NETwork (TOXNET):** TOXNET is a cluster of more than 10 databases covering toxicology, hazardous chemicals, environmental health, and related topics. It is a primary reference for toxicologists, poison control centers, public health administrators, physicians, and other environmental health professionals. In 2006, the Hazardous Substances Data Bank, which contains comprehensive information on more than 5,000 substances, was expanded to include a general record for [ionizing radiation](#) and a series of specific radionuclide records. In 2007, LactMed, a peer-reviewed and fully referenced database of drugs to which breast-feeding mothers may be exposed, was added to TOXNET.

- [Wexler P. \*Toxicology\*. 2004;198:161-8](#), PMID: 15138039
- [Tomasulo P. \*Med Ref Serv Q\*. 2007 Spring;26:51-8](#), PMID: 17210549
- For more information, see <http://toxnet.nlm.nih.gov>
- (I) (NLM)

**National NeuroAids Tissue Consortium (NNTC):** The NNTC is a repository of brain tissue and fluids from highly characterized HIV+ individuals. Established as a resource for the research community, the NNTC includes information from over 2,000 individuals, including approximately 641 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

- For more information, see <http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-08-021.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NIMH, NINDS)

**ClinicalTrials.gov:** Established in 2000 in response to congressional mandate (Pub. L. No. 105-115), [ClinicalTrials.gov](#) has grown to become the largest clinical trial registry in the world with information on clinical research studies for hundreds of diseases and conditions conducted in 148 countries. At the end of September 2007, it contained more than 47,000 registered trials—more than double the number of entries 2 years earlier. Legislation enacted in September 2007, the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85), expanded the scope of trials to be registered with [ClinicalTrials.gov](#) and the registration information to be provided. It also mandates the inclusion of specified results information beginning in September 2008.

- [Drazen JM, et al. \*N Engl J Med\*. 2007;356:184-5](#), PMID: 17215537
- [Zarin DA, et al. \*N Engl J Med\*. 2005;353:2779-87](#), PMID: 16382064
- For more information, see <http://clinicaltrials.gov>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I) (NLM)

**Influenza Virus Resource:** This database of more than 40,000 influenza virus sequences allows researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic, and vaccine targets. The resource was developed by NCBI using data obtained from NCBI's Influenza Virus Sequence Database and from NIAID's Influenza Genome Sequencing Project, which has contributed sequences of the complete genomes from over 2,500 influenza samples. In FY 2006 more than 11,000 influenza virus sequences were entered into the database, and new search and annotation tools were added to assist researchers in their analyses.

- [Wolf YI, et al. \*Biol Direct\* 2006;1:34](#), PMID: 17067369
- [Chang S, et al. \*Nucleic Acids Res\* 2007;35:D376-80](#), PMID: 17065465
- For more information, see <http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>
- For more information, see <http://www.niaid.nih.gov/dmid/genomes/mscs/influenza.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*, Chapter 3: *Molecular Biology and Basic Sciences*, and Chapter 3: *Genomics*
- (1) (NLM, NIAID)

**PubChem:** PubChem provides information on the biological activities of small molecules. It is a component of NIH's Molecular Libraries Roadmap Initiative. By the end of 2007, PubChem contained information on more than 38 million substances, 18 million compounds, and 710 bioassays.

- For more information, see <http://pubchem.ncbi.nlm.nih.gov/>
- (E) (Roadmap—all ICs participate)

**Databases for Cervical Cancer Research:** NIH has developed data analysis and image recognition tools for studying biomedical images of human papillomavirus (HPV) infection and cervical neoplasia. Image data include 100,000 cervicographs (high-definition cervical photograph), Pap test, and histology images. Tools allow the exploration of visual aspects of HPV and cervical cancer for research, training, and teaching.

- [Castle PE, et al. \*Cancer Res.\* 2006;66:1218-24](#), PMID: 16424061
- [Jeronimo J, et al. \*J Low Genit Tract Dis.\* 2006;10:39-44](#), PMID: 16378030
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 2: *Cancer*.
- (I) (NLM, NCI)

## Genomic Information Systems

**Database of Genotype and Phenotype (dbGaP):** Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics and other scientific data, NIH established dbGaP to house this growing body of information, particularly the results of GWAS, which examine genetic data of subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2007, dbGaP included results from more than a dozen GWAS, including genetic analyses added to the landmark Framingham Heart Study and trials conducted under the Genetic Association Information Network. dbGaP is to become the central repository for many NIH-funded GWAS

in order to provide for rapid and widespread distribution of such data to researchers and accelerate the advance of personalized medicine.

- For more information, see <http://view.ncbi.nlm.nih.gov/dbgap>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*.
- (I) (NLM)

**Genome-Wide Association Studies (GWAS) and Database of Genotype and Phenotype (dbGaP):** In December 2006, NIH released the initial dbGaP dataset using genome-wide association data from the Age-Related Eye Diseases Study (AREDS), a landmark study of the clinical course of age-related macular degeneration (AMD) and cataracts. AREDS documents, protocols, and aggregated data are made available with no restrictions. In order to protect patient confidentiality, de-identified individual-level patient characteristics and family data are accessible only by authorized investigators. Correlating phenotype and genotype data provides information about the genetic and environmental interactions involved in a disease process or condition, which is critical for better understanding complex diseases and developing new diagnostic methods and treatments. Using these data, recent studies have linked two genes with progression to advanced AMD. After controlling for other factors, certain forms of the genes increased risk of AMD progression 2.6- to 4.1-fold; smoking and body weight further increased risk with these gene variants.

- [Seddon JM, et al. JAMA 2007;297:1793-800](#), PMID: 17456821
- For more information, see <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gap>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (NEI, NIA, NLM)

**NIMH Genetics Repository:** Over the last 9 years, NIMH has built the infrastructure for large-scale genetics studies through the NIMH Human Genetics Initiative. Through this Initiative, NIMH established a repository of DNA, cell cultures, and clinical data—serving as a national resource for researchers studying the genetics of complex mental disorders.

- For more information, see <http://nimhgenetics.org/>
- This example also appears in Chapter 3: *Genomics* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH)

**NINDS Human Genetics Repository:** In 2003, NINDS established this Repository to collect, store, characterize, and distribute DNA samples and cell lines and standardized clinical data for the research community. By June 2007, the repository held material from 16,683 subjects, including stroke (4,363), epilepsy (1,065), Parkinson’s disease (3,585), motor neuron diseases such as ALS (2,445), and control samples (4,767). The ethnically diverse collection represents populations from the United States and several other countries. Investigators have submitted or published more than 50 scientific articles based on data from this resource, and technological advances allowing “whole genome screening” for disease genes have also enhanced its value.

- For more information, see <http://ccr.coriell.org/Sections/Collections/NINDS/?SsId=10>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NINDS)

**Candidate Gene-Association Resource:** Over the years, NHLBI has supported a number of major population studies that have collected extensive data on cardiovascular disease and its risk factors and manifestations. To increase the utility of the data for conducting genetic association studies, NIH initiated the Candidate Gene Association Resource program in FY 2006. This new resource will have the capacity to perform high-throughput genotyping for up to 50,000 subjects in cohort studies that have stored samples and data available on a wide array of characteristics (phenotypes) associated with heart, lung, blood, and sleep disorders. The linked genotype-phenotype data will form an invaluable resource for investigators seeking to identify genetic variants related to those disorders.

- For more information, see <http://public.nhlbi.nih.gov/GeneticsGenomics/home/care.aspx>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (NHLBI)

**Alzheimer's Disease (AD) Genetics Initiative and Data Storage:** Only one of the four validated AD genes, APOE, has been definitively linked with the more common late-onset form of the disease. A fifth gene, SORL1, has recently been linked with late-onset Alzheimer's disease (LOAD) in some studies. The goal of the AD Genetics Initiative is to develop the resources necessary for identifying the LOAD risk factor genes and the interactions of genes with the environment. In FY 2006, NIH achieved its goal to recruit 1,000 families with two or more siblings living with AD through an unprecedented alliance of AD Centers, researchers, and outreach with the Alzheimer's Association. To facilitate access by qualified investigators, all genetic data derived from NIH-funded studies on LOAD genetics are deposited at a central data storage site at Washington University in St. Louis, another NIH-approved site, or both. Discovery of risk factor genes will help illuminate the underlying disease processes of AD, open up novel areas of research, and identify new targets for drug therapy.

- For more information, see <http://www.niageneticsdata.org/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NIA)

**Autoimmune Diseases and Genetics:** With the advancement of genomic science, more information has been gained about the genetic component of autoimmune diseases. Susceptibility genes have been identified for rheumatoid arthritis, lupus, psoriasis, and alopecia areata. Understanding the genetic influence of these diseases provides essential information for the design of new therapies.

- [Kumar KR, et al. \*Science\* 2006;312:1665-9](#), PMID: 16778059
- [Nair RP, et al. \*Am J Hum Genet\* 2006;78:827-51](#), PMID: 16642438
- [Haas CS, et al. \*Arthritis Rheum\* 2006;54:2047-60](#), PMID: 16804865
- [Martinez-Mir A, et al. \*Am J Hum Genet\* 2007;80:316-28](#), PMID: 17236136
- See [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2006/lupus\\_susceptibility\\_gene.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/lupus_susceptibility_gene.asp)
- This example also appears in Chapter 2: *Autoimmune Diseases*.
- (E) (NIAMS, NCRR, NHLBI, NIAID, NIMH)

## Disease Registries and Surveillance Systems

**Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS):** In a joint effort, NHLBI, the Center for Medicare & Medicaid Services, and the U.S. Food and Drug Administration created INTERMACS, a national registry for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure. Data from INTERMACS are expected to improve patient evaluation and management, aid in the development of safer, more effective devices, and enhance research.

- For more information, see <http://www.uab.edu/ctsresearch/mcsd/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Technology Development*.
- (E) (NHLBI)

**Resuscitation Outcomes Consortium:** Recognizing the critical importance of early intervention for victims of cardiopulmonary arrest and traumatic injury, in FY 2004 NIH and its U.S. and Canadian partners initiated the Resuscitation Outcomes Consortium, a large-scale network to conduct clinical trials of promising approaches to improving outcomes. During FY 2006-2007, two Consortium clinical trials began enrolling patients—one to compare the efficacy of three fluids for initial resuscitation of hypotensive or brain-injured patients and the other to test two strategies for increasing blood flow during cardiopulmonary resuscitation. The Consortium also established a pre-hospital Cardiac Arrest and Trauma Registry across the United States and Canada. In addition, emergency medicine fellowship training programs established at several study sites are enhancing training in resuscitation medicine.

- For more information, see <https://roc.uwetc.org/>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NHLBI, NINDS)

**A Look at Drug Abuse Trends: Local to International:** Several major systems of data collection are helping to identify substance abuse trends locally, nationally, and internationally: Monitoring the Future Survey (MTF), the Community Epidemiology Work Group (CEWG), and the Border Epidemiology Work Group (BEWG). All help to surface emerging drug abuse trends among adolescents and other populations, and guide responsive national and global prevention efforts. The MTF project, begun in 1975, has many purposes, the primary one being to track trends in substance use, attitudes, and beliefs among adolescents and young adults. The survey findings are also used by the President's Office of National Drug Control Policy to monitor progress towards national health goals. The MTF project includes both cross-sectional and longitudinal formats – the former given annually to 8th, 10th, and 12th graders to see how answers change over time, and the latter given biennially, or every 2 years (until age 30, then every 5 years) to follow up on a randomly selected sample from each senior class. CEWG, established in 1976, provides both national and international information about drug abuse trends through a network of researchers from different geographic areas. Regular meetings feature presentations on selected topics, as well as those offering international perspectives on drug abuse patterns and trends. A recently established Border Epidemiology Work Group represents a collaboration of researchers from both sides of the U.S.-Mexico border. Of special interest are drug abuse patterns and problems in geographically proximal sister cities/areas. Development of



a Latin American Epidemiology Network is under way. NIH has also provided technical consultation for the planning and establishment of an Asian multi-city epidemiological network on drug abuse.

- For more information, see <http://www.monitoringthefuture.org/>
- For more information, see <http://www.drugabuse.gov/about/organization/CEWG/CEWGHome.html>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIDA)

**Parkinson's Disease Registry:** NIEHS has begun to address the need for more precise data on the incidence and prevalence of Parkinson's disease through support of a Parkinson's disease registry in the State of California, where the large and diverse population, coupled with the wide range of exposures that exist through agriculture and other activities, provide a unique opportunity to investigate disease-environment links. The United States does not have a national health registry to supply data on Parkinson's disease, so estimates are based on sampling by individual studies in specific locales. The Parkinson's registry in California will allow us to base national estimates on a registry drawing upon a cross-section of the population in our most populous state.

- For more information, see <http://www.thepi.org/site/parkinson/section.php?id=101>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIEHS)

### **Surveillance, Epidemiology, and End Results (SEER) Program and Software Analysis**

**Tools:** The program is an authoritative source of information on cancer incidence and survival in U.S. publications, such as the Annual Report to the Nation on the Status of Cancer, or interpretation of recent declines in breast cancer incidence to inform the public, researchers, Federal and private agencies, and Congress on national cancer rates and trends. SEER is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis, patient survival, and treatment. Linkage with Medicare and other Federal databases yields information sources that are used routinely to answer major questions on quality, cost, and variability of cancer care as well as differences by racial and ethnic populations. SEER currently collects and publishes data from approximately 26 percent of the U.S. population. The team is developing computer applications to unify cancer registration systems, to analyze and disseminate data, and to provide limited access to the public file. SEER is considered the standard for quality among cancer registries around the world.

- For more information, see <http://seer.cancer.gov>
- For more information, see <http://surveillance.cancer.gov/>
- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI)

**Gene Expression Changes in Facioscapulohumeral Muscular Dystrophy (FSHD):** Results from a genome-wide scan of skeletal muscle biopsies suggest a link between eye blood vessel defects and muscle defects that characterize FSHD. Patient subjects were recruited from the National Registry for Myotonic Dystrophy and FSHD Patients and Family Members.

- [Osborne RJ, et al. \*Neurology\* 2007;68:569-77.](#) PMID: 17151338
- For more information, see [http://www.niams.nih.gov/Funding/Funded\\_Research/registries.asp#dystrophy](http://www.niams.nih.gov/Funding/Funded_Research/registries.asp#dystrophy)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Genomics*.
- (E) (NIAMS, NCRR, NINDS)

**Genetic Susceptibility for Alopecia Areata:** Scientists supported by NIH have identified loci on four chromosomes that appear to play a role in the development of alopecia areata, an autoimmune disease characterized by hair loss that can affect the whole scalp or, in rarer cases, the entire body. Many U.S. families recruited for the study were identified through the Alopecia Areata Registry.

- [Martinez-Mir A, et al. \*Am J Hum Genet\* 2007;80:316-28,](#) PMID: 17236136
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2007/alopecia\\_areata.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/alopecia_areata.asp)
- This example also appears in Chapter 2: *Autoimmune Diseases*.
- (E) (NIAMS, NIMH)

## Enhancing the Utility of Data Resources: Tools and Standards

**A Clearinghouse for Neuroimaging Informatics Tools and Resources:** NIH understands that researchers seeking neuroimaging analysis software tools need a convenient way to find and compare useful software. Indeed, the best or most suitable neuroimaging analysis technologies for research may be hidden in someone's laboratory or some obscure corner of cyberspace. NIH is creating a Neuroimaging Informatics Tools and Resources Clearinghouse. The 14 NIH ICs that participate in the Neuroscience Blueprint have supported the development of sophisticated, high-quality neuroimaging informatics tools and resources. The clearinghouse is intended to facilitate the dissemination of those tools and resources and promote their adoption within the extended neuroimaging community. A contract has been awarded to the Turner Consulting Group, which specializes in delivering tailored information management solutions, to create the clearinghouse infrastructure. The infrastructure will include a Web site that will provide not only access to tools and resources, but also ongoing opportunities for public comment in order to guide future development and enhancement of the tools. In addition to the contract award, grant awards are being made to individual extramural scientists to enable them to render their tools more suitable for this initiative. The awards will fund the enhancement of tools to make them easier to use, more broadly applicable, or more compatible with other existing tools. The clearinghouse will be released to the public in October 2007.

- For more information, see <http://www.nitrc.org/>
- For more information, see <http://neuroscienceblueprint.nih.gov/>

- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Genomics*.
- (NIBIB, NCCAM, NCRR, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

**Health IT Standards:** NIH's UMLS Metathesaurus is a distribution mechanism for standard code sets and vocabularies used in health data systems. NIH supports, develops, or licenses key health terminologies to enable their free use in U.S. electronic health record systems. In 2007, NIH helped to establish the International Health Terminology Standards Development Organization to promote more cost-effective maintenance and international adoption of the SNOMED CT clinical terminology. NIH supports ongoing development and distribution of the LOINC nomenclature for laboratory tests and patient observations and produces RxNorm, a standard clinical drug vocabulary. Another NIH resource, the Daily Med, is an official distribution mechanism for FDA-approved packaging information (drug label inserts) that links to other sources of drug information, including NIH's MedlinePlus, ClinicalTrials.gov, and PubMed. More than 60,000 people subscribe to its RSS data feeds.

- For more information, see <http://www.nlm.nih.gov/healthit.html>
- (I) (NLM)

**UMLS Knowledge Sources:** NIH's Unified Medical Language System<sup>®</sup> (UMLS) aims to facilitate the development of computer systems that behave as if they understand the meaning of biomedical and health terms. The UMLS tools underpin many production information retrieval systems at NLM and elsewhere and are heavily used in advanced research in biomedical natural language processing and data-mining across the country and around the world. The most recent UMLS Metathesaurus contains more than 1.3 million biomedical concepts and 6.4 million concept names from more than 100 source vocabularies.

- For more information, see <http://www.nlm.nih.gov/research/umls/>
- (I) (NLM)

**Radiation Event Medical Management (REMM):** As a part of an effort to improve public health emergency preparedness and response, NIH and the HHS Office of the Assistant Secretary for Preparedness and Response announced in 2007 a new downloadable online diagnostic and treatment toolkit to guide health care providers during a mass casualty radiation event. The REMM toolkit includes easy-to-follow procedures for diagnosis and management of radiation contamination and exposure, guidance for the use of radiation medical countermeasures, and a variety of other features to facilitate medical responses to radiation emergencies.

- For more information, see <http://remm.nlm.gov>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (I) (NLM)

**Patient-Reported Outcomes Measurement Information System (PROMIS):** This NIH Roadmap initiative is developing ways to measure symptoms—such as pain, fatigue, physical functioning, social role participation, and emotional distress—that influence quality of life across numerous chronic diseases.

- For more information, see <http://www.nihpromis.org/default.aspx>
- For more information, see [http://www.niams.nih.gov/News\\_and\\_Events/Announcements/2007/PROMIS\\_supp.asp](http://www.niams.nih.gov/News_and_Events/Announcements/2007/PROMIS_supp.asp)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (Roadmap—all ICs participate)

**The Cancer Control P.L.A.N.E.T:** This Web portal is a collaboration aimed at providing access to data and resources that can help cancer control planners, health educators, program staff, and researchers design, implement, and evaluate evidence-based cancer control programs. It assists local programs with the resources that help them determine cancer risk and the cancer burden within their State. It also helps States identify potential partners and provides online resources for interpreting research findings and recommendations, and accessing products and guidelines for planning and evaluation.

- For more information, see <http://cancercontrolplanet.cancer.gov/>
- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI)

## Informatics/Computational Biology Initiative

**Biomedical Informatics Research Network (BIRN):** Modern biomedical research generates vast amounts of diverse and complex data. Increasingly, these data are acquired in digital form, allowing sophisticated and powerful computational and informatics tools to help scientists organize, store, query, mine, analyze, view, and, in general, make better use and sense of their data. Moreover, the digital form of these data and tools makes it possible for them to be easily and widely shared across the research community at large. NIH has supported development of the BIRN infrastructure to share data and tools by federating new software tools or using the infrastructure to federate significant datasets. BIRN fosters large-scale collaborations by utilizing the capabilities of the emerging national cyberinfrastructure. The project includes a Coordinating Center at the University of California, San Diego, which serves the critical task of developing, deploying, and maintaining key infrastructure components, including high-bandwidth connectivity, grid-based security, file management and computational services, techniques to federate databases, and shared visualization and analysis environments.

- For more information, see [www.nbirn.net](http://www.nbirn.net)
- This example also appears in Chapter 3: *Technology Development*.
- (E) (NCRR)

**National Database for Autism Research (NDAR):** The NDAR is a collaborative biomedical informatics system being created by NIH to provide a national resource to support and accelerate research in autism.

- For more information, see <http://ndar.nih.gov>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NIMH, CIT, NICHD, NIDCD, NIEHS, NINDS)

**National Centers for Biomedical Computing (NCBCs):** The NIH Roadmap Bioinformatics and Computational Biology initiative provides a networked national effort to build computational tools and infrastructure for biomedical computing. The centers are devoted to all facets of biomedical computing, from basic research in computational science to providing the tools and resources that biomedical, clinical, and behavioral researchers need to do their work. The seven centers currently supported by the NIH Roadmap have made substantial progress in software development, data resources, and scientific ontologies. These advances are currently being used by the research community for studying a broad range of biological problems including cerebral palsy, autism, diabetes, asthma, Alzheimer's disease, Huntington's disease, schizophrenia, bipolar disorder, HIV/AIDS, and prostate cancer. The long-term goal of the initiative is to create a national software engineering system that will enable biomedical and clinical researchers to share and analyze data using a common set of software tools.

- For more information, see <http://nihroadmap.nih.gov/bioinformatics/>
- This example also appears in Chapter 3: *Technology Development*.
- (E) (Roadmap—all ICs participate)

## **Biomedical Informatics Research and Training**

**Discovery Initiative:** The Discovery Initiative aims to maximize the utility of NIH biomedical data resources by better exploiting their inter-linkages. For example, a PubChem record on a chemical structure might link to records for similar proteins, related protein structures, and relevant journal articles. Such linkages provide users with tremendous opportunities for exploration and scientific discovery but are currently underutilized. The Discovery Initiative aims to improve the retrieval and presentation of results so that users are more readily drawn to related data that could lead to serendipitous discoveries.

- (I) (NLM)

**Informatics Training for Global Health:** Information technology is required in almost all research programs, both to access the vast information resources available internationally and to apply to research design and analysis. This program is intended to increase the capacity of developing country scientists and medical professionals to design, access, and use modern information technology in support of health sciences research. Specifically, this program supports innovative training programs for developing country biomedical and behavioral scientists and engineers, clinicians, librarians, and other health professionals to increase their capacity to access, manage, analyze, interpret, manipulate, model, display, and share biomedical

information electronically. Among other skills, this will increase their ability to conduct multisite clinical trials and international disease surveillance and prevention programs.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/itgh/index.htm](http://www.fic.nih.gov/programs/training_grants/itgh/index.htm)
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (FIC, NHGRI, NIBIB, NLM)

**Informatics Research Training Programs:** To address the national need for computational scientists competent in biology and medicine, NLM reviewed its University Informatics Research Training Programs and issued a new call for applications. Curricula were updated to reflect current computing needs in clinical translational research and public health. Eighteen 5-year grants, totaling more than \$75 million, for research training in biomedical informatics, were awarded in 2006. Approximately 270 trainees are currently enrolled in these programs.

- For more information, see <http://www.nlm.nih.gov/ep/AwardsTrainInstitute.html>
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (NLM)





## TECHNOLOGY DEVELOPMENT

*In July of 2002 A U.S. team of surgeons performed surgery on a patient by remote control 4,000 miles away in France. The surgeons were in New York, where they monitored the patient on the screen as they used tools connected to hi-tech sensors. The sensors turned the movement of the surgeon's hands into signals that sped across the Atlantic through fiber-optic lines to guide robots that operated on a 68-year-old woman in Strasbourg. The patient had no complications and was discharged 2 days later. The 54-minute procedure, dubbed "Operation Lindbergh" in honor of Charles Lindbergh's solo flight across the Atlantic, was the first of its kind. This technological milestone raises the possibility of remote robot surgery on wounded soldiers on battlefields, astronauts in space, and individuals in remote rural settings. Also, patients needing particularly difficult surgeries may have worldwide access to top surgeons without the need to travel.*

### Introduction

NIH support of technology development has triggered a revolution in the understanding of health and disease. A notable example is the Human Genome Project (jointly funded by NIH and the Department of Energy), which culminated in the sequencing of the human genome. Technology development, ranging from rapid DNA sequencing machines to complex computational tools to assemble the sequences, was critical to the successful sequencing of the human genome, as well as the genomes of numerous other organisms. This led to the development of a comprehensive map of human genetic variation and improved understanding of fundamental biological processes. This new knowledge continues to fuel the development of new clinical treatments, improving patient outcomes and quality of life.

During the past several decades, scientists have developed new technologies to create innovative animal models that closely mimic complex human disease. For example, through genetic engineering, a mouse model was created that mimics Alzheimer's disease. NIH-funded researchers are now using this model to study disease progression in the degenerating brain. This research is further enabled by the technological development of new imaging tools used to track the degeneration. This work provides an important step in the pathway to the discovery of new medications to treat Alzheimer's disease and perhaps change its course. Biotechnology and nanotechnology are examples of technology development. Biotechnology combines disciplines like genetics, molecular biology, biochemistry, embryology, and cell biology, which are in turn linked to practical disciplines like information technology, robotics, and bioengineering to enable the development of new or enhanced tools and devices to further basic scientific research as well as lead to improvements in human health. Nanotechnology refers broadly to a field whose unifying theme is the control of matter on the molecular level in scales smaller than one thousandth of a millimeter and the fabrication of devices within that size range. It is a highly multidisciplinary field, drawing from fields such as applied physics, materials science, supramolecular chemistry, and mechanical and electrical engineering.

Other examples of major breakthroughs spurred by NIH-supported technology development include:

- Progress in physical therapy for stroke survivors using wearable upper extremity robotic devices to mimic normal arm movements
- A new method of communication via a brain/computer interface for individuals with amyotrophic lateral sclerosis and other neuromuscular disorders
- Improved epilepsy surgery outcomes using an integrated imaging system with precision-guided surgery to remove seizure-causing regions in the brain
- New diagnostic and imaging methods for the early detection of cancer and other diseases
- Innovative high-throughput methods for detecting and characterizing disease-causing alterations in genes and proteins
- Sensor technologies combining multiple analytical functions into self-contained, portable tabletop devices that can be used by non-specialists to rapidly detect and diagnose disease
- Cochlear implants to restore hearing to hearing-impaired individuals
- Left ventricular assist devices to aid the failing heart
- New treatments for abnormal heart rhythms such as atrial fibrillation

The interactions among technology development, basic research, and clinical application drive the engines of biomedical research, enabling scientists and clinicians to use sophisticated tools to unravel fundamental biological questions that underlie health and disease, as well as to develop new therapies considered inconceivable just a few years ago. For example, technological developments in electrodes, computers, and materials were critical in developing the scientific understanding of the nature of some abnormal heart rhythms. Those same basic technological developments are now critical for treatment of abnormal heart rhythms using advanced imaging and ablation techniques.

Interdisciplinary or team research offers one of the best opportunities to develop new technologies and refine current ones. A team approach may identify problems and develop innovative solutions more quickly than a researcher working alone. NIH fosters and cultivates cooperative research so that fundamental discoveries and tools can be developed, even when their specific applications might not be obvious. For example, the laser was originally developed in the context of communication research. In medicine, the technology has been adapted to invent microscopes that are critical to many research areas as well as a variety of surgical tools including systems for laser eye surgery. Continued success in the future will require strong linkages among engineering, clinical medicine, physical science, computational science, and the biological sciences.

## Scope of NIH Activity in Technology Development

To truly revolutionize medicine and improve human health, scientists need a more detailed understanding of the vast networks of molecules that make up cells and tissues, their interactions, and their regulation. Researchers also must have a more precise knowledge of the combination of molecular events leading to a given disease. In 2002, NIH recognized that a gap existed in the support of crosscutting technology development. In response to that need, the NIH Roadmap theme, [New Pathways to Discovery](#), was initiated to advance understanding of biological

systems and build a better “toolbox” for medical research in the 21st century. To capitalize on the completion of the human genome sequence and recent discoveries in molecular and cell biology, the research community needs wide access to technologies, databases, and other scientific resources that are more sensitive, robust, and easily adaptable to researchers’ individual needs. The NIH Roadmap is supporting the development of these resources through five components of the New Pathways to Discovery theme, including Building Blocks, Biological Pathways, and Networks; Molecular Libraries and Molecular Imaging; Structural Biology; Bioinformatics and Computational Biology; and Nanomedicine. The Roadmap was created to fulfill the need to apply crosscutting technology to numerous biomedical research and health challenges.

Technology development for a specific disease or organ system is supported by the relevant disease-specific NIH Institute. For example, NHLBI supports technology development to treat abnormal heart rhythms and stroke while NCI supports the development of technology to more effectively diagnose and treat cancer. In addition to the disease-specific Institutes, NIBIB and NCRR support broad areas of technology development and infrastructure. For example, NIBIB’s mission is to improve health by leading the development and acceleration of the translation of biomedical technologies. NIBIB supports interdisciplinary research aimed at developing fundamental or crosscutting technologies that can be translated into several biomedical applications. This work often is done in collaboration with a disease-specific Institute as the work moves closer to clinical application. Similarly, NCRR provides laboratory scientists and clinical researchers with the research infrastructure and tools to develop technology to understand, detect, treat, and prevent a wide range of diseases.

Recognizing the potential benefits to human health to be realized from applying and advancing the field of bioengineering, the [Bioengineering Consortium](#) (BECON) was established at NIH in 1997. BECON is composed of senior-level representatives from each of the NIH Institutes as well as other Federal agencies. BECON’s mission is to foster new basic understanding, collaboration, and transdisciplinary initiatives among the biological, medical, physical, engineering, and computational sciences—all important and necessary components in technology development.

NIH supports technology development through several complementary mechanisms, including:

- High-risk, innovative projects with very little preliminary indication of the likelihood of success but a potentially significant impact (e.g., R21 funding mechanism). These projects may have small budgets and short timeframes, aimed at proof of principle.
- Research project grants with a sound basis in preliminary data, directed at development of a particular technology; some projects may take only a few years while others continue for a decade or more.
- Bioengineering research partnerships, which bring together multiple disciplines such as engineering, cell biology, physics, and neurology to develop solutions to specific biomedical questions or diseases.
- Specialized centers that represent a critical mass of expertise and technology, in which multidisciplinary development of complex, often unique technologies is pursued, typically in the context of challenging research problems that cannot be approached with

existing tools. The Biomedical Technology Research Resources program creates these unique technologies, applies them to the most challenging problems in biology and medicine, and disseminates these capabilities into the broader research community. This program serves as an engine for translation of advances in the physical sciences into tools for biomedical and clinical research.

- Small business grants foster highly innovative projects to bring technological advances into the marketplace for the broadest possible availability and impact. These programs allow NIH to leverage the unique resources and perspectives available in the private sector to complement the work done at universities.

## Summary of NIH Activities

### Toward a New Era in Medicine

By 2030, just over 970 million people will be age 65 years or older worldwide. Medical advances will increase life expectancy and make acute diseases less frequent. However, chronic diseases and disabilities will have a major impact on health care in terms of both costs and patient management.<sup>10</sup> Health care in the future must be prepared to manage the challenges of an older population as well as continue to improve quality of life for younger individuals. Developments in technology will be central to the scientific advances that will lead to predictive, personalized, and preemptive medicine to equip our health care system to meet these challenges.

One example from past advances illustrates the potential of new technologies. A major breakthrough in the last 30 years, the cochlear implant, is an electronic device that gives individuals who are profoundly deaf or severely hard of hearing an opportunity to experience sounds. Although the device does not restore normal hearing, it does enable these individuals to understand and discern not only sounds in the environment but human speech as well. In the United States about 22,000 adults and nearly 15,000 children have received the implant. NIH has supported the initial development and continuing improvements of this technology over the past 30 years. According to scientists, profoundly deaf children who receive an implant at an early age develop language skills at a comparable rate to children with normal hearing. This device is allowing researchers to undertake large studies to determine how treatments such as the cochlear implant lead to better speech and language acquisition, academic performance, and economic outcomes for children with the implant. Results from these studies could lead to new recommendations for early intervention among infants who are profoundly deaf.<sup>11</sup>

The research pipeline is replete with similar examples of NIH's commitment to technology development, its foresight in identifying emerging needs and emerging areas of investigation, and its ability to foster the development of technology that links basic research with clinical applications. Advances in research will continue to alter conventional medicine and lifestyle and NIH-supported technology development initiatives are central to improved understanding of scientific processes as well as improvements in health care. The following is an overview of technology development activities at NIH.

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<sup>10</sup> For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a2.htm>

<sup>11</sup> [Nicholas JG, Geers AE. \*Ear Hear\* 2006;27:286-98](#), PMID: 16672797

## Gene Sequencing and Beyond

Mapping the human genome has created the opportunity to predict which individuals or groups may develop a disease or condition. To enter an era where personalized medicine is more readily available, in which specific genetic differences conferring susceptibility to disease can be easily determined and tailored therapies provided, researchers will need innovative sequencing technologies that are more efficient and cost-effective than current approaches. Relatively inexpensive sequencing devices would enable clinicians to tailor prevention, diagnosis, and treatment to each individual's unique genetic profile. To this end, NIH is awarding "\$1,000 Genome Grants" to develop breakthrough technologies that will enable an entire human-sized genome to be sequenced for \$1,000 or less. Currently, only analyses of ~ 500,000 Single Nucleotide Polymorphisms (SNPs) are being performed commercially at this cost; an individual's complete genome sequence (~ 3 billion base pairs) would offer vastly more information. Researchers will investigate use of nanotechnology, spectroscopy, and lab-on-chip approaches to find low-cost approaches to sequencing DNA. [Lab-on-chip](#) devices integrate multiple laboratory functions on a single microelectromechanical device of only millimeters to a few square centimeters in size.

## Probing Proteins

Information from the Human Genome Project is now helping scientists as they begin to study proteins, the tiny powerhouses within cells responsible for cell function. Each protein is encoded with a specific sequence based on information found in genes but few tools have been available to examine protein structures and functions. A better understanding of protein activities could provide important information on why a disease develops. It also could lead to targeted drug therapies. As a result of the NIH-sponsored [Protein Structure Initiative](#) (PSI), investigators now have a more potent set of tools to examine the protein in three dimensions. Many of the technologies conceptualized during PSI's first phase have been commercialized and are being used in laboratories. Some of the developments include:

- Miniaturization of samples needed to grow, purify, and crystallize proteins
- Robotic systems to handle samples and image crystals
- Enhanced software to analyze structural data and create higher resolution images
- More accurate screening processes to detect crystals suitable for imaging
- Improved systems for making proteins from machines instead of cells

These advances have reduced the cost, time, and space needed to carry out structural studies and have improved the generation and analysis of quality data.<sup>12</sup> By visualizing protein structures, researchers gain a better understanding of many of the biochemical processes related to health and disease. This information also can be used to design drugs that target specific parts of a bacteria, virus, or tumor. Recently, PSI-funded scientists discovered a protein thought to be responsible for a lethal bacterial infection that affects the lungs of cystic fibrosis patients. Following this discovery, another set of researchers designed an experiment that provided

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<sup>12</sup> For more information, see <http://www.nigms.nih.gov/News/Results/110606a.htm>



important information on how the bacteria work. This collaborative effort could result in the development of a new drug to treat the infection.

## Insights From Animal Models

Another key tool in discovering how a gene or protein malfunctions and causes disease is the use of animal models of disease. Over the last 25 years researchers have bred countless animals with deliberately altered genes that serve as models for studying normal and disease states. These “transgenic” animal models are assisting in fundamental research for a broad range of diseases and conditions. For example, NIH-supported scientists have developed various animal models of human cancer including breast, colon, lung, and others. These models are being used in cancer drug development to answer fundamental questions of drug pharmacology and toxicity. This knowledge is essential to the design of Phase I clinical trials in which the safety, dose level, and response to a new drug are studied in humans. NIH-supported researchers are also using mouse models whose brains contain genetically altered neurons to study how Alzheimer’s and Parkinson’s diseases mediate brain activity. In this research investigators activate or inhibit neurons using specific light frequencies. The work could be extended to clinical application by targeting neurons or cells involved in the disease process. In the case of Parkinson’s disease, electrode-based deep-brain stimulation provides symptomatic relief but also can have side effects. Optical therapeutics that target diseased neurons could offer more precise therapy with fewer side effects.<sup>13</sup>

## Imaging Biological Systems

Better tools and techniques to understand activities within cells, tissues, and organ systems enable researchers to probe deeper to gain an understanding of the biological systems and networks that control both normal function and diseased states. For example, an NIH-funded team created a new optical microscope that permits scientists to see proteins that make up individual structures in a cell. The technique, known as photoactivated localization microscopy (PALM), may enable researchers to examine, for example, the proteins that control the organization and growth of HIV, the virus that causes AIDS. This information could be used to identify targets for drug development to halt viral replication.

Noninvasive molecular imaging using positron emission tomography (PET) and magnetic resonance imaging (MRI) is a fast developing area of research. By itself PET reveals information about such processes as metabolism or gene expression and is a key tool in basic cancer research as well as in providing clinical information for diagnosis and treatment of cancer patients. MRI provides information on anatomical structures. Two NIH-supported groups are developing imaging systems that combine PET and MRI. This research could lead to further understanding of how drugs disperse after administration; cardiac, central nervous system, and tumor cell metabolism; and mapping of neuroreceptors in small-animal brains. None of this is possible using current technology. A second group recently announced the first images of the human brain with a combined PET/MRI system. PET/MRI studies could allow clinicians to more definitively determine cognitive impairment and atrophy.<sup>14</sup>

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<sup>13</sup> Zhang F et al. *Nature* 2007;446:633-9, PMID: 17410168

<sup>14</sup> Judenhofer MS et al. *Radiology* 2007;244:807-14, PMID: 17709830

## **Image-Guided Interventions**

To detect disease in its earliest stages, and thereby preempt it before symptoms appear, clinicians will need to examine smaller, more localized areas of the body. Image-guided interventions (IGI)—treatments or procedures that precisely target areas within the body with the aid of imaging techniques such as MRI or computed tomography (CT)—enable clinicians to look beneath the surface anatomy to visualize underlying pathology. As a result, images can be used to navigate the anatomy for biopsy and treatment of disease. In addition to diagnosing at-risk individuals, IGI may offer a safer, less invasive approach to many surgical procedures. Compared with traditional open surgery, minimally invasive procedures result in less tissue trauma, less scarring, and faster postoperative recovery time, which translates into shorter hospital stays and a more rapid return to family and work.

As an emerging clinical tool, IGI shows great promise but is hindered by a number of factors.<sup>15</sup> An NIH-sponsored workshop noted that collaboration was one of the biggest hurdles facing the field. Interdisciplinary research and collaboration in the fields of biology, medicine, computer science, physics, and engineering will help create fast, reliable, and cost-effective IGIs.

Technological advancements require:

- More refined robotics technology for surgery and biopsies
- Expanded data integration
- Improvements in real-time modeling and three-dimensional visualization techniques
- Better approaches to image acquisition

## **Diagnostics and Point-of-Care Technology**

Ideally, patients would have access to high-quality and consistent health care and treatment regardless of where they live. Realizing this vision necessitates the development of portable, reliable, and inexpensive equipment. To achieve this will also require the leveraging of technologies developed in other fields such as telecommunications. Advances in fiber-optic and wireless communications devices allow physicians to engage in telemedicine, or the transmission via the Internet of medical information, to communicate with other physicians or pathologists thousands of miles away. In Tucson, Arizona, for example, a breast health center provides same-day mammogram, biopsy, and diagnosis of breast cancer to women in rural locations using a pathology tool developed by NIH-funded engineers. By combining rapid tissue processing with telepathology and teleoncology, cancer diagnosis times have dropped to a matter of hours rather than a 1- to 2-week wait.

Point-of-care technologies for use in pathology laboratories, emergency rooms, doctors' offices, and homes will be a key component of the evolving health care system. Current devices range from handheld glucose monitoring systems used by diabetics to monitor their blood sugar levels, to laptop-sized ultrasound scanners. Among the technologies on the horizon is a laboratory analyzer developed with NIH support that can identify specific bacteria responsible for urinary

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<sup>15</sup> From Final Report of the Image-Guided Interventions 2004 Workshop, May 13-14, 2004, Bethesda, Maryland.

tract infections from a single drop of urine and do so in a matter of minutes rather than the 48 hours normally required in standard cultures.

Recent NIH-supported efforts in the design and microfabrication of electronic, optical, mechanical, and fluidic components for sensors and imaging devices have led to major advances in laboratory sample analysis. Several efforts target portable diagnostic platforms. One group has created a user-friendly miniaturized system that precisely measures levels of various antibodies, antigens, and nucleic acids found in saliva. The prototype is a low-cost disposable device that processes small amounts of saliva, amplifies its DNA, and detects the levels of DNA sequences of interest. Another group has developed a product to improve oral cancer detection. Created for dental office use, the handheld device emits a cone of light into the mouth that causes molecules within the cells to fluoresce. Normal oral tissue emits a pale green fluorescence while early oral tumor cells appear dark green or black.

Understanding the role that environment plays in the disease process requires accurate quantitative assessment. One novel NIH program aims to support development of technologies that make precise quantitative measurements of personal exposure to environmental chemical/biological agents, diet, physical activity, and psychosocial stress. Relatively inexpensive, lightweight, portable monitors and sensors such as wristbands, watches, or phones can be used to relay data from an individual to a central collective data bank.

NIH, along with the National Science Foundation, sponsored a workshop in 2006 to assess technological developments needed for advances in point-of-care testing and to identify clinical problems that could benefit from a point-of-care approach. As a result, NIH is supporting a program designed to create a national network of expertise to develop technologies that will address unmet clinical needs in global health, early detection of neurological emergencies (strokes), and detection of pathogens in emergency and disaster situations.

While some technologies have experienced widespread acceptance, several barriers must be overcome to make point-of-care diagnostics the norm. These include:

- Combining individual components into fully integrated systems that can handle all aspects of analysis
- Capturing data from these devices and transmitting it to clinical information systems
- Facilitating assessment of clinical opportunities in point-of-care testing to guide the development of emerging technologies
- Developing infrastructure to create multidisciplinary research collaborations that facilitate clinical testing early in the development process
- Validating results from point-of-care technologies
- Developing user-friendly devices
- Proving that point-of-care testing provides a clinical benefit over analysis at a central laboratory

## Large-Scale Collaborative Activities

Multidisciplinary teams are essential to solving the complex problems that many emerging fields present. NIH-supported investigators in the promising field of tissue engineering and regenerative medicine, for instance, draw on the expertise of chemists, physicists, biologists, engineers, and computer scientists, among others. Coordinated efforts among these different groups are vital to continue progress made over the last two decades that has included fabrication of the first artificial organs. To make engineered tissue a viable clinical option, new computer programs must be designed to model the tissue in three dimensions. Novel approaches to fabrication and manufacturing are also needed for widespread use.

In an effort to develop new collaborations, NIH has implemented the Partnerships to Promote Innovation program. Examples of activities supported through this program include a cooperative research and development agreement, under which NIH and Siemens Medical Solutions will design new MRI technologies to diagnose and treat heart disease. Another agreement between NIH and the German National Research Center for the Environment will enable key genetic mouse models to be transferred to NIH investigators from the German Gene Trap Consortium.

The [Biomedical Technology Research Resources](#) (BTRRs) programs supported by NIH serve a unique purpose in the broad context of NIH-funded research. They represent a critical mass of technological and intellectual resources with a strong focus on service and training for outside investigators. They develop new technologies and tools in areas including imaging, informatics, synchrotrons, electron microscopy, proteomics and glycomics, optics, and lasers. Access to these technologies is critical to enabling research because they are frequently too advanced or expensive to be widely available. There are approximately 50 BTRRs located throughout the country that disseminate and promote the application of cutting-edge technologies they have developed across the full spectrum from bench to bedside. These centers are multidisciplinary and collaborative, and serve as catalysts for integrating the diverse efforts of NIH-supported researchers, providing technological infrastructure, experimental and computational resources, and expertise.

The goal of the NIH-funded [Biomedical Informatics Research Network](#) (BIRN) is to allow researchers to collaborate by sharing data and tools. The BIRN is developing the informatics infrastructure necessary to allow any group of investigators to share data among themselves or with a broader community (see also the section on *Disease Registries and Other Data Systems* in Chapter 3). The resulting collaborative environment extends beyond the boundaries of individual laboratories to enable collaborations that cross geographic and disciplinary boundaries. Basic and clinical investigators are able to share disparate data as well as powerful new analytical tools and software across animal models and among multiple sites. This major initiative initially was developed to allow neuroimagers to share data and tools, but the infrastructure is generic and therefore applicable to other disciplines. With the infrastructure in place and the lessons learned from the neurology projects, NIH has just released a set of program announcements to expand BIRN to support other large-scale, collaborative investigations.

## Transforming Health Care

The combination of new tools and techniques developed to improve basic research as well as those aimed at delivering better health care will transform the current medical paradigm into one that is predictive, personalized, preemptive, and participatory. These new tools and techniques are critical as the population ages and chronic, rather than acute, conditions become the norm.

NIH-supported researchers are leading the way toward a new paradigm in which technology is a central feature of fast and effective health care delivery. NIH funding of technology development provides an environment that enables investigators to think beyond what is conventional, to do so across disciplines, and to take the health care system to a level that will engage scientists, patients, and physicians in a collaborative experience.

### Notable Examples of NIH Activity

#### Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

## Toward a New Era in Medicine

**Pediatric Circulatory Support:** Options for the circulatory support of pediatric patients younger than 5 years are currently limited to short-term extracorporeal devices, the use of which is often complicated by infection, bleeding, and blood clots. Recognizing the need for additional options, NIH established a program to facilitate the development of new circulatory support systems for infants and children with congenital or acquired cardiovascular diseases. The program supports five research groups developing a variety of devices for different pediatric applications. The common objective for the devices is to provide reliable circulatory support for infants and children while minimizing adverse effects.

- For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-HL-03-004.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NHLBI)

**Cochlear Implants:** One of the more groundbreaking biomedical achievements in the last 30 years has been the cochlear Implant, an electronic device that provides a sense of sound to individuals who are profoundly deaf or severely hard of hearing. Cochlear implants process sounds from the environment and directly stimulate the auditory nerve, bypassing damaged portions of the inner ear. Nearly 100,000 individuals worldwide have been fitted with a cochlear implant. In the United States, roughly 22,000 adults and nearly 15,000 children have received one. Derived in part from NIH-funded research that dates back to the early 1970s and continues today, this remarkable technology has enabled deaf and severely hard-of-hearing individuals to enjoy an enhanced quality of life. NIH-supported scientists showed that profoundly deaf children who receive a cochlear implant at a young age develop language skills at a rate comparable to

children with normal hearing. NIH-supported scientists found that the benefits of the cochlear implant far outweigh its costs in children. Scientists can now study the large groups of children who were identified early for hearing loss and use this knowledge to document how treatments such as cochlear implants can lead to improved speech and language acquisition, academic performance, and economic outcomes for these children.

- [Nicholas JG, Geers AE. \*Ear Hear\* 2006;27:286-98](#), PMID: 16672797
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDCD)

**Hearing Aids and Directional Microphones:** Approximately 32.5 million American adults report some degree of hearing loss (NCHS/NHIS data for 2003). Although almost 95 percent of Americans with hearing loss could have their hearing treated with hearing aids, only about 20 percent of Americans with hearing loss have hearing aids and many who wear them are dissatisfied with their aids. Hearing in noisy environments is a major unsolved problem faced by hearing-aid users, and, of all available technologies, directional microphones currently show the most promise for addressing this problem. NIH-supported scientists have been studying the tiny fly *Ormia ochracea*, which has such sensitive directional hearing that it has inspired ideas for a new generation of hearing aids. The fly's ear structure, which permits ultrasensitive time coding and localization of sound, provides a model for scientists and engineers to use in developing new miniature directional microphones for hearing aids that can focus sound amplification on speech. To improve hearing aid technology so that users can better understand speech in a noisy background, NIH-supported scientists successfully completed a prototype of a low-power, highly directional microphone small enough to fit into a hearing aid. The use of improved directional microphones in hearing aids will improve the quality of life for individuals with hearing loss who depend on hearing aids to understand spoken language.

- [Miles RN, Hoy RR. \*Audiol Neurootol\* 2006;11:86-94](#), PMID: 16439831
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NIDCD) (GPRA Goal)

## Gene Sequencing and Beyond

**The Cancer Genome Atlas (TCGA):** TCGA is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. The goal of TCGA is to develop a free, rapidly available, publicly accessible, comprehensive catalogue, or atlas, of the many genetic changes that occur in cancers, from chromosome rearrangements to DNA mutations to epigenetic changes – the chemical modifications of DNA that can turn genes on or off without altering the DNA sequence. The overarching goal of TCGA is to improve our ability to diagnose, treat, and prevent cancer.

- For more information, see <http://cancergenome.nih.gov/index.asp>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Genomics*.
- (E/I) (NCI, NHGRI)



**ENCODE:** The ENCyclopedia Of DNA Elements (ENCODE) is an international research consortium organized by NIH that seeks to identify all functional elements in the human genome. The initial 4-year pilot phase has just been completed, and the consortium has published a series of papers describing an intricate network in which genes and other regulatory mechanisms interact in complex ways. Other insights include the discovery that the majority of DNA in the human genome is transcribed into functional molecules, called RNA, and that these transcripts extensively overlap one another. These findings challenge long-held beliefs that the genome has small sets of genes and vast amounts of “junk” or untranscribed DNA. Until now, most studies have concentrated on the functional elements of specific genes, and have not provided information about functional elements in the vast majority of the genome that does not contain genes. ENCODE’s exciting discoveries may well reshape the way scientists think about the genome and pave the way for more effective approaches to both understanding and improving human health.

- [The ENCODE Project Consortium, et al. \*Nature\*. 2007;447:799-816](#), PMID: 17571346
- For more information, see <http://www.genome.gov/10005107>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHGRI)

**Genome Technology and the \$1,000 and \$100,000 Genome Initiatives:** DNA sequencing spells out the order in which our chemical building blocks are arranged, making DNA sequencing a powerful resource for biomedical research. Although DNA sequencing costs have dropped by more than three orders of magnitude since the start of the Human Genome Project, sequencing an individual’s complete genome for medical purposes is still prohibitively expensive. Developing technology to make whole-genome sequencing more affordable would enable the sequencing of individual genomes to become part of routine medical care. The Genome Technology program supports research to develop new methods, technologies, and instruments to rapidly and at low cost:

- ▷ transcribe DNA sequences
- ▷ check sequences for genetic variations (SNP genotyping)
- ▷ aid research to understand the effects of genetic variations on genomic function.

Additionally, NHGRI supports two types of sequencing grants: (1) “Near-Term Development for Genome Sequencing” grants support research aimed at sequencing a human-sized genome at 100 times lower cost than is possible today (\$100,000) and (2) “Revolutionary Genome Sequencing Technologies” grants aim to develop breakthrough technologies that will enable a human-sized genome to be sequenced for \$1,000 or less. Currently, only analyses of ~ 500,000 Single Nucleotide Polymorphisms (SNPs) are being performed commercially at this cost; an individual's complete genome sequence (~ 3 billion base pairs) would offer vastly more information.

- For more information, see <http://www.genome.gov/10000368>
- For more information, see <http://www.genome.gov/19518500>
- This example also appears in Chapter 3: *Genomics*.
- (E) (NHGRI)

**Large-Scale Sequencing Program:** NIH's Large-scale Sequencing Program funds three major research centers in the United States to conduct genetic sequencing. During and since the completion of the Human Genome Project, NIH-funded centers have used their industrial-scale enterprises to improve DNA sequencing methods, thereby substantially decreasing costs and increasing capacity. For many years, the Program has achieved twofold decreases in cost approximately every 20 months. One of the main projects now under way is the sequencing of the genomes of other primates, such as orangutan, baboon, gibbon, and marmoset (in addition to chimpanzee and macaque, which are complete). By comparing the human genome to that of other primates, researchers can find important information about both health and abilities that are uniquely human and those shared with other species. The Program also supports the genomic sequencing of human pathogens (organisms that cause disease in humans) and their vectors, the organisms that carry those pathogens. Also, many mammals are being sequenced to identify elements that are functionally important to human biology. These studies will undoubtedly unveil new biological insights to increase our understanding of how the human genome works.

- [Rhesus Macaque Genome Sequencing and Analysis Consortium, et al. \*Science\*. 2007;316:222-34, PMID: 17431167](#)
- For more information, see <http://www.genome.gov/10001691>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHGRI)

**Population Genomics, GAIN, and GEI:** In February 2006, the U.S. Department of Health and Human Services announced the creation of two related groundbreaking initiatives in which NIH is playing a leading role. The Genetic Association Information Network (GAIN) and the Genes, Environment, and Health Initiative (GEI) will accelerate research on the causes of common diseases. GAIN is a public-private partnership among NIH, Foundation for the NIH, Pfizer, Affymetrix, Perlegen, Broad Institute, and Abbott. GEI is a trans-NIH effort combining comprehensive genetic analysis and environmental technology development to understand the causes of common diseases. Both GAIN and GEI are powered by completion of the "HapMap," a detailed map of the 0.1 percent variation in the spelling of our DNA that is responsible for individual predispositions for health and disease. Data from GAIN will narrow the hunt for genes involved in six common diseases. In June 2007, the first GAIN dataset, on attention deficit hyperactivity disorder, was released. GEI will provide data for another approximately 15 disorders, and will develop enhanced technologies and tools to measure environmental toxins, dietary intake, and physical activity, as well as an individual's biological response to those influences.

- For more information, see <http://www.genome.gov/19518664> <http://www.genome.gov/19518663>
- For more information, see <http://genesandenvironment.nih.gov/> <http://www.genome.gov/11511175>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E/I) (NHGRI)

## Probing Proteins

**NIGMS/NCI Collaborative Access Team (GM/CA-CAT):** Structural biology is a field in which scientists learn about molecules by determining their three-dimensional structures in atom-by-atom detail. Enormous facilities called synchrotrons allow researchers to use x rays to determine molecular structures more easily, quickly, and cheaply than ever before. Two NIH institutes (NIGMS and NCI) funded the development of a new section of the synchrotron at Argonne National Laboratory (the Advanced Photon Source). The new section includes three stations (beamlines) that scientists from across the United States will be able to use to determine the detailed, three-dimensional structures of molecules. This sort of research is important to understanding basic biological processes and designing drugs. The facility was to be in full operation in the last quarter of 2007.

- For more information, see <http://www.nigms.nih.gov/Initiatives/PSI/>
- (E) (NIGMS, NCI)

**Clinical Proteomic Technologies Initiative for Cancer:** The completion of the Human Genome Project in 2003 has been a major catalyst for proteomics research and NIH has taken a leading role in facilitating the translation of proteomics from research to clinical application through its Clinical Proteomic Technologies Initiative for Cancer. The overall objective of this Initiative is to build the foundation of technologies (assessment, optimization, and development), data, reagents and reference materials, computational analysis tools, and infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate discovery research and clinical applications.

- For more information, see <http://proteomics.cancer.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Genomics*.
- (E/I) (NCI)

**Protein Structure Initiative:** Scientists learn a lot by studying the detailed, three-dimensional structures of proteins. This knowledge helps them better understand the biochemical processes involved in health and disease. It can also greatly advance the design of medicines to treat a wide range of diseases. Recognizing this, NIGMS established the Protein Structure Initiative (PSI) in 2000. This multimillion dollar initiative involves hundreds of scientists across the Nation and is a collaborative effort between the Federal government, universities, and industries. Already, members of the PSI have determined thousands of structures and have developed new technologies that improve the speed and ease of determining molecular structures. In addition to benefiting the PSI team, this work has accelerated research in other fields.

- For more information, see <http://www.nigms.nih.gov/Initiatives/PSI/>
- (E) (NIGMS)

**Membrane Protein Production and Structure Determination:** The NIH Roadmap on Structural Biology seeks to develop innovative approaches and technologies for rapidly producing membrane proteins – the proteins tightly wedged within the lining of our cells. These protein samples can then be used to determine the proteins' underlying structures which will help researchers clarify the role of proteins in health and disease. Scientists currently have enormous

difficulty pulling membrane proteins from cells in a condition suitable for functional and structural studies. Although these challenging proteins account for about 30 percent of all cellular proteins and are targets of 60-70 percent of known drugs, only about 100 structures of membrane proteins have been identified. In contrast, over 20,000 soluble protein structures have been determined. With the development of efficient protein-producing methods, researchers will be able to study and understand how membrane proteins function and interact with microbes, viruses, other cells, and drugs. By shifting the emphasis from hypothesis-driven research to technology development, the NIH Roadmap on Structural Biology has significantly impacted the membrane protein community. It has initiated collaborations among chemists, cell biologists, biophysicists, modelers, and physicists. Ultimately, the research will expand our knowledge of membrane protein structures, which may lead to improvements in drug design.

- For more information, see <http://nihroadmap.nih.gov/structuralbiology/>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-003.html>
- (E) (Roadmap—all ICs participate)

## Insights From Animal Models

**Tools to Reveal the Mechanisms Governing Behavior:** Newly acquired but rapidly evolving tools and techniques that monitor or probe discrete brain systems have allowed NIH-supported researchers to begin filling in the information gap between molecular or cellular events and behavioral outcomes. A notable preclinical example of this trend is the development of a genetically engineered method to turn the electrical impulses of brain cells on and off with pulses of light, in synch with the split-second pace of real-time neuronal activity. The novel technique borrows genes from light-responsive algae and bacteria to unravel the intricate workings of brain circuits with extreme precision. This powerful new tool could be used to assess the role of neuronal activity in regulating normal behavior and disease processes. On the clinical side, an array of brain imaging devices has produced much information on how neural circuits develop and process information under normal conditions, and how they become impaired by a disease-like addiction. These advances have led to the fertile concept that the transition from abuse to addiction is not a switch but a gradual degradation of the ability of different circuits to “talk” to each other as they attempt to compensate for their deficiencies. Interestingly, these studies are also showing significant overlap in the circuits involved in drug abuse and the circuits underlying compulsive overeating and obesity. Moreover, in preclinical studies, compounds that interfere with food consumption in animal models of compulsive eating also interfere with drug administration.

- For more information, see <http://www.nimh.nih.gov/press/lightswitchneurons.cfm>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDA, NIMH)

**The Knockout Mouse Project (KOMP):** The NIH Knockout Mouse Project (KOMP) is an NIH-wide effort to create a publicly available resource of knockout mouse mutations that can be used to study human disease. Knockout mice are strains of mice in which specific genes have been completely disrupted, or knocked out. By studying these mice, researchers can evaluate the effect of this systematic disruption of different genes on physiology and development.

Understanding the effects of gene disruption in mice will provide powerful tools to develop better models of inherited human disease. NIH has awarded 5-year cooperative agreements for the creation of knockout mice lines to Regeneron Pharmaceuticals Inc. to a collaborative team from Children's Hospital Oakland Research Institute, and to the Wellcome Trust Sanger Institute in England. NIH has also recently awarded \$4.8 million to the University of California, Davis, and the Children's Hospital Oakland Research Institute to establish and support a repository for the KOMP. The repository will enable many more researchers to have access to the knockout mice and will ensure product quality for the 8,500 types of knockout mice currently available.

- [Austin CP, et al \*Nat Genet.\* 2004;36:921-4](#), PMID: 15340423
- For more information, see [www.komp.org](http://www.komp.org)
- This example also appears in Chapter 3: *Genomics*.
- (E/I) (NHGRI)

**Multimodal PET and MRI Imaging Instrumentation:** Investigators are developing a small animal PET/MRI system to study diseases such as cancer using animal models. This project will exploit the strengths of two widely used medical imaging modalities – positron emission tomography (PET) and magnetic resonance imaging (MRI). PET is a highly sensitive nuclear medicine imaging modality but requires radionuclides and has poor spatial resolution. On the other hand, MRI has poor sensitivity but provides high spatial resolution and does not require radionuclides. One expected application of the small animal PET/MRI system would be to develop imaging biomarkers for cancer. These biomarkers could provide new ways to monitor and test novel therapeutics, which may improve health care for cancer patients.

- [Catana C, et al. \*J Nucl Med.\* 2006;47:1968-76](#), PMID: 17138739
- For more information, see <http://atlasserv.caltech.edu/~petmri/>
- (E) (NIBIB)

## Imaging Biological Systems

**The Cancer Imaging Program (CIP):** The mission of CIP is to promote and support cancer-related basic, translational, and clinical research in imaging sciences. CIP initiatives include (a) development and delivery of image-dependent interventions for cancer and precancer, (b) standardized models for the design of clinical trials using imaging, (c) development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening, and (d) development of imaging methods to detect, treat, and monitor response to therapy.

- For more information, see <http://imaging.cancer.gov/>
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NCI)

**Imaging Initiative From Molecules to Cells:** Much human suffering is caused by the breakdown of the intricate and highly dynamic organization of the body at every level, starting with the structure of macromolecules such as proteins, progressing through ensembles of proteins that make molecular machines, to the sets of these machines that form organelles (mini-organs within cells), right up through cells and tissues. To make progress in fighting these diseases, we need to make progress in learning exactly how a pathogen, cancer cell, or faulty

gene disorganizes living matter. The time is now ripe to turn the powerful new imaging approaches developed in physics and biophysics laboratories to the imaging of living material in health and disease, because then we can see exactly how things work and what goes wrong. IC intramural program leaders have collaboratively developed a strategic plan for trans-NIH efforts to realize the full potential of these powerful technologies for biomedical research. All of the NIH Institutes will play a role in moving forward on this plan, with leadership from the NIBIB, NICHD, and NCI.

- (I) (NIBIB, NCI, NICHD)

**Molecular Imaging of G-Protein Coupled Receptors for Drug Development:** What do over 50 percent of all therapeutic drugs have in common? They act on a specific type of receptor on the surface of cells known as the G-protein coupled receptor (GPCR). GPCRs form a large family of membrane-bound proteins containing seven trans-membrane helices connecting an extracellular receptor site to an intracellular G-protein binding site. This transmembrane nature provides extracellular control over important intracellular functions. To date, all of the drugs that target GPCRs have been developed using screening approaches. These approaches have been effective but their cumbersome and expensive nature severely limits widespread development of novel GPCR-targeted drugs for cancer, heart disease, obesity, and many other illnesses. Novel “structure-based” methods can overcome these problems and have been very successful with HIV protease inhibitors. However, structure-based drug design methods have not been possible with GPCRs because of the complexity of the structure and the fact that it sits within the cell membrane. NIH-funded researchers are developing and extending novel “solid-state” NMR technology to design new approaches that can obtain “atomic resolution” three-dimensional structures of GPCRs in their natural environment of the cell membrane. This new approach to drug design may substantially increase the rate of development of specific GPCR-targeted drugs.

- [Park SH, et al. \*J Am Chem Soc.\* 2006;128:7402-3, PMID: 16756269](#)
- [Nevzorov AA, et al. \*J Biomol NMR.\* 2007;37:113-6, PMID: 17216304](#)
- For more information, see <http://nmresource.ucsd.edu/facility/index.html>
- For more information, see <http://www.nibib.nih.gov/Research/ResourceCenters/Listname/Opella>
- (E) (NIBIB)

**New Light Microscope:** By blending emerging advances in physics and microbiology, NIH researchers developed a new light microscope that allows scientists for the first time to visualize and determine how proteins are arranged and compose individual structures within a cell. Known as photoactivated localization microscopy, or PALM, the new technique enables researchers to better view cell structures and understand the complexity of proteins, the cells’ building blocks. For example, using PALM, researchers could study several cellular subsystems, including those that provide energy for the cell’s activities. In addition, researchers could visualize the distribution of the proteins involved in the assembly and budding of the AIDS virus from a host cell, literally giving scientists new insights into targets to stop viral replication.

- [Betzig E et al. \*Science.\* 2006;313:1642-5, PMID: 16902090](#)
- For more information, see [http://www.nichd.nih.gov/news/releases/microscope\\_view\\_protein.cfm](http://www.nichd.nih.gov/news/releases/microscope_view_protein.cfm)
- (I) (NICHD)



**Visualizing Transcription of Genes in Living Cells:** Most genes serve one main purpose: as recipes for the body's proteins. The first step in using genes to produce proteins is called transcription. Although scientists think they know how transcription works, it has not been well studied in real-time in living cells. Now, NIH-supported researchers have developed fluorescent dyes and new techniques in microscopy that will enable them to watch transcription from individual genes. Faulty gene transcription can lead to cancer, so a detailed understanding of the process may lead to new ways to treat disease.

- [Yao J, et al. \*Nature\*. 2006;442:1050-3](#), PMID: 16929308
- For more information, see <http://www.nature.com/nature/journal/v442/n7106/extref/nature05025-s3.mov>
- (E) (NIGMS)

## Image-Guided Interventions

**Development of Image-Guided Interventions:** Image-guided interventions (IGI) provide therapy that can minimize trauma and improve patient outcomes. They are applicable in procedures such as biopsy, surgery, radiation treatment, vascular interventions, and guidance during delivery of devices, drugs, cells, or genes. These improved capabilities are particularly important in light of the shifting trend in medicine toward a model of early, presymptomatic detection of disease. The need to support research and development in this area has been identified at multiple workshops sponsored by NIH and other Federal agencies. In response, in August 2006, NIH issued a request for applications to support the first phase of a two-phase project that will deliver high-impact IGIs. Multidisciplinary collaborations and partnerships with industry were encouraged, with the goal of developing multipotential technologies with high clinical impact applicable across a range of diseases and disorders.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-06-003.html>
- (E) (NIBIB, NCI) (GPRA Goal)

## Diagnostics and Point-of-Care Technologies

**Diabetes Research in Children Network (DirecNet):** The risk of hypoglycemia is now the main obstacle to successfully managing type 1 diabetes mellitus (T1DM) in children of all ages. Severe hypoglycemia can lead to seizures or unconsciousness. In 2001, NIH established DirecNet to assess the accuracy and efficacy of continuous glucose monitoring devices, evaluate the effectiveness of the devices as tools to help control blood sugar levels, and determine the incidence of hypoglycemia. DirecNet also focuses on possible changes in neurocognitive function in children with T1DM who have frequent bouts of hypoglycemia. The network was recently renewed to use new tools to evaluate factors and mechanisms contributing to hypoglycemia, such as exercise and diet. The goal is to continue to improve management of T1DM and prevent hypoglycemia by “closing the loop” between measuring glucose levels and delivering insulin.

- For more information, see <http://www.nichd.nih.gov/research/supported/directnet.cfm>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-06-020.html>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NICHD, NIDDK, NINDS)

**Advances in Oral Cancer Detection:** The first product of a current NIH-funded research project to integrate new technologies into a reliable clinical protocol to improve oral cancer detection and survival has reached the market. Researchers report success using a customized optical device that allows dentists to visualize in a completely new way whether a patient might have a developing oral cancer. The simple, handheld device emits a cone of light into the mouth that excites molecules within our cells, causing them to absorb the light energy and re-emit it as visible fluorescence. Remove the light, and the fluorescence disappears. Changes in the natural fluorescence of healthy tissue can indicate light-scattering changes caused by developing tumor cells. Health care providers shine a light onto a suspicious sore in the mouth, look through an attached eyepiece, and check for changes in color. Normal oral tissue emits a pale green fluorescence, while early tumor cells appear dark green to black. The instrument is an effective screening adjunct and is useful for helping surgeons determine how far to extend the surgical borders when removing tissue for biopsies.

- For more information, see <http://clincancerres.aacrjournals.org/cgi/content/full/12/22/6716>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDCR)

**Salivary Diagnostics:** NIH stands at the forefront of efforts to develop salivary diagnostics, the use of saliva as a robust, sensitive, reliable, low-cost, user-friendly “point of care” mechanism for early disease diagnosis, monitoring drug levels, and detecting environmental insults. Salivary tests can be performed on the spot and require no painful needle sticks. A number of grantees are currently working to develop a tiny automated machine that can precisely measure levels of the various antibodies, antigens, and nucleic acids present in saliva. Recently, the promise of salivary diagnostics moved closer to becoming technologically feasible with the fabrication of the first disposable, low-cost miniaturized diagnostic platform to process small amounts of saliva, amplify its DNA, and detect the levels of DNA sequences of interest. Once development of a similarly robust sample preparation process is complete, the cassette will offer the first fully integrated, highly flexible platform for multiple analysis paths.

- [Wang J, et al. \*Lab Chip\*. 2006;6:46-53](#), PMID: 16372068
- (E) (NIDCR)

**New Genetics Tools Shed Light on Addiction:** NIH-supported research is taking full advantage of the massive databases and rapid technologies now available to study how genetic variations influence disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms and the genetic predispositions underlying diseases like addiction. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as “gene chips” (e.g., the *neurexin* gene has been found to play a role in drug addiction). A next-generation “neurochip” is being developed with 24,000 gene variants related to substance use and other psychiatric disorders. Applying this tool to addiction and other brain disorders will advance our understanding of not only vulnerability to addiction and its frequent comorbidities, but also ways to target treatments based on a patient’s genetic profile (i.e., a “pharmacogenetic” approach). To complement these efforts, NIH is investing heavily in the emerging field of *epigenetics*, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions

between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. A focus on gene by environment interactions has recently been expanded to incorporate developmental processes, now known to also affect the outcome of these interactions. The resulting Genes, Environment, and Development Initiative (GEDI) seeks to investigate how interactions among these factors contribute to the etiology of substance abuse and related phenotypes in humans.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/rfa-da-07-012.html>
- For more information, see <http://nihroadmap.nih.gov/roadmap15update.asp>
- This example also appears in Chapter 3: *Genomics* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NIDA, NCI, NIAAA, NIMH) (GPRA Goal)

**Exposure Biology Program of the GEI:** As a major partner in the Genes, Environment, and Health Initiative within NIH, NIEHS has especially focused on the Exposure Biology/Exposure Measurement dimension of this initiative, through which we will improve the technologies for detection and measurement of the actual exposures sustained by human or other organisms that are currently often weak and imprecise. This is in contrast to the robust tools employed in the fields of genetics and genomics. Personalized measures of environmental exposure must be developed that are equivalent to the ability to measure genetic variability between individuals. The increasing sophistication of our understanding of the biological pathways involved in host response to a given exposure points the way toward the use of that knowledge to develop improved methods for detecting and measuring environmental exposures. Needed are relatively inexpensive, highly portable monitors – a wristband, watch, phone, or lightweight tote for example – that could accurately collect and retain large amounts of data on exposures and to some degree process that data into useful form. Recent advances in environmental and biological sensors suggest that the technologies are at hand, or can be readily engineered to provide precise measure of chemical and biological hazards at the point of contact and/or to characterize the biological fingerprint left by a class of environmental stressors. The value of these technologies would far exceed even the ingenuity required to create them, in enabling researchers to detect associations between environmental exposures and disease.

- For more information, see <http://www.gei.nih.gov/exposurebiology/index.asp>
- (E) (NIEHS) (GPRA Goal)

**Alcohol Biosensors Program:** This Advanced Research Program, modeled on the U.S. Department of Defense's DARPA (Defense Advanced Research Projects Agency) program, was developed by NIH to generate a technical solution to address the need for continuous measurement of alcohol concentrations over time in clinical and basic research on alcohol use disorders. NIH awarded five research and development contracts for alcohol biosensor development. Each research group employed a different technological approach for alcohol measurement, and all have made substantial progress in engineering commercially viable alcohol biosensors, some of which will likely make their way to market in the next few years.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIAAA)

**Point-of-Care Research Network:** The need to improve the quality and accessibility of care while reducing costs is a significant challenge currently faced by the Nation's health care system. Adding to this challenge is the need to reduce health disparities and provide care for an aging population. Significant improvements in health care delivery can be achieved through the development of point-of-care systems that can be integrated into the health care delivery system through information and communications technologies. A major challenge in this effort is to evaluate the clinical feasibility of integrated technology in sensors, microsystems, imaging, and informatics. To address this challenge, NIH is establishing a Research Network that will develop integrated systems that address unmet clinical needs in point-of-care testing. This will be accomplished through the creation of multidisciplinary partnerships that will interact across the network to enable broad coverage of clinical and technological issues in point-of-care testing.

- For more information, see <http://www.nibib.nih.gov/NewsEvents/SympReports/2006Apr11>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-06-002.html>
- (E) (NIBIB)

**Newborn Screening:** Screening and treating newborns for phenylketonuria (PKU) and hypothyroidism have virtually eliminated these conditions as a cause of mental retardation in the United States. A new, trans-NIH collaborative effort will build on this success to develop a new generation of microchips and related technologies that should enable screening programs across the Nation to rapidly test newborns for hundreds of genetic conditions in a single test using one drop of an infant's blood. Complementing the technology development is an initiative to stimulate development of new treatments for such conditions as short chain Acyl CoA dehydrogenase deficiency (SCAD), tyrosinemia, and the genetic causes of hearing loss with the promise of significantly reducing the lifelong health burden of these and other conditions.

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NICHD, NIDCD, NIDDK)

**Wireless Information System for Emergency Responders (WISER<sup>®</sup>):** WISER is a system designed to assist first responders in hazardous material incidents by providing a wide range of information on hazardous substances, including substance identification support, physical characteristics, human health information, and containment and suppression advice. In 2007, several important features were added to WISER, including radiological support with data for over 20 isotope substances and tools/reference materials for radiological incidents. A new partnership with the U.S. Department of Transportation (DoT) enabled integration of the DoT's Emergency Response Guidebook (ERG) 2004 with WISER and the development of a stand-alone ERG 2004 Mobile version. Widely used by first responders, WISER is available for downloading onto PDAs and Windows-based platforms or for browsing on the Web.

- For more information, see <http://wiser.nlm.nih.gov>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (I) (NLM)

**Genes, Environment, and Health Initiative, Exposure Biology Program:** This trans-NIH initiative supports the development of environmental sensors for measurement of chemicals, dietary intake, physical activity, psychosocial stressors, and addictive substances and of

“fingerprints” (markers) of biological response to exposures to these environmental factors. These new methods will ultimately be used to monitor environmental exposures that interact with genetic variations that influence health and disease. In addition, a workshop on measuring psychosocial stress and the social environment is planned for early FY 2008.

- For more information, see <http://www.gei.nih.gov/exposurebiology/>
- (E) (OD)

## Large-Scale Collaborative Activities

**Partnerships to Promote Innovation:** NIH has implemented new collaborations with electronics and pharmaceutical industry leaders and with the German government to develop innovative technologies and their application to biomedical research. A Cooperative Research and Development Agreement (CRADA) between NIH and Siemens Medical Solutions has been adopted to promote the design of new magnetic resonance imaging methods for the diagnosis and treatment of heart disease. A material transfer agreement between NIH and the German National Research Center for the Environment is being negotiated to facilitate the transfer of important mouse genetic models from the German Gene Trap Consortium mouse distribution facility to NIH investigators. Additionally, a Materials-CRADA has been negotiated between NIH and Merck & Co. to facilitate transfer of proprietary Merck biologics and compounds for internal NIH research and development, with the specific aims of reducing transaction costs and getting necessary research materials into the hands of NIH investigators quickly and efficiently.

- [Kellman P. et al. \*Magn Reson Med.\* 2005;53:194-200](#), PMID: 15690519
- For more information, see <http://tikus.gsf.de>
- (I) (NHLBI)

**Innovative Technologies for Engineering Small Blood Vessels:** NIH has initiated a program of basic research studies to enlighten future development of replacements for damaged or diseased small blood vessels. Thousands of patients each year could benefit from small blood vessel substitutes (e.g., to bypass coronary artery or peripheral vascular occlusions or to establish arteriovenous shunts for hemodialysis), but currently available replacement grafts have a high failure rate. Recent advances in materials science, bioengineering, and tissue engineering, as well as the availability of better computational tools, are providing opportunities for the development of replacement blood vessels with properties that closely match those of natural blood vessels.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHLBI)

**The NCI Alliance for Nanotechnology in Cancer:** This is a comprehensive, systematized initiative encompassing the public and private sectors, designed to accelerate the application of the best capabilities of nanotechnology to cancer. The program supports research on novel nanodevices that may detect and pinpoint the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real time whether these drugs are effective at killing malignant cells. Nanotechnology will likely change the very foundations of cancer diagnosis, treatment, and prevention.

- For more information, visit <http://nano.cancer.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NCI)

**Biomedical Informatics Research Network (BIRN):** Modern biomedical research generates vast amounts of diverse and complex data. Increasingly, these data are acquired in digital form, allowing sophisticated and powerful computational and informatics tools to help scientists organize, store, query, mine, analyze, view, and, in general, make better use and sense of their data. Moreover, the digital form of these data and tools makes it possible for them to be easily and widely shared across the research community at large. NIH has supported development of the BIRN infrastructure to share data and tools by federating new software tools or using the infrastructure to federate significant datasets. BIRN fosters large-scale collaborations by utilizing the capabilities of the emerging national cyberinfrastructure. The project includes a Coordinating Center at the University of California, San Diego, which serves the critical task of developing, deploying, and maintaining key infrastructure components, including high-bandwidth connectivity, grid-based security, file management and computational services, techniques to federate databases, and shared visualization and analysis environments.

- For more information, see <http://www.nbirn.net/>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NCRR)

**Biomedical Technology Research Resources (BTRRs):** The BTRRs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Resources and through intensive collaborations with other leading laboratories. The BTRRs are used annually by nearly 5,000 scientists from across the United States and beyond, representing over \$700 million of NIH funding for 22 institutes and centers. As an example, optical technologies enable researchers to:

- ▷ Harness the power of light to “see” biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- ▷ Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

- For more information, see [http://www.ncrr.nih.gov/biomedical\\_technology/](http://www.ncrr.nih.gov/biomedical_technology/)
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCRR)

**Glycomics Technology Development, Basic Research, and Translation Into the Clinic:** Complex carbohydrates are ubiquitous, found on the surfaces of cells and secreted proteins.



Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules are thus critical for basic and clinical research across the spectrum of health and disease, but widely regarded as among the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- ▷ Biomedical Technology Research Resources are developing and sharing cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- ▷ Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
- ▷ Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- ▷ A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.
  - For more information, see [http://www.ncrr.nih.gov/biomedical\\_technology/biomedical\\_technology\\_research\\_resources/technology\\_for\\_systems\\_biology/glycomics.asp](http://www.ncrr.nih.gov/biomedical_technology/biomedical_technology_research_resources/technology_for_systems_biology/glycomics.asp)
  - For more information, see <http://www.functionalglycomics.org/static/index.shtml>
  - This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
  - (E) (NCRR, NCI, NHLBI, NIGMS, NINDS)

**Enabling Technologies in Tissue Engineering and Regenerative Medicine:** Tissue engineering and regenerative medicine are interdisciplinary fields in which basic science aimed at understanding the cellular machinery combines with computational and engineering processes to control and direct the aggregate behavior of cells to form tissues and organs. While much progress has been made over the 20 or so years since the field first started, key technologies such as technology to rapidly expand, direct (along a specific cell line path), preserve, and track cells are not yet in place to accelerate development on all fronts. A program announcement sponsored by NIH, the National Science Foundation, and the National Institute of Standards and Technology was issued in 2006 and is focused on developing new infrastructural tools for the field. The funding opportunity will be open through FY 2008 in order to attract the best and most innovative ideas and research plans to advance the field.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-504.html>
- (E) (NIBIB, NHLBI, NIAMS, NICHD, NIDCD, NIDCR)

**National Centers for Biomedical Computing (NCBCs):** The NIH Roadmap Bioinformatics and Computational Biology initiative provides a networked national effort to build computational tools and infrastructure for biomedical computing. The centers are devoted to all facets of biomedical computing, from basic research in computational science to providing the tools and resources that biomedical, clinical, and behavioral researchers need to do their work. The seven centers currently supported by the NIH Roadmap have made substantial progress in

software development, data resources, and scientific ontologies. These advances are currently being used by the research community for studying a broad range of biological problems including cerebral palsy, autism, diabetes, asthma, Alzheimer's disease, Huntington's disease, schizophrenia, bipolar disorder, HIV/AIDS, and prostate cancer. The long-term goal of the initiative is to create a national software engineering system that will enable biomedical and clinical researchers to share and analyze data using a common set of software tools.

- For more information, see <http://nihroadmap.nih.gov/bioinformatics/>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (Roadmap—all ICs participate)

## Transforming Health Care

**New Medical Adhesive Boasts Unique Wet-Dry Abilities:** One day, tissue engineering will make it possible to regenerate lost facial components. Until then, victims of massive craniofacial trauma or extensive surgeries due to cancer often must depend on maxillofacial prosthetics to provide the form and function needed to resume their day-to-day lives. Current adhesives are not always retentive over long periods or changing conditions. The loss of retention can result in visible margins or even dislodgement of the prosthesis. Now NIH-supported scientists report they have merged two of nature's most elegant strategies for wet and dry adhesion. As reported in *Nature*, the scientists designed a synthetic material that starts with the dry adhesive properties of the gecko lizard and supplements it with the underwater adhesive properties of a mussel. The hybrid material, which they call a geckel nanoadhesive, proved in initial testing to be adherent under dry and wet conditions, and also adhered much longer under both extremes than previous gecko-based synthetic adhesives, a major issue in this area of research. According to the authors, their findings mark the first time that two polar opposite adhesion strategies in nature have been merged into a man-made reversible adhesive. It is envisioned that the new adhesive will be used for many medical applications including enhancing the retention of oral/maxillofacial prosthetics.

- [Lee H, et al. \*Nature\* 2007;448:338-41](#), PMID: 1763766
- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2007/PR07182007.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDCR)

**Suture Developed Using DNA Technology:** Supported by an SBIR award, scientists at Tepha, Inc., have developed a new, bioabsorbable surgical suture that is stronger, more flexible, and capable of retaining its strength longer than existing absorbable sutures. The scientists created the suture material in a new way, by genetically engineering bacteria to produce it for them. In February 2007, the FDA approved Tepha's ability to market the sutures. The company hopes that, in the future, the same material will be used for other medical devices, like surgical meshes

for hernia repair, artificial heart valves, absorbable stents, and devices to repair and replace ligaments and tendons.

- For more information, see <http://www.tepha.com/publications/media.htm?ident=21>
- (E) (NIGMS)

**Neural Prosthesis Program:** Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. The NINDS Neural Prosthesis program pioneered the development of this technology beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants for the hearing impaired, respiratory and hand grasp devices for people with spinal cord injuries, and deep brain stimulation for patients with Parkinson's disease, among other contributions. Current work aims to restore standing and voluntary bowel and bladder control after spinal cord injury, to allow paralyzed persons to control devices directly from their brains, and to control seizures. Ongoing research also seeks to improve cochlear implants and to advance deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community, now including private-sector companies, and represents a cooperative effort among several NIH Institutes, which coordinate their efforts with programs now under way in the Department of Veterans Affairs and DoD.

- For more information, see <http://www.ninds.nih.gov/funding/research/npp/index.htm>
- For more information, see <http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NINDS, NIBIB, NIDCD, NICHD, NEI)

**The Cancer Biomedical Informatics Grid™ (caBIG™):** The caBIG initiative has been launched to accelerate research discoveries and improve patient outcomes by linking researchers, physicians, and patients throughout the cancer community. caBIG™ completed its 3-year pilot project in March 2007. This date represents a new phase of evolution, as NIH is committed to bringing caBIG™ into an enterprise model that can be extended and sustained across a broader community.

- For more information, see <http://cabig.cancer.gov/>
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NCI)

**Shared Instrumentation Grant and High-End Instrumentation Programs:** The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the \$100,000-\$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the \$750,000-\$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located on core facilities with trained technical staff to assist in protocol

development and to facilitate integration of new technologies into basic and translational research. In FY 2006 and 2007 the SIG program funded a total of 264 grants for \$95.2 million; the HEI funded a total of 39 awards for \$55.9 million.

- For more information, see [http://www.ncrr.nih.gov/biomedical\\_technology/shared\\_instrumentation/](http://www.ncrr.nih.gov/biomedical_technology/shared_instrumentation/)
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCRR)

**Analytical Methods and Reference Materials (AMRM) Program:** The rapid expansion of the dietary supplement marketplace has resulted in a proliferation of ingredients and products and overtaken the pace of development of reliable analytical methods. Precise, accurate, and rugged analytical methods and reference materials are essential for verification of ingredient identity and measuring the amounts of declared ingredients in raw materials and finished products. Also, dietary supplement labels are required to list certain facts about product identity and content and to be truthful and not misleading. For example, a dietary supplement that boasts “500 mg of Vitamin C from rosehips per tablet” on its label should be expected to contain both 500 mg of Vitamin C and rosehips. That this is not always the case is due in part to the lack of proven and agreed-upon methods to precisely assess the quantity of constituents of many supplements and supplement ingredients. NIH’s AMRM program is intended to assist in providing these critical tools for quality assurance. The program promotes development, validation, and dissemination of analytical methods and reference materials for commonly used dietary supplement ingredients. An external panel of experts recently reviewed the Program and found that it had substantially raised the awareness of the need for better quality-control measures within the dietary supplement community and provided research funding crucial for development, validation, and dissemination of reference materials and analytical methods.

- For more information, see <http://ods.od.nih.gov/pubs/odsupdate/Summer2007.pdf>
- (E) (ODS)

**Evidence-Based Review Program:** In FY 2001, congressional appropriations report language included text asking that NIH review the current scientific evidence on the efficacy and safety of dietary supplements and identify research needs. In response, NIH established an evidence-based review program using the Evidence-based Practice Centers Program established by the Agency for Healthcare Research and Quality to conduct systematic reviews of the scientific literature and prepare reports of their findings. These reports have resulted in the publication of a number of articles in the peer-reviewed literature, and have helped NIH make decisions on research priorities in these areas. NIH institutes and centers have found these reports invaluable in presenting what is and is not known in a research area, thus laying a sound foundation for identifying gaps in knowledge and providing a strong scientific basis for the development of a research agenda. Currently, NIH is sponsoring an evidence report on *Effectiveness and Safety of Vitamin D* that will be used to establish a research agenda to answer important public health questions about vitamin D, and as the basis of a conference planned for September 2007 with the

goal of presenting a balanced overview of the available evidence on the efficacy and safety of vitamin D as an update to the 2003 NIH Conference on Vitamin D and Bone Health.

- For more information, see <http://vitamindandhealth.od.nih.gov/>
- For more information, see <http://ods.od.nih.gov/Research/EvidenceReports.aspx>
- (E) (ODS)

## Multidisciplinary and Interdisciplinary Research

**Microneedle-Based Immunization Against Pandemic Influenza:** NIH is supporting a team of investigators under the Bioengineering Research Partnership grant mechanism to develop a low-cost, room temperature-stable, microneedle-based trans-dermal vaccine patch that could be rapidly distributed through pharmacies, fire stations, or the U.S. mail and self-administered in a painless manner by patients. This dose-sparing delivery system will not produce any sharp, biohazardous waste and would avoid the expensive and time-consuming hypodermic vaccination process administered by medical personnel, thus allowing for a rapid pandemic influenza response. This innovative application impacts the U.S. Department of Health and Human Services Pandemic Influenza Response and Preparedness Plan and NIH's directives on High Priority Influenza Research Areas.

- For more information, see <http://www.hhs.gov/nvpo/pandemicplan>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIBIB)

**Systems Biology and Systems Genetics:** NIH launched the Integrative Cancer Biology Program to focus on networks that can be measured, modeled, and manipulated rather than individual components. Multidisciplinary teams are critical to integrating the disciplines of biology, medicine, engineering, mathematics, and computer science (e.g., computational biology). Equally important to our understanding of cancer is *systems genetic research* (systems biology + genetics). Networks of genes can be found and their associations tested and quantified, with parallel association studies on relevant human populations.

- For more information, see <http://icbp.nci.nih.gov/>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCI)

## Critical Issues in eHealth Research Conference: Toward Quality Patient Centered Care

**(September 2006):** This second of two eHealth conferences served three purposes: (1) to highlight research methodologies that intersect across information technology, health communications, behavioral science, medical science, and patient care research, (2) to showcase existing and emerging technologies relevant to communications among patients and their health care teams, and (3) to discuss conceptual issues related to patient-centered eHealth research.

- [Atienza AA, et al. \*Am J Prev Med.\* 2007;32:S71-4.](#) PMID: 17466821
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (OBSSR, NCI, ODP/ORD)

**Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences:** Merging scientific insights and technologies gleaned from behavioral and social sciences with approaches from other scientific disciplines offers the promise of further advancing the public health mission of NIH. This NIH Roadmap initiative funds projects that develop new/innovative measures, methods, and technologies that support the integration of human social and/or behavioral science with other disciplines across varying levels of analysis.

- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp>
- (E) (Roadmap—all ICs participate)

**Nanomedicine Development Centers (NDC):** The structures inside living cells operate at the nanoscale (about 1/10,000 the thickness of human hair). Recent advances in nanotechnology, which refers to the understanding and control of materials at the nanoscale, have yielded new tools to probe and manipulate objects at the nanoscale. These tools, as well as a variety of newly engineered nanostructures, are starting to be used in biomedical research. Nanomedicine, an offshoot of nanotechnology, is a rapidly emerging, multidisciplinary field that was identified as one of the nine initial NIH Roadmap initiatives. In late 2006, NIH completed the establishment of a national network of eight NDCs after an intensive 2-year planning and application process that involved extramural stakeholders from scientifically and medically diverse fields. The overarching goal of these centers is to understand and control the nanomachinery inside living cells in order to diagnose or treat disease and repair tissue. The work at these centers, which involve over 120 biomedical researchers located in 30 institutions, 12 States, and 6 countries, is geared toward understanding the fundamental properties of intracellular structures with great precision so that highly specific treatment or possibly even replacement of these structures can be achieved with few or no side effects. Unlike traditional, translational research targeting a specific medical problem, these centers are beginning with basic science studies and, over a 10-year period, will apply their tools, technologies, and newly developed structures to a variety of disease or wound conditions that will be identified in parallel with, and as a consequence of, the technological developments. It is expected that this novel approach will stimulate the emergence of nanomedicine as a major contributor to improving human health in a variety of medical specialties.

- For more information, see <http://nihroadmap.nih.gov/nanomedicine/index.asp>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (Roadmap—all ICs participate)

**NIH Roadmap Interdisciplinary Methodology and Technology Summit:** The purpose of this NIH Roadmap Summit (August 2006) was to identify opportunities for developing research methodologies and technologies at the intersection of behavioral and social sciences with other disciplines. Topics discussed at the meeting included the following: large complex datasets, multilevel approaches, intergenerational approaches, economics/econometrics, Geographical Information Systems and neighborhood data, ecological momentary assessment, and combining qualitative and quantitative methods.

- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/summit0806/>
- (E) (Roadmap—all ICs participate)





## RESEARCH TRAINING AND CAREER DEVELOPMENT

*For years the sense of smell had remained the most enigmatic of our senses. The basic principles for recognizing and remembering about 10,000 different odors were not understood. However, in 2004 Dr. Richard Axel and Dr. Linda Buck received the Nobel Prize in Physiology or Medicine for determining how the sense of smell or olfaction actually works. Their seminal discovery was that the mammalian genome contains a family of genes that make receptors for odorants. They also found that these receptors are located on olfactory receptor cells, which occupy a small area in the inner lining of the nose, where they bind odorant molecules and signal the brain that a smell has been detected. The NIH is particularly proud that Dr. Buck was awarded a Nobel Prize because, as she followed the long path to becoming a scientist, Dr. Buck was the recipient of a National Research Service Award fellowship, which supported her postdoctoral research training from 1980 to 1982, training that very likely contributed to solving the mystery of the sense of smell.*

### Introduction

Louis Pasteur wrote that “Chance favors the prepared mind.” NIH research training and career development programs aim to prepare new minds for research and ensure that diverse pools of highly trained scientists are available in adequate numbers and with appropriate expertise to generate new discoveries, meet the needs of rapidly moving science, and address complex and evolving health care challenges. These critical means of building and maintaining research capacity are long-term investments that bring competitive advantage to the Nation as well as dividends in the form of renewed generations of investigators with novel and bright ideas. Training is where cures begin. This investment in “intellectual capital” provides the source of ideas for investigator-initiated research projects, which historically have been the primary engine for generating scientific breakthroughs. Each generation of scientists paves the way for the discoveries of the next generation; thus, it is critical to ensure that there is a continually reconstituted pool of highly trained investigators in the pipeline pursuing new knowledge and better therapies. NIH’s research training and career development programs cover a broad range of basic biomedical, behavioral, and clinical research, including the interdisciplinary junctures among the fields.

By sponsoring training and career development programs in universities, teaching hospitals, NIH laboratories, and other research-intensive settings, NIH expects that trainees and newly trained investigators not only will be exposed to the latest research findings and techniques, but also will be prepared to rise to the challenge of emerging problems in medicine and health. To further ensure that the research workforce will be poised to respond to evolving public health needs, NIH takes steps to recruit future researchers from underserved and underrepresented populations; strengthen research capacity in developing countries from which health threats often originate; and encourage individuals to focus on targeted or underresearched areas (such as clinical and translational research, rare diseases, health disparities, and global health priorities).

Aligning the requisite expertise with public health needs is complicated by the evolving nature of biomedical, behavioral, and clinical research; the time required for research training; the international nature of research; and the global mobility of the research workforce. Preparing for a career in research generally requires a commitment of 8 to 12 years or more of predoctoral and postdoctoral training and career development, during which time science is advancing, new diseases are emerging, and existing diseases are becoming better understood, diagnosed, and prevented.

In determining how best to sustain the continuing need for biomedical and behavioral scientists, NIH is guided by regularly scheduled analyses of the research workforce. Chief among these assessments are recurring studies conducted by the National Academies, which provide guidance on the fields in which researchers are likely to be required and on the number of new investigators needed in the basic biomedical, behavioral, and clinical sciences. NIH also routinely evaluates the outcomes of its training programs, comparing the subsequent research involvement of students and postdoctoral scholars who participate in NIH research training with their counterparts who were trained through other channels. Beyond such agency-wide assessments, individual ICs determine the need for new scientific personnel in mission-specific research areas through targeted evaluations, input from extramural investigators, and guidance from their national advisory councils.

NIH offers a broad range of research training and career development opportunities in the extramural and intramural research communities, through institutional training awards and individual fellowships, individual and institutional career development awards, continuing education, workshops, research grants, and awards and supplements to promote diversity or reentry into health-related research careers. While its programs are largely directed toward graduate students and newly trained investigators, NIH offers a number of highly focused training and career development opportunities for individuals at other career stages, including college students and established scientists.

All NIH training and career development programs foster and encourage participation of a diverse population of subjects. NIH expects that efforts to diversify the scientific workforce will lead to the recruitment of the most talented researchers from all groups, improved quality of the educational and training environment, more balanced and broader perspectives in setting research priorities, enhanced ability to recruit subjects from diverse backgrounds into clinical research protocols, and improved capacity to address and eliminate health disparities. In addition to NIH's dedication to inclusion of minorities and other disadvantaged populations in the biomedical research workforce (see section on Minority Health and Health Disparities in Chapter 2), NIH also is committed to the recruitment, retention, reentry, and advancement of women in biomedical research careers. Perhaps the most visible recent NIH activity in this regard is the NIH Director's establishment of the [NIH Working Group on Women in Biomedical Careers](#). This Working Group is examining the issues raised and the challenges posed by [Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering](#), a 2007 report from the National Academies. The report itself was stimulated by NIH hearings and a workshop. Now, with the report in hand, NIH is carefully considering its recommendations to government agencies on maximizing the potential of women scientists and will develop innovative strategies to advance women's careers.

## Summary of NIH Activities

### Extramural Programs and Progress: Research Training

#### *Trans-NIH Programs and Initiatives*

Training for a career in research typically requires a combination of specialized coursework and hands-on research experiences under the guidance of an established investigator. A majority of NIH-supported research training activities are focused on predoctoral students and postdoctoral scholars and are provided through institutional training grants (T awards) or individual fellowships (F awards). The principal NIH research training program for U.S. citizens and permanent residents, in size and breadth of coverage, is the [Ruth L. Kirschstein National Research Service Award](#) (NRSA) program. The goal of the NRSA program is to support promising students and postdoctoral scholars with the potential to become productive, independent investigators in fields relevant to NIH's mission. Training activities can be in basic biomedical or clinical sciences, in behavioral or social sciences, in health services research, or in any other discipline relevant to the NIH mission. All ICs with funding authority award NRSA institutional research training grants and fellowships, except FIC and NLM. Reflecting the unique nature of their missions, the latter two ICs have distinct training authorities, separate from the NRSA program. NIH also supports a substantial amount of research training indirectly through its research grants. Though not an NIH "program" per se, the impact of this support is significant. Graduate students and recent postdoctoral scholars participating as research assistants gain knowledge, skills, and experience that help prepare them for careers in research.

Through the NIH-wide program of NRSA institutional training grants and fellowships, NIH ICs supported nearly 16,600 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every State in fiscal year (FY) 2006. Institutional training grants form the core of NIH's research training programs, providing support to more than 80 percent of all NRSA program participants. Training grants play a particularly important role at the predoctoral level: approximately three-fifths of trainees are graduate students, often engaged in coursework and laboratory rotations in preparation for identifying an area of research for focused study. (See Appendix D for a breakdown on the demographics of NRSA participants and a summary of the number and type of doctoral degrees awarded to predoctoral NRSA recipients.)

Individuals interested in research training in universities or departments where there are no institutional training grants, as well as advanced students and postdoctoral scholars seeking tailored training opportunities, have the option of applying directly to NIH for an individual research training fellowship. Slightly more than one-half of the NRSA fellowships in FY 2006 were awarded to postdoctoral scholars, providing recipients valuable experience in initiating and testing their own research ideas before becoming full-fledged investigators.<sup>16</sup>

NRSA training grants and fellowships may target broad-based or field-specific research training, depending on the needs identified by the administering IC. In recent years, this flexibility has

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<sup>16</sup> For more information, see [http://grants1.nih.gov/training/data/tf\\_trends.ppt](http://grants1.nih.gov/training/data/tf_trends.ppt)

allowed the NRSA program to respond to interest in greater integration of training activities across NIH in order to fulfill workforce needs shared by multiple ICs. The result has been a series of trans-NIH research training initiatives through the [NIH Roadmap for Medical Research](#) and other channels.

At its inception in 2003, for example, the NIH Roadmap identified interdisciplinary and clinical research training as NIH-wide priorities and initiated new NRSA research training awards in these areas. The Roadmap Interdisciplinary Research Training Initiative, in particular, is designed to overcome disciplinary boundaries and broaden the knowledge base of future investigators so they might bring new insights and analytical approaches to health problems.

As the early Roadmap research training initiatives have matured, some have been selected for continuation and further expansion. One such former Roadmap initiative—a trans-NIH NRSA institutional research training grant in clinical and translational research—has now been incorporated as an option in every [Clinical and Translational Science Award](#) (CTSA). The CTSA program is an ambitious effort to spur the transformation of clinical and translational research in order to accelerate the development of new treatments. Creating multidisciplinary research teams that include physicians, basic scientists, statisticians, specially trained research nurses, informatics experts, and others is central to this transformation. The CTSA program will grow through 2012 to serve about 60 academic sites, providing research training and career development opportunities in areas such as clinical research design, epidemiology, biostatistics, pharmacology, biomedical informatics, behavioral science, and ethics to more than 1,200 NRSA trainees and new investigators. (CTSA trainees are included in the data provided in Appendix D.)

Efforts to coordinate research training in neuroscience preceded the NIH Roadmap by several years and provided an early model for addressing research training challenges across NIH. In 1997, a number of ICs announced that [the Jointly Sponsored Predoctoral Training Program in the Neurosciences](#) would support NRSA institutional training grants to provide broad neuroscience training for graduate students in the first and second years of study. This program has since become affiliated with the [NIH Blueprint for Neuroscience Research](#), a framework that brings together the 16 NIH Institutes, Centers, and Offices that support neuroscience research and training, and provides a channel for coordinating their efforts. Other more recent Neuroscience Blueprint research training activities include initiatives to provide training in translational research relevant to neurobiology of disease, neuroimaging, computational neuroscience, and neurodegeneration. Many programs funded through these new initiatives will include special features to foster collaborative interdisciplinary relationships, such as cross-training basic and clinical researchers and providing dual mentors to every trainee, each with a different area of expertise.

To help ensure the diversity of the research workforce, NRSA training grants and fellowships include features designed to provide research training opportunities to individuals from populations and backgrounds typically underrepresented in research (see also the section on *Minority Health and Health Disparities* in Chapter 2). NRSA policy requires institutional training grant directors to take steps to recruit and retain trainees who are disabled, from underrepresented racial and ethnic groups, or from disadvantaged backgrounds. Through the [Ruth L. Kirschstein NRSA Individual Predoctoral Fellowship \(F31\) to Promote Diversity in](#)

[Health-Related Research](#), Section 487(a)(4) of PHS Act, as amended, NIH provides biomedical and behavioral research and research training programs that will result in the recruitment of women and individuals from disadvantaged backgrounds (including racial and ethnic minorities).

Part of the inherent challenge of recruiting talented individuals into graduate programs is to have a pool of competitive undergraduates from which to draw. [The Minority Access to Research Careers \(MARC\) Undergraduate Student Training in Academic Research, Institutional NRSA Research Training Grant \(T34\)](#) is intended to support undergraduate research training to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to the Nation's biomedical and behavioral research agenda. These are honors students majoring in the sciences who have an express interest in a biomedical research career and who intend to pursue postgraduate education leading to the Ph.D., M.D.-Ph.D., or other combined degree. To help program directors recruit suitable students for doctoral programs, the Community for Advanced Graduate Training was launched in 2007 to connect MARC undergraduate students with predoctoral research training grant programs. The MARC program is an institutional program and does not use race/ethnicity as a criterion for individuals supported by the program.

The relative diversity of NRSA participants reflects NIH's commitment to cultivating a broad-based scientific workforce. Among FY 2006 trainees and fellows who reported their race and ethnicity, 67 percent were White, 14.8 percent were Asian, 9.1 percent were African American, 6.5 percent were Hispanic, 1.1 percent were Native American, and 0.06 percent were Native Hawaiian or Pacific Islanders. Nearly 52 percent of NRSA trainees and fellows in FY 2006 were women.<sup>17</sup>

### ***IC Programs and Initiatives***

Because each NIH IC has its own specific research agenda, individual ICs are responsible for specifying the need for scientists in their respective scientific fields, selecting individuals and institutions for NRSA or other research training awards to meet the needs identified, and reviewing annual progress toward building or enhancing capacity in the research workforce. Areas targeted for research training initiatives reflect the full array of IC funding interests, from basic research training in biology, biostatistics, dentistry, epidemiology, and population, to topics at the intersection of two or more fields. As an example, NIGMS promotes interdisciplinary, collaborative, and innovative research through 11 different predoctoral training areas of interest to the Institute. In July 2007, it funded the first two awards of a new institutional NRSA training grant program focused on [Predoctoral Training at the Interface of the Behavioral and Biomedical Sciences](#). Several ICs support combined M.D./Ph.D. training, including NIGMS, which funds the [Medical Scientist Training Program](#). This program supports exceptional students pursuing an integrated program of graduate training in the biomedical sciences and clinical training offered through medical schools.

Other current IC initiatives include research training programs in the areas of chemical biology of cancer; infectious diseases; complementary and alternative medicine; chemistry related to drug abuse and addiction; genomic analysis; human genes and the environment; reproductive, perinatal, and pediatric epidemiology; medical informatics; and interdisciplinary research; as

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<sup>17</sup> For more information, see [http://grants.nih.gov/grants/policy/sex\\_gender/q\\_a.htm#q13](http://grants.nih.gov/grants/policy/sex_gender/q_a.htm#q13)



well as fellowship opportunities in complementary and alternative medicine, nursing, orthopedic surgery, muscle disease, and embryonic stem cell research.

While focusing on and supporting activities that address their respective missions and disease areas, ICs follow NIH-wide guidelines for NRSA research training and frequently collaborate to sponsor specific initiatives where there are overlapping interests or to stimulate interest in emerging fields. For example, in January 2007, NIEHS and NHGRI jointly sponsored a new [Human Genes and the Environment Training Program](#) that seeks to build on the established foundations in exposure biology and high-throughput genomics, to produce a new generation of scientists who are equally at home in genomics and environmental health sciences and can seamlessly interact with investigators from both fields. This new cadre of scientists not only will be equipped to advance methodologies and technologies in environmental genomics/genetics, but also will be able to use these tools and resources to disentangle and evaluate the enormous number of environmental factors that directly influence or interact with genetic factors to cause disease.

[NLM institutional training grants and fellowships](#) generally parallel the structure and requirements of the NRSA program and reflect NLM's unique role as the primary federal sponsor of biomedical informatics research and training. Like the ICs that provide NRSA research training, NLM prepares the next generation of informatics researchers and health information specialists through both institutional grants (T15s) and fellowships (F37s). The institutional programs support graduate and postdoctoral training in a broad range of topics, including health care information, bioinformatics, systems biology, imaging informatics, and public health informatics. NLM's individual fellowship programs provide opportunities for librarians, scientists, health professionals, and others interested in serving as information-specialist members of professional teams, whether in clinical or basic biomedical research or related health fields. Unlike NRSA research training awards, some NLM training programs are open to master's degree holders seeking further graduate level coursework and hands-on training.

Reflecting the FIC mission to build research capacity in the developing world, FIC institutional training grants (D43s) differ from those offered by the NRSA program or by NLM by allowing a broader range of participants and emphasizing the development of institutional partnerships and collaborations between U.S. and international universities and scientists. Most FIC programs focus on providing research training to individuals from developing nations, but a number of selected programs provide opportunities to U.S. students and postdoctoral scholars interested in international health research. FIC training programs are contributing to the building of sustainable research capacity in the developing world to enhance prevention, treatment, and control of infectious diseases, including HIV/AIDS, TB, and malaria, which are major causes of morbidity and mortality in those regions. Other FIC programs target research training in the areas of clinical, operational, and health services research; noncommunicable diseases; population studies and reproductive biology; environmental and occupational health; trauma and injury; and informatics training for global health. In order to foster long-term scientific partnerships between U.S. and foreign investigators, most FIC training grants require a joint collaboration between an American and a foreign institution.

### ***Strength From Partnerships***

Research training involves collaboration between NIH and its grantee institutions in the form of shared responsibilities and funding. In making NRSA training grant awards, for example, NIH relies on universities and other sites that receive support to select the best trainees, determine the curriculum and other aspects of the training program, and provide mentorship and supplemental funding to participating students and postdoctoral trainees. Although NRSA fellowships are targeted to individual students or postdoctoral scholars, NIH expects the sponsoring institutions to provide fellows with experienced mentors and supplemental research funding support. In some targeted NRSA research training programs, NIH also partners with other agencies, private foundations, and professional societies to achieve shared research training goals.

Partnerships between NIH and the private sector are helping to accelerate research training in creative ways. In 2006, for example, NIH announced public-private partnerships with the American Skin Association and the Orthopaedic Research and Education Foundation to increase the number of dermatologists and orthopedic surgeons with research training in epidemiology, clinical trials, and outcomes research. The ultimate goal of these two research training initiatives is to enhance the workforce of trained investigators who can design and carry out studies on the prevalence of skin diseases and bone conditions and hasten progress in their treatment by evaluating the effectiveness of therapeutic interventions. The fellowships resulting from this public-private partnership support up to 2 years of advanced training and provide approximately \$30,000 in additional funds annually to supplement stipends or other research training expenses for each fellow.

### ***NIH Training Program Evaluations and Assessments***

Since the NRSA program was established in 1974, NIH training programs have been regularly reviewed and evaluated. The National Academies have undertaken regular reviews of the medical research workforce and made recommendations for modifications in the size and focus of the NRSA program. In addition, the NRSA program has undergone multiple independent outcome evaluations, has assessed its processes and outcomes against several Government Performance and Results Act (GPRA) goals, and recently completed a Program Assessment Rating Tool review by the White House Office of Management and Budget (OMB) with flying colors. These reviews have been coordinated by the NIH Office of Extramural Research (OER), which oversees the NRSA program. Increasingly, however, individual ICs also are undertaking evaluations of their specific NRSA and other research training programs.

**National Academies Reviews.** Over the past 30 years, the NRSA program has been the subject of more than a dozen studies by NAS, which have provided expert guidance on the fields in which researchers are likely to be required and on the number of new investigators needed in the basic biomedical, behavioral, and clinical sciences. The recurring nature of these studies ensures that NIH research training programs reflect changes in science and research needs that inevitably occur over time. In the early 1980s, for example, NIH reduced the size of the NRSA training program after committees of the National Academies concluded that the number of new scientists entering the research workforce exceeded the number of permanent research positions available. More recently, NIH has followed recommendations from National Academies

committees for enhancing stipend levels, promoting the early completion of research training, and improving workforce data collection and analysis.

Members of the committee producing the most recent report from the National Academies, published in 2005, commended the NRSA program, noting “quality is an essential ingredient for progress. In this regard, the NRSA Program plays a unique role... [setting] the standards for the entire research training establishment. In addition, they attract high-quality students into research and into fields of particular need. The record of success of NRSA holders in obtaining research funding is impressive.”<sup>18</sup>

**Independent Outcome Evaluations of NRSA Training.** Evaluations of the outcomes of NRSA research training routinely have found that graduate students participating in NRSA programs complete their degrees faster, are more likely to pursue research careers, and have greater subsequent success in research than do students not participating in NRSA programs.<sup>19,20</sup> Similarly, a 2006 evaluation of NRSA postdoctoral training found that NRSA postdoctoral fellows were more likely to successfully pursue research careers. Over 32 percent of former NRSA postdoctoral fellows applied for and successfully received NIH research funding within 10 years of completing their training, compared to about 20 percent of other postdoctoral fellows.<sup>21</sup>

**Government Performance and Results Act (GPRA) Goals.** Every year, NIH assesses NRSA research training outcomes and program management against two goals established under GPRA. In the first of these goals, NIH seeks to measure the quality of its programs and ensure that substantial numbers of trainees and fellows are retained in research careers, by comparing the proportion of former NRSA trainees and fellows that apply for and successfully receive NIH support against their peers. Subsequent NIH support reflects the impact of NRSA research training on the ability of trainees and fellows to successfully pursue and sustain a research career.

The second training-related GPRA goal measures NIH progress in improving the efficiency of NRSA program management by developing and implementing an electronic system for appointing trainees to institutional training grants. By 2012, NIH expects the new system to be fully implemented and that 100 percent of trainees will be appointed to training grants electronically rather than through paper appointment forms. The new system, known as xTrain, will be pilot-tested by nine institutions beginning in fall 2007. When available for general use, xTrain is expected to save substantial staff time and eliminate data entry errors, increasing NIH’s efficiency and enhancing the integrity of NRSA data used for program monitoring and evaluation purposes.<sup>22</sup>

**Program Assessment Rating Tool Review.** In 2006, NIH training and career development programs underwent a Program Assessment Rating Tool review and received the highest rating possible from OMB examiners. OMB judged the NIH Research Training and Career Development programs as “effective” in training and retaining researchers in the biomedical

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<sup>18</sup> For more information, see [http://www.nap.edu/catalog.php?record\\_id=11275#toc](http://www.nap.edu/catalog.php?record_id=11275#toc)

<sup>19</sup> For more information, see [http://grants.nih.gov/training/career\\_progress/index.htm](http://grants.nih.gov/training/career_progress/index.htm)

<sup>20</sup> For more information, see [http://www.nsf.gov/statistics/showsrvy.cfm?srvy\\_CatID=3&srvy\\_Seri=5](http://www.nsf.gov/statistics/showsrvy.cfm?srvy_CatID=3&srvy_Seri=5)

<sup>21</sup> For more information, see [http://grants1.nih.gov/training/NRSA\\_report\\_5\\_16\\_06-2.doc](http://grants1.nih.gov/training/NRSA_report_5_16_06-2.doc)

<sup>22</sup> NIH FY 2008 Performance Detail, pp. 275-76.

research field, recognized the programs for having successfully met ambitious long-term and annual goals, and praised NIH for its long tradition of independent evaluation.

**Institute and Center Training Evaluations.** In addition to scheduled NIH-wide assessments of the programs coordinated through OER, individual NIH ICs undertake periodic, targeted evaluations to improve implementation and assess outcomes of their own training programs. Institute-specific evaluations typically focus on research training needs in particular areas and are often conducted by independent “blue ribbon” panels of scientific leaders from around the country. For example, NCCAM convened an independent expert panel to evaluate its programs in light of the unique training needs of complementary and alternative medicine research.<sup>23</sup> Other ongoing IC assessments include evaluations of how effectively CTSA training grants foster pediatric and other clinical researchers and of the outcomes of the NIAMS research training (T32 and F32) programs.

## **Extramural Programs and Progress: Career Development**

Given the pace at which science advances, novel techniques and methods are introduced, and new fields emerge, maintaining a vibrant workforce requires support for scientific talent to fully develop and stay up to date. NIH [Career Development Awards](#) (K awards) address that need.<sup>24</sup> Collectively, more than a dozen types of K awards support investigators as they establish their research careers, pursue new directions, or dedicate themselves to training and mentoring the next generation of scientists. Like the T and F training awards, some career development awards support institutional activities to nurture careers and others directly support individual development.

Many career development awards are designed for researchers at specific career stages, particularly newly trained investigators. The new NIH-wide [Pathway to Independence Award](#) accelerates the transition from mentored to independent research by providing a bridging mechanism. The initial 1- to 2-year mentored phase of the award allows investigators to complete their supervised research work, publish results, and search for an independent research position. The second, independent phase, allows awardees to establish their own research program and apply for independent research support. In addition, many ICs offer their own Career Transition Award to support new investigators as they make the move to faculty positions. Other “mentored” career development awards provide support for a sustained period of protected time for intensive research career development under the guidance of an experienced mentor, or sponsor. The expectation is that, with this experience, awardees will be able to take the final steps toward establishing independent research careers and becoming competitive for new research project grant funding. For example, ORWH supports the [Building Interdisciplinary Research Careers in Women’s Health](#) program, which pairs junior faculty with senior investigators in an interdisciplinary environment. At the other end of the career spectrum, a number of ICs provide Senior Scientist Research and Mentorship Awards. These awards provide salary support for outstanding senior scientists and recognized leaders so that, through an interval of protected time, they can focus intensively on their research and mentor new investigators.

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<sup>23</sup> For more information, see <http://nccam.nih.gov/training/report.htm>

<sup>24</sup> For more information, see <http://grants.nih.gov/training/careerdevelopmentawards.htm>

Several career development awards foster the involvement of clinicians in research. The Mentored Clinical Scientist Research Career Development Award continues a long-standing NIH commitment to provide support and protected time to individuals with a clinical doctoral degree so that they can engage in an intensive, supervised research career development experience. The award supports both didactic study and mentored research for individuals with a wide variety of clinical degrees, including the M.D., D.D.S., D.V.M., and Pharm.D. A sister program, the Mentored Patient-Oriented Research Career Development Award, supports the career development of clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research.

Other career development programs target specific areas of science. Examples here include the [Career Enhancement Award for Stem Cell Research](#), which enables investigators to acquire new research capabilities in the use of human or animal embryonic, adult, or cord blood stem cells, and the Mentored Quantitative Research Career Development Award, which encourages investigators from quantitative science and engineering fields to focus on questions of health and disease.

### **Coordination and Oversight by the NIH Office of Extramural Research**

Much as NIH collaborates with grantee institutions in conducting research training, OER partners with ICs to coordinate and monitor awards for research training and career development across NIH. With active input from the ICs, OER establishes and implements policies and guidelines for each of the programs; determines broad national needs for basic biomedical, behavioral, and clinical research personnel; coordinates NIH-wide evaluations; develops trans-NIH research initiatives in which NIH ICs participate; and develops and maintains information systems to enhance program efficiencies. OER convenes monthly meetings of the NIH Training Advisory Committee to provide an agency-wide forum to identify and discuss issues related to research training and to provide opportunities to coordinate activities pertinent to the review, administration, management, and evaluation of training grants and fellowships.

### **Intramural Activities**

The NIH intramural program provides opportunities for students, postdoctoral scholars, and clinicians to gain research experience within the more than 1,140 intramural laboratories of NIH.<sup>25</sup> A multifaceted array of programs provides a vibrant, scholarly environment and ensures strong research training experiences for future investigators and the continued professional development of intramural scientists.

Summer internships are available for high school, college, and graduate students. Recent college graduates who plan to apply to graduate or professional school can spend a year engaged in biomedical research working side by side with NIH scientists. Current graduate students can spend a summer, or even a year, as fellows engaged in biomedical research at NIH. The [Graduate Partnerships Program](#) (GPP) enables students to pursue research at NIH toward their degrees in partnership with a participating academic institution. By linking academic

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<sup>25</sup> For more information, see <http://www.training.nih.gov/>

environments with the breadth and depth of research at NIH, the GPP creates a valuable graduate experience, one that purposefully focuses on skills of the future scientist and how discoveries will be made in the decades ahead. The [Clinical Research Training Program](#) (CRTP) is a yearlong program designed to attract the most creative, research-oriented medical and dental students to the NIH campus. CRTP fellows spend a year engaged in a mentored clinical or translational research project, in an area that matches their personal interests and goals.

Training opportunities continue when scholars gain their graduate degrees. Year-round, NIH intramural laboratories employ fellows from the United States and abroad, creating a thriving, multidisciplinary intramural research community. The [Postdoctoral Intramural Research Training Award](#) provides the opportunity for recent doctoral degree recipients, who are U.S. citizens or permanent residents, to enhance their research skills in the NIH intramural environment. Trainees pursue both basic and clinical research. A parallel program, Visiting Fellowships, serves foreign national doctoral-level scientists. For clinicians, there are opportunities for residency and subspecialty training, including graduate medical education-accredited programs (for program completion data, see Appendix D). A wide array of accredited joint, NIH, and other sponsored programs are available. These GME programs enable research-oriented clinicians to weave research experience and training into their post-medical school training.

The intramural program also offers numerous targeted training programs and fellowships as varied as the [Imaging Sciences Training Program](#), the NIH Dietetic Internship, and the Social Work Field Instruction Program. Many specialized programs address the need for a diverse research workforce, including the [Women's Health Postdoctoral Fellowship](#), (Also see the *Minority Health and Health Disparities* section of Chapter 2).

All members of the NIH community benefit from access to a plethora of NIH courses, seminars, and science career resources. For example, every day across the NIH campus there are scientific seminars and frequent colloquia addressing the latest developments and discoveries in biomedical science; meetings of more than 100 Scientific Interest Groups that host forums and lecture series on cutting-edge issues of interest ranging from the Bioethics Interest Group to the Integrative Neural Immune Interest Group; and short- and long-term course offerings such as “*Introduction to the Principles and Practice of Clinical Research*” and “*Principles of Clinical Pharmacology*.”

## **NIH Loan Repayment Programs**

The NIH Loan Repayment Programs (LRP) are a vital component of our Nation's efforts to attract eligible doctoral-level professionals to research careers in fields of special importance—clinical, pediatric, health disparities, contraception and infertility, and AIDS research. To encourage qualified scientists to pursue research in these critical areas, the LRP provides financial assistance for educational debt in exchange for a 2- or 3-year research commitment. Program participants may receive up to \$35,000 annually in loan repayment and can fulfill their commitments by conducting research in the specified fields in any nonprofit, university, or government organization, or as an NIH employee. The LRP serves the extramural and intramural



communities by awarding LRP benefits to more than 1,600 research scientists annually.<sup>26</sup> Each program is competitive and serves to recruit talented biomedical scientists and physicians to research careers addressing important public health needs.

The initiatives and program reviews highlighted in the next section all point to the considerable progress made by NIH in meeting the long-term goal of building and maintaining research capacity to help ensure that highly trained scientists are available to address biomedical, behavioral, and clinical research needs, with the ultimate goal of uncovering new knowledge that will lead to better health for all Americans.

## Notable Examples of NIH Activity

### Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

## Trans-NIH Initiatives and Major Programs

**Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32):** The objective of the NRSA program is to support graduate and postdoctoral research training to help ensure that a diverse and highly trained workforce is available to carry out and lead the Nation's biomedical, behavioral, and clinical research agenda. This program supports predoctoral and postdoctoral research training programs at domestic institutions of higher education. The NRSA program has been the primary means of supporting graduate and postdoctoral research training programs since enactment of the NRSA legislation in 1974. Training activities can be in basic biomedical or clinical sciences, in behavioral and social sciences, in health services research, or in any other discipline relevant to the NIH mission. Institutional research training grants allow universities, research institutes, and teaching hospitals to select specific trainees and develop a curriculum of study and research experiences tailored to provide high-quality research training. The training grant award provides stipends and offsets the cost of tuition for appointed trainees.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-06-468.html>
- For more information, see <http://grants.nih.gov/training/nrsa.htm>
- (E) (OD/OER)

**Interdisciplinary Research Training Programs:** The NIH Roadmap Interdisciplinary Research Teams of the Future program addresses the challenges of developing, sustaining, and administering interdisciplinary research and team science. Interdisciplinary research is the melding of multiple disciplines to arrive at new experimental approaches, and it requires the participants to be educated in more than one discipline. Although this is often accomplished through teams of investigators learning from each other via collaborations, formal training in multiple disciplines can allow individual investigators to develop interdisciplinary approaches.

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<sup>26</sup> <http://www.lrp.nih.gov/brochure.pdf>

The NIH Roadmap Interdisciplinary Training Program consists of four initiatives that were intended to provide this type of formal training to investigators at all levels of their careers.

- ▷ *Training for a New Interdisciplinary Research Workforce.* These institutional training grants aim to catalyze the production of a scientific workforce capable of integrative research crossing traditional disciplinary boundaries. Awardees develop and implement novel training programs focused on interdisciplinary science.
- ▷ *Interdisciplinary Health Research Training - Behavior, Environment, and Biology.* Institutional Training Grants provide doctoral-level trainees with additional postdoctoral training in a new discipline. Trainees must either have been trained in the social and behavioral sciences or be seeking training in these areas. The intent is to encourage interdisciplinary approaches to complex health problems involving behavioral and social factors.
- ▷ *Short Programs for Interdisciplinary Research Training.* These programs range from 2 to 8 weeks in duration and are intended to provide an opportunity for investigators at all career stages to receive basic instruction in a new discipline.
- ▷ *Curriculum Development Award in Interdisciplinary Research.* These awards provide funds to develop creative curricula for interdisciplinary training. Once developed, these curricula are intended to be broadly available for use in multiple settings.

- For more information, see <http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp>
- (E) (Roadmap—all ICs participate)

**Training Activities of the Clinical and Translational Science Award Program:** Comparing new disease treatments and prevention strategies against those in current use requires dedicated clinical and translational research teams that include physicians, basic scientists, and statisticians and informatics experts, among others. Clinical research requires unique skills in addition to those needed to care for patients, so academic health centers must equip promising individuals with the special training they need to succeed in research careers. To address this need, NIH has expanded its clinical research training programs, first through the Roadmap T32 and K12 programs and, more recently, through Clinical and Translational Science Awards (CTSAs). Each program is based on placing the trainees in a mentored environment, where they learn the skills needed to cultivate multidisciplinary research team collaborations and design research projects to successfully compete for funding. The CTSA program will grow through 2012 to serve about 60 academic sites, providing research training and career development opportunities to a combined total of more than 1,200 trainees and new investigators covering multiple individual disciplines.

As mandated in Section 106 of the National Institutes of Health Reform Act (Pub. L. No. 109-482), NIH will conduct an evaluation and comparison of the outcomes and effectiveness of the CTSA training programs. This evaluation will be part of a much larger comprehensive evaluation of the CTSA program as a whole. Each individual CTSA is expected to include its training activities in its own evaluation. To coordinate and share information, including results of training activity evaluations, there is a CTSA Education/Career Development Steering Committee which provides a forum for the advancement of integrated and interdisciplinary education, training, and career development in the clinical and translational sciences and serves as a clearinghouse for clinical research training. Since the CTSA program was only recently initiated (September 2006), significant evidence of the long-term impact of the CTSA program is more likely to be

measurable after 7 or more years. However, short-term process milestones and intermediate outcomes are expected in 1 to 7 years.

- For more information, see [nihroadmap.nih.gov/clinicalresearch/overview-training.asp](http://nihroadmap.nih.gov/clinicalresearch/overview-training.asp)
- For more information, see <http://www.ctsaweb.org/>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (Roadmap—all ICs participate)

**The NIH Blueprint for Neuroscience Research:** The Blueprint is a collaborative framework that brings together 16 NIH Institutes, Centers (IC), and Offices that support neuroscience research. The Blueprint catalyzes research progress by developing tools, resources, and training opportunities that transcend the mission of any single NIH IC and serve the entire neuroscience community. In FY 2006, the Blueprint launched initiatives to develop new neuroimaging technologies; a clearinghouse to distribute and improve existing neuroimaging software; core resource centers; a neurological and behavioral assessment tool; and new genetically modified mouse models. The Blueprint also supported training programs in neuroimaging, computational neuroscience, and translational research. In FY 2007, the Blueprint released funding announcements to identify biomarkers for neurodegeneration, develop new ways to deliver therapeutics to the nervous system, and provide interdisciplinary training in neurodegeneration research.

- For more information, see <http://www.neuroscienceblueprint.nih.gov/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NINDS, NCCAM, NCCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

**HIV Research Training Programs:** The AIDS International Training and Research Program (AITRP) builds institutional, national, and regional HIV research capacity in low- and middle-income countries. Over the past 19 years, this program has been responsible for many of the first generation of research scientists from these countries, with many more in the pipeline. The program offers multidisciplinary biomedical, behavioral, and social science research training to a wide range of professionals. Building on the AITRP, the Clinical, Operational and Health Services Research Training Program for HIV/AIDS and TB (ICOHRTA AIDS/TB) began in 2002 to strengthen the capacity for clinical, operational, and health services research in low- and middle-income countries where AIDS, TB, or both are significant problems. Through training health professionals that reach across the spectrum of clinical and public health research, this program is strengthening the capacity of scientists, program managers, and policymakers to evaluate and better implement large-scale prevention, treatment, and care interventions that are locally relevant and effective. Many local leaders of programs supported by the President's Emergency Plan for AIDS Relief have received or are receiving their research training through the AITRP and the ICOHRTA AIDS/TB programs.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/aitrp/index.htm](http://www.fic.nih.gov/programs/training_grants/aitrp/index.htm)
- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/icohrta/aids\\_tb.htm](http://www.fic.nih.gov/programs/training_grants/icohrta/aids_tb.htm)
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (FIC, NCI, NHLBI, NIDA, NIDCR, NIMH, NINDS, NINR, OAR, ORWH)

**Research Career Development Programs:** One of the most challenging transitions in any research career is the transition from postdoctoral trainee to independent scientist. NIH has long used the [Research Scientist Development Award \(K01\)](#) to support the successful transition of individuals who hold a research or health-professional doctoral degree or equivalent, as well as newly independent investigators and midcareer investigators who need protected time to make a shift in their research careers or enhance their ability to conduct scientifically sophisticated studies in their chosen fields. Junior-level clinically-trained individuals are encouraged to apply for the [Mentored Clinical Scientist Development Award \(K08\)](#), or the [Mentored Patient-Oriented Research Career Development Award \(K23\)](#), as appropriate, to realize their potential to develop into productive clinical investigators. Transition awards such as the Career Transition Award (K22) and the [Pathway to Independence Program \(K99/R00\)](#) provide mentoring, protected time, and financial support to postdoctoral fellows seeking to transition to faculty positions. Many specific career development awards are tailored to meet the needs of different research areas and recipients at different career levels.

- For more information, see <http://grants.nih.gov/training/careerdevelopmentawards.htm>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-06-001.html> (K01)
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-06-512.html> (K08)
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-05-143.html> (K23)
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-06-133.html> (K99/R00)
- (E) (OD/OER)

**NIH Basic and Clinical Intramural Research Training:** Candidates selected for NIH intramural research training and career development programs may be funded by any one of a number of mechanisms depending on availability of funding, the type of research to be conducted, the center or laboratory sponsoring the research, and qualifications of the candidate. These mechanisms include the NIH [Postdoctoral Intramural Research Training Award \(IRTA\)](#); the [Clinical Research Training Program \(CRTP\)](#), a year-long program designed to attract the most creative, research-oriented medical and dental students to the NIH campus where the participants, known as fellows, engage in a mentored clinical or translational research projects.

- For more information, see <http://www.training.nih.gov/postdoctoral/pdopps.asp>
- (I) (OIR)

**LRP Outreach Campaign:** The NIH's Loan Repayment Program (LRP) "Strength in Numbers" campaign debuted September 6, 2007. This campaign offers a renewed commitment to qualified postdoctoral scientists who are seeking careers in biomedical and behavioral research. The program funds up to \$35,000 annually in loan repayment for eligible individuals. From September 1 to December 1, 2007, the NIH accepted applications for health professionals pursuing careers in one of the five LRPs offered by the NIH (Clinical Research, Clinical Research for Individuals from Disadvantaged Backgrounds, Contraception and Infertility Research, Health Disparities Research, and Pediatric Research). The programs also provide reimbursement for Federal and State tax liabilities resulting from the loan repayment award.

- For more information, see <http://www.lrp.nih.gov/HomePage.aspx>
- (E) (OER)

**Re-entry Program:** The Re-entry Program, now supported by 23 NIH institutes, was originally developed to help fully trained scientists (women and men) reestablish careers in biomedical or behavioral science after taking time off to care for children or parents, or to attend to other family responsibilities. The program was expanded in concept and participants during FY 2006 and FY 2007 and provides administrative supplements to existing NIH research grants to support full-time or part-time research by these individuals in a program geared to update research skills and knowledge.

- For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-068.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-04-126.html>
- (E) (ORWH, NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NEI, NIGMS, NHLBI, NHGRI, NIMH, NINDS, NLM, NINR, NCRR, NCCAM, FIC, ODS)

**NIH Working Group on Women in Biomedical Careers:** Led by the NIH Director and the Director, ORWH, this working group is reviewing NIH policies and programs to determine ways to enhance the careers of women in science, research, and engineering. The working group is also reviewing recommendations from the National Academies Report: *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering* and concerns of intramural women scientists.

- For more information, see <http://womeninscience.nih.gov/>
- For more information, see [http://www.nap.edu/catalog.php?record\\_id=11741](http://www.nap.edu/catalog.php?record_id=11741)
- (E, I) (ORWH, OD)

**ORWH/Office of Intramural Training and Education Programs:** NIH supports a series of training programs for postdoctoral fellows, graduate students, summer students, and postbaccalaureate trainees, as well as career enhancement workshops for intramural scientists.

- For more information, see <http://www.training.nih.gov/postdoctoral/womenshealth.asp>
- (I) (ORWH, OIR)

**Intramural Program on Research on Women's Health (IPRWH):** The IPRWH is a trans-NIH interdisciplinary collaboration on women's health and sex/gender research. The IPRWH consists of:

- ▷ The Women's Health Special Interest Group (WHSIG), which is a focused research interest group that, among other activities, sponsors scientific lectures of interest to intramural women's health researchers.
- ▷ The ORWH Women's Health Seminar Series, which features nationally recognized leaders in women's health research who present the latest information on topics important to women's health for the NIH extramural and intramural scientific and public communities.
- ▷ The NIH Women's Health Fellowships in Intramural Women's Health Research, which, in 2006, announced the selection of the first recipients.

- For more information, see <http://orwh.od.nih.gov/news/iprwh.html>
- For more information, see <http://orwh.od.nih.gov/news/whsig.html>

- For more information, see [http://tango01.cit.nih.gov/sig/home.taf?\\_function=main&SIGInfo\\_SIGID=122](http://tango01.cit.nih.gov/sig/home.taf?_function=main&SIGInfo_SIGID=122)
- For more information, see <http://orwh.od.nih.gov/news/whss.html>
- For more information, see <http://orwh.od.nih.gov/news/2006Fellows.html>
- (I) (ORWH)

## IC-Specific Programs and Initiatives

**Medical Scientist Training Program:** The need for investigators who are well trained in both basic science and clinical medicine has long been recognized within the biomedical science community. To help meet this need, NIH established the Medical Scientist Training Program (MSTP). This program encourages and supports the training of students with outstanding credentials and potential who are motivated to undertake careers in biomedical research and academic medicine. MSTP students participate in an integrated program of graduate training in the biomedical sciences and clinical training offered through medical schools. Graduates receive the combined M.D.-Ph.D. degree, and the majority of them pursue careers in basic biomedical or clinical research. MSTP grants are a type of National Research Service Award.

- For more information, see <http://www.nigms.nih.gov/Training/InstPredoc/PredocOverview-MSTP.htm>
- (E) (NIGMS)

**NIGMS Community for Advanced Graduate Training (CAGT):** To increase interactions between the Institute's MARC prebaccalaureate research training programs and its predoctoral graduate-level research training programs, NIGMS has created the Community for Advanced Graduate Training (CAGT) network. Launched in summer 2007, the CAGT is an interactive Web-based system that works to identify mentoring opportunities between MARC undergraduate students and NIGMS predoctoral research training grant program directors. The system aims to improve the ability of MARC students to find suitable predoctoral training opportunities and to apply directly to those graduate institutions. The system also will boost the ability of NIGMS research training grant program directors to recruit suitable students for their graduate (Ph.D.) programs. Moreover, MARC students will be able to access information regarding summer recruitment opportunities at these research-intensive graduate institutions.

- (E) (NIGMS)

**HIV Research Training Programs:** The AIDS International Training and Research Program (AITRP) builds institutional, national, and regional HIV research capacity in low- and middle-income countries. Over the past 19 years, this program has been responsible for many of the first generation of research scientists from these countries, with many more in the pipeline. The program offers multidisciplinary biomedical, behavioral, and social science research training to a wide range of professionals. Building on the AITRP, the International Clinical, Operational and Health Services Research and Training Award for HIV/AIDS and TB (ICOHRTA AIDS/TB) Program began in 2002 to strengthen the capacity for clinical, operational, and health services research in low- and middle-income countries where AIDS, TB, or both are significant problems. Through training health professionals who reach across the spectrum of clinical and public health research, this program is strengthening the capacity of scientists, program managers, and policymakers to evaluate and better implement large-scale prevention, treatment, and care



interventions that are locally relevant and effective. Many local leaders of programs supported by the President's Emergency Plan for AIDS Relief have received or are receiving their research training through the AITRP and the ICOHRTA AIDS/TB programs.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/aitrp/index.htm](http://www.fic.nih.gov/programs/training_grants/aitrp/index.htm)
- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/icohrta/aids\\_tb.htm](http://www.fic.nih.gov/programs/training_grants/icohrta/aids_tb.htm)
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (FIC, NCI, NHLBI, NIDA, NIDCR, NIMH, NINDS, NINR, OAR, ORWH)

**Global Infectious Disease Research Training:** A major barrier to improved treatment and control of infectious diseases is the scarcity in endemic countries of scientists with infectious disease research expertise. This program supports U.S. and developing country institutions to train scientists from developing countries to engage in non-HIV/AIDS infectious disease research. It is contributing to the long-term goal of building sustainable research capacity in endemic infectious diseases at developing country institutions to enhance prevention, treatment, and control of infectious diseases that cause major morbidity and mortality in the developing world.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/gid.htm](http://www.fic.nih.gov/programs/training_grants/gid.htm)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (FIC, NIAID)

**Informatics Training for Global Health:** Information technology is required in almost all research programs, both to access the vast information resources available internationally and to apply to research design and analysis. This program is intended to increase the capacity of developing country scientists and medical professionals to design, access, and use modern information technology in support of health sciences research. Specifically, this program supports innovative training programs for developing country biomedical and behavioral scientists and engineers, clinicians, librarians, and other health professionals to increase their capacity to access, manage, analyze, interpret, manipulate, model, display, and share biomedical information electronically. Among other skills, this will increase their ability to conduct multisite clinical trials and international disease surveillance and prevention programs.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/itgh/index.htm](http://www.fic.nih.gov/programs/training_grants/itgh/index.htm)
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (FIC, NHGRI, NIBIB, NLM)

**International Collaborative Trauma and Injury Research Training Program:** Each year, more than 5 million deaths and countless disabilities result from injuries. This program is strengthening the scientific expertise in developing countries in human injury-related research and funds 11 collaborations between institutions in high-income countries and low- or middle-income countries. These collaborations support research training in applied science, the epidemiology of risk factors, acute care and survival, rehabilitation, and long-term mental health

consequences of trauma and injury. The program is also supported by the World Health Organization, Pan American Health Organization, and Centers for Disease Control and Prevention.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/trauma/index.htm](http://www.fic.nih.gov/programs/training_grants/trauma/index.htm)
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (FIC, NHLBI, NIAAA, NIBIB, NIMH, NINR, OBSSR, ORWH)

**International Training and Research in Environmental and Occupational Health:** This program is building global capacity and collaboration to better understand, investigate, control, and prevent environmental and occupational health problems in developing countries and in the United States. Through this program, NIH is developing and strengthening centers of research excellence in environmental and occupational health-related sciences in target countries through long-term partnerships with U.S. institutions, with particular emphasis on research activities that will have the potential to benefit a whole region. The program was recompeted in 2007 and is jointly funded by NIH and the Centers for Disease Control and Prevention.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/itreoh/index.htm](http://www.fic.nih.gov/programs/training_grants/itreoh/index.htm)
- (E) (FIC, NIEHS)

**International Training and Research Program in Population and Health:** This program supports U.S. universities that provide training to scientists from developing countries in population studies or reproductive biology. Objectives of this program include enhancing population research programs and international collaborative studies on (a) reproductive processes and contraceptive development and (b) demographic processes, including aging, mortality, morbidity, fertility, migration, and linkages between health and economic development; strengthening the ability of scientists from developing nations to contribute to global population research efforts and advance knowledge in support of population policies appropriate for their home countries; and developing and strengthening centers of research excellence in population-related sciences in developing countries.

- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/itrph/index.htm](http://www.fic.nih.gov/programs/training_grants/itrph/index.htm)
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (FIC, NICHD, ODS)

**Interdisciplinary Training in Environmental Health Science and Genetics:** The new Human Genes and the Environment Training Program, as a part of the Genes, Environment and Health Initiative, will provide grants to train scientists in the emerging inter-discipline of environmental genomics/genetics to pursue a career path that integrates environmental sciences with human genetics and population genetics and genomics. This cadre of scientists will not only be equipped to advance methodologies and technologies in environmental genomics/genetics, but will also use these tools and resources to disentangle and evaluate the enormous number of environmental factors which directly influence or interact with some genotypes to determine the resultant

phenotypic expression and clinical or physiologic endpoints associated with the etiology and treatment of complex diseases.

- For more information, see <http://www.gei.nih.gov/traininggrants.asp>
- (E) (NIEHS, NHGRI)

**Predoctoral Research Training in Biostatistics:** A workforce of biostatisticians with a deep understanding of statistical theory and new methodologies is vital to meet the biomedical, clinical, and behavioral research needs of the United States. With that end in mind, NIGMS has funded 13 predoctoral training programs in biostatistics to support 43 predoctoral trainees. The program was initiated at the request of several NIH institutes, which provided cofunding to help launch the effort. The training program integrates biostatistical theory and evolving methodologies with basic biomedical research, including bioinformatics, genetics, molecular biology, cellular processes, and physiology, as well as epidemiological, clinical, and behavioral studies.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/par-04-132.html>
- (E) (NIGMS)

**Predoctoral Training at the Interface of the Behavioral and Biomedical Sciences:** In 2006, NIGMS announced a new institutional training grant program focused on “Training at the Interface of the Behavioral and Biomedical Sciences.” The first two awards were made in July 2007. The programs provide an interdisciplinary research training experience and curriculum for predoctoral trainees that integrate both behavioral and biomedical perspectives, approaches, and methodologies. Through coursework, laboratory rotations, and programmatic activities that reinforce training at this interface, the program aims to develop basic behavioral scientists with rigorous training in the biomedical sciences who are available to assume leadership roles related to the Nation’s biomedical, behavioral, and clinical research needs. This new training grant program is one of eleven predoctoral research training areas supported by NIGMS that promotes interdisciplinary, collaborative, and innovative research training.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-503.html>
- For more information, see <http://www.nigms.nih.gov/News/Results/BehavioralBiomedical070207.htm>
- (E) (NIGMS)

**Research on Interventions That Promote Research Careers:** This new initiative funds research that will inform programs designed to increase the number of underrepresented minority students entering careers in mainstream biomedical and behavioral research. Comparative research will analyze the experience of all ethnicities in order to place that of underrepresented students in context and to learn whether and how interventions should be tailored to make more underrepresented students successful in biomedical careers. The results of this initiative could inform the NRSA training communities about diversity recruitment.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-08-005.html>
- (E) (NIGMS)

**NINR Intramural Training Initiatives:** NIH concluded its 6<sup>th</sup> and 7<sup>th</sup> annual Summer Genetics Institutes (SGI) in June/July 2006 and 2007, respectively. The SGI is an intense, 2-month, full-time summer research training program targeted at faculty, graduate students, and advanced-practice nurses. Hosted by NINR's Division of Intramural Research, the SGI features classroom and laboratory components that are designed to provide a foundation in molecular genetics for use in clinical practice and the research laboratory. The SGI develops research capacity among graduate students and faculty in nursing and provides a basis for clinical practice in genetics among advanced-practice nurses.

For recently graduated, doctorally prepared nurse scientists, NIH sponsors the K22 Career Transition Awards, which are designed to facilitate the successful transition of postdoctoral trainees to independent research careers. Awardees receive up to 3 years of postdoctoral research training in the NINR intramural laboratories in Bethesda, Maryland, followed by 2 years of extramural support as they begin tenure-track faculty positions. In addition, NINR participates in the NIH Graduate Partnership Program, in which the Institute partners with schools of nursing to support the research training of doctoral students in symptom management, genetics, or end-of-life/palliative care in the NIH intramural laboratories. In supporting such initiatives, NIH seeks to expedite the development of productive nurse scientists, many of whom can also go on to serve as nursing faculty.

- For more information, see <http://www.ninr.nih.gov/Training/TrainingOpportunitiesIntramural/>
- (I) (NINR)

**Building Interdisciplinary Research Careers in Women's Health (BIRCWH):** BIRCWH is an innovative career development program to support the training of junior faculty researchers in an interdisciplinary mentored environment in women's health research by pairing junior researchers with senior investigators. The program bridges advanced training with research independence, in addition to integrating scientific disciplines in an interdisciplinary nature. In FY 2006 and FY 2007, the BIRCWH program funded 36 additional awards.

- For more information, see <http://orwh.od.nih.gov/interdisciplinary/bircwhmenu.html>
- (E) (ORWH, ODS, NICHD, NIA, NIDA, AHRQ)

**Women's Reproductive Health Research Career Development Program:** The ORWH cosponsored with NICHD the funding of 20 institutional career development awards designed to increase the number of obstetricians and gynecologists conducting research in women's health.

- For more information, see <http://www.nichd.nih.gov/research/supported/wrhr.cfm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (ORWH, NICHD)

**Informatics Research Training Programs:** To address the national need for computational scientists competent in biology and medicine, NLM reviewed its University Informatics Research Training Programs and issued a new call for applications. Curricula were updated to reflect current computing needs in clinical translational research and public health. Eighteen 5-

year grants, totaling more than \$75 million, for research training in biomedical informatics, were awarded in 2006. Approximately 270 trainees are currently enrolled in these programs.

- For more information, see <http://www.nlm.nih.gov/ep/AwardsTrainInstitute.html>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NLM)

**Addressing the Unique Training Needs of CAM Research:** NCCAM supports two unique NRSA funding opportunities for predoctoral and postdoctoral fellows who wish to be trained specifically in research related to complementary and alternative medicine. These programs support conventional researchers and trainees as well as CAM practitioners. NCCAM also supports NRSA institutional training grants (T32) through the NIH-wide mechanism. Many of the training programs supported are unique in that they accept CAM practitioners who wish to transition to a research career. Others involve collaboration between a conventional research intensive institution and a school that trains CAM practitioners. For example a partnership between Bastyr University School of Naturopathic Medicine and the University of Washington provides postdoctoral training opportunities for CAM practitioners as well as individuals with conventional scientific academic backgrounds.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-384.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-319.html>
- For more information, see <http://grants2.nih.gov/grants/guide/pa-files/PA-06-468.html>
- (E) (NCCAM)

**International Research Scientist Development Award (IRSDA):** Through IRSDA, Fogarty International Center provides career development and research support to U.S. postdoctoral scientists in the formative stages of their careers to solidify their commitment to global health research. For example, under this program, Fogarty supported the career development of Dr. Nathan Wolfe, whose work in Cameroon advanced our understanding of how retroviruses enter into human populations, and determined that the likely point of transmission of the HIV virus occurred between primates and bushmeat hunters. Dr. Wolfe has now received the NIH Director's Pioneer Award. Cofunded by Fogarty and NIAID, this award builds on Dr. Wolfe's IRSDA-supported research and is enabling the establishment of the first global network to monitor the transmission of new viruses – including pandemic disease threats such as ebola, anthrax, and monkeypox – from animals into human populations. This hunter cohort distributed throughout key habitats will provide a framework for a range of research projects aimed at predicting and preventing disease emergence, including studies of risk factors associated with primary and secondary infections with zoonotic microorganisms, anthropological studies of hunting and meat processing practices that lead to exposure, and ecological studies of the animal and human populations that influence transmission among and between groups.

- [Wolfe ND, et al. Proc Natl Acad Sci U S A. 2005;102:7994-9, PMID: 15911757](#)
- For more information, see [http://www.fic.nih.gov/programs/training\\_grants/irsda.htm](http://www.fic.nih.gov/programs/training_grants/irsda.htm)
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (FIC, NIAID)

## Public-Private Partnerships

**Partnerships to Support Training for Research on Aging:** NIH collaborates with private organizations and foundations to prepare scholars for research on aging. For example, partnerships with the American Federation for Aging Research, the John A. Hartford Foundation, and other foundation partners support two efforts:

- ▷ The Summer Research Training in Aging for Medical Students program provides a series of coordinated Institutional National Research Service Award (NRSA) grants designed to expose medical students, early in their training, to the excitement of ongoing research and encourage them to consider careers in research on aging.
- ▷ The Paul B. Beeson Career Development Awards in Aging Research offer 3- to 5-year faculty development awards to outstanding junior and mid-career faculty committed to academic careers in aging-related research, training, and practice. For over a decade, these awards have been extraordinarily successful in preparing participants to take leadership roles in research that has added exponentially to our understanding of aging and age-related diseases and conditions.
- ▷ A third partnership is with the Alzheimer's Association to support the unique and highly successful Summer Institute on Aging Research. For 21 years, this program has assisted emerging scholars in making the transition to independent funding for research relevant to aging. The program provides junior investigators an opportunity to be mentored in the substance and methodology of aging research by recognized experts in the field with the goal to enhance participants' potential for success as independent investigators. In 2004, the John A. Hartford Foundation partnered with NIH to sponsor a preconference to the Summer Institute to address issues of clinical research.
  - For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-05-002.html>
  - For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-07-001.html>
  - For more information, see <http://www.nia.nih.gov/NewsandEvents/Calendar/summerinstitute2008.htm>
  - (E) (NIA, ODS)

**Research Training Partnerships:** NIH has signed a Memorandum of Understanding with both the American Skin Association and the Orthopaedic Research and Education Foundation to provide supplemental support to fellows funded under the National Research Service Award program.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-536.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAR-06-539.html>
- (E) (NIAMS)

**HHMI-NIH Interfaces Initiative:** Interdisciplinary research that builds from the foundations of multiple traditional disciplines including biology, physics, engineering, chemistry, informatics, and medicine has become an essential feature of modern biomedical research. Training the interdisciplinary researchers of the future and reducing the barriers to interdisciplinary graduate education is the goal of a public-private partnership between NIH and the Howard Hughes Medical Institute (HHMI). This initiative is developing cross-department mentoring programs,



interdisciplinary courses, and a cadre of students being trained in an interdisciplinary environment. Programs are under development at 10 universities at the present time.

- For more information, see <http://www.hhmi.org/grants/institutions/nibib.html>
- For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-EB-05-002.html>
- For more information, see <http://www.nibib.nih.gov/Training/Predoctoral#HHMI>
- (E) (NIBIB)

## NIH Training Program Evaluation

**Annual Assessments of Research Training:** Every year, NIH assesses NRSA research training outcomes and program management against two goals established under the Government Performance and Results Act (GPRA). In the first of these goals, NIH seeks to measure the quality of its programs and ensure that substantial numbers of trainees and fellows are retained in research careers, by comparing the subsequent research activity of former NRSA trainees and fellows against their peers. The second of these two GPRA goal measures NIH progress on improving the efficiency of the NRSA program by developing and implementing an electronic system for appointing trainees to institutional training grants. By 2012, NIH expects the new system to be fully implemented and that 100 percent of trainees will be appointed to training grants electronically rather than through paper appointment forms. This is a new goal and NIH will report its performance in transitioning to electronic appointments in February 2009.

- For more information, see [http://officeofbudget.od.nih.gov/PDF/FY08%20PB%20Performance%20Detail%20Vol%20II%20FIN%20AL%20\(PB%20Submitted\).pdf](http://officeofbudget.od.nih.gov/PDF/FY08%20PB%20Performance%20Detail%20Vol%20II%20FIN%20AL%20(PB%20Submitted).pdf)
- (E) (OD/OER) (GPRA Goal)

**Program Assessment Rating Tool (PART) Review of NIH Research Training:** In 2006, NIH training programs underwent PART review by the Office of Management and Budget and received the highest rating possible. The OMB judged the NIH program to be “effective at training and retaining researchers in the biomedical research field,” to be successfully meeting “its ambitious long-term and annual goals,” and to have conducted independent evaluations of the program since its inception in 1974. The NIH training program also has a plan to improve performance and management over time, and held accountable for meeting improvement targets.

- For more information, see <http://www.whitehouse.gov/omb/expectmore/summary/10003543.2006.html>
- (E) (OD/OER)

**Evaluation of Extramural Research Training and Career Development Programs at NIAMS:** The NIAMS is currently conducting an outcome evaluation designed to examine the effectiveness of its research training (T32 and F32) programs and career development award (K01 and K08) programs.

- (NIAMS)

**Assessment of CAM Research Training Needs:** A formal evaluation by an independent expert panel of opportunities for training in research on complementary and alternative medicine

(CAM) highlighted the unique needs of the field. In particular, building capacity in the CAM research workforce requires specific efforts targeted at: 1) training CAM experts, who frequently have little scientific background, in scientific research methodology; and 2) creating opportunities for investigators from conventional scientific, who generally know little about CAM, to learn about CAM practices and modalities. This report continues to guide NCCAM's training initiatives which are aimed at creating programs to establish sustainable research training infrastructure, programs targeted to CAM practitioners, and career transition awards specifically aimed at helping CAM researchers establish independent research careers.

- For more information, see <http://nccam.nih.gov/training/report.htm>
- (E) (NCCAM)



## HEALTH INFORMATION AND COMMUNICATION

### HEALTH COMMUNICATIONS AND INFORMATION CAMPAIGNS AND CLEARINGHOUSES

*When Ruth walked into the locker room at work, she realized something was wrong. She couldn't speak. She tried to pick up her lock, but her right hand couldn't grab it. Luckily, her friend knew the signs of stroke (sudden numbness or weakness of the face, arm, or leg—especially on one side of the body; sudden confusion; trouble speaking or understanding speech; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, or loss of balance or coordination; or sudden severe headache with no known cause) and called an ambulance. In the emergency room the doctors ran some tests and administered a clot-busting drug into her IV. Within 10 minutes she could speak again. Ruth didn't know a thing about stroke before she had one. Now, she makes sure that all the members of her family know the signs of stroke and that getting help within the first hour after a stroke, not waiting to see if it gets "better," is key to the best possible outcome—the outcome Ruth had.*

*After much investigation followed by clinical trials, scientists provided the treatment that enabled the good outcome for Ruth. But public knowledge, based on targeted and repeated dissemination of science-based information, using multiple avenues, helps the public reach the treatment. The [Know Stroke. Know the Signs. Act in Time.](#)<sup>27</sup> public education campaign helps build awareness of the symptoms of stroke and the need to act quickly.*

### Introduction

Reaching the public in an efficient way with science-based, trustworthy information is an important part of NIH's mission. As the focal point of the national biomedical and behavioral research enterprise, NIH has a responsibility to communicate useful public health and science information to a wide range of audiences, including the public, patients, family members, health care providers, scientists, public health workers, voluntary health organizations, policy leaders, and industry. Strategic health communications and information campaigns and clearinghouses are the primary means NIH uses to fulfill this mission.

Health communication is a complex task. More than simply conveying information, it involves using carefully developed and tailored strategies and an armamentarium of appropriate tactics to inform individual and community decisions that contribute to enhanced health. Effective health communication requires:

- Needs assessment and preevaluation
- Environmental scans, that is, what is known and who are the interested parties
- Cultural competency

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<sup>27</sup> For more information, see <https://ice.iq solutions.com/ninds/profstrokepubs.asp>

- Audience analysis
- Defining core messages
- Finding audiences where they are
- Making the materials useful for each audience
- Careful selection of the appropriate channels of communication
- Constant reevaluation of the effectiveness of communications programs

To support the agency's health communications goals, NIH reaches out to the public through a variety of programmatic efforts. Public information campaigns are coordinated efforts to raise public awareness of critical health issues, and communications clearinghouses provide educational materials and resources on a variety of health-related topics. In addition to campaigns and clearinghouses, NIH also offers a wide variety of information resources utilizing the Internet, television, radio, print outlets, and other methods of communication. NIH Web sites are increasingly powerful communication tools, evidenced by the fact that they are accessed more than 1 billion times each year by health professionals, scientists, and the public. The role of intermediaries who use the Web, such as public health workers, demonstrates the additional powerful reach of clear, useful, accurate information produced by NIH, but delivered at the local level, tailored to the needs of the community or the individual.

Certain efforts may target specific audiences, such as populations that are at greater risk for particular diseases. Sometimes the communication effort is developed with the direct input of a community. Each communications approach has a different purpose, includes different elements, has the potential for reaching different audiences, and can be ongoing or time specific.

For example, an information campaign may be targeted to raise awareness or to take urgent and specific action based on a scientific discovery. This type of campaign must be carefully designed to reach affected audiences, which may include such diverse populations as patients, physicians, caregivers, industry, children, the aging, or, for example, women susceptible to heart attack or African American males susceptible to stroke, usually within a finite period of time. A campaign often consists of multiple communication products delivered via a variety of outlets and has the desired goal of either provoking a specific action or bringing about a behavioral change.

Clearinghouses are information development and dissemination services sponsored by NIH ICs. Some services provided by clearinghouses include working with the ICs to develop materials, evaluate programs, assist in responding to phone, mail, fax, and e-mail inquiries, and distribute free publications in hard copy and electronic formats.

Each year, NIH distributes nearly 30 million science-based, health information publications to requestors who rely on NIH and its news stories, press releases, and publications for authoritative information about the latest research developments while making more and more information available via the Web. Recent research has shown that a majority of Americans who request NIH information not only use it, but also share it with others. More than 40 percent who use Web materials related to health take that information with them to their physicians' offices.

Each IC shares a similar challenge: identifying and selecting appropriate communication outlets for key audiences. As a way to make knowledge more meaningful, NIH strives to present

information in teachable moments and in culturally competent, accessible ways. These offices work directly with the intramural and extramural scientists in their mission areas to ensure that the materials they produce are based on the soundest science. The OD Office of Communications and Public Liaison (OCPL) provides leadership and guidance and speaks for NIH as a whole. The result of these efforts is a broad-based communication program that uses the best of both traditional and new approaches to reach vast, ever-emerging audiences.

### Summary of NIH Activities

NIH ICs are congressionally mandated<sup>28</sup> to provide health information, based on scientific discovery, to the public. This is a significant component of NIH efforts to translate research to improve the health of the Nation. Health information resources also reflect the change in science itself. For example, scientific advances led to genetic testing, which makes it possible, in some cases, for an individual to know the likelihood of developing certain diseases. This in turn creates needs and opportunities for communication of preventive health information. The ability to intervene before the first sign of disease occurs, or to prevent disease through increased awareness, enables the public to be increasingly involved in monitoring their health and participating in their own care. Improving public knowledge about disease processes, opportunities for disease prevention, and treatment options helps raise the health literacy of the public in ways that improve the quality and length of life and reduce the burden of disease.

Advances in biomedical and behavioral research have brought our Nation's health care enterprise to the brink of a new paradigm, summarized by the "4 Ps" listed below.

- *Predictive*, the ability to determine an individual's risk for developing a disease
- *Personalized*, the ability to analyze each individual's health risks and individualize the treatment, dosage, or approach to disease
- *Preemptive*, the possibility of preventing disease altogether
- *Participatory*, the importance of having the practitioner and patient work together as a team to develop a treatment plan.

While this new paradigm carries the possibility of keeping individuals healthier, it also means that people must become more involved in managing their own health and in making informed decisions. To meet this need, NIH is employing a wide variety of health communication approaches and making more information available through the most current range of communication outlets and strategies.

Technology now complements proven communication approaches, such as print materials. For some groups communication strategies that make use of technology may be more advantageous than traditional formats. With our changing population, it is important that materials are produced with culturally appropriate content and formats and delivered by the most effective and direct system available.

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<sup>28</sup> Although many ICs have specific language that is variable (some as specific as mandating clearinghouses or education programs or others indicating the responsibility to make science-based information available to the public), the general authority is covered by Section 402(e) of the PHS Act.



## **Delivering Health News to the Public**

First and foremost, NIH is responsible for keeping the public informed about new developments in NIH research that affect health. In addition, putting a human face on a scientific finding not only helps the public understand research, but also helps them comprehend the practical implications of a research finding for their own health and behavior, critical information for public participation in improving health.

For individuals who may have questions about science and health research, NIH has developed general materials that can be used for answering basic questions. For example, a variety of vetted health information resources are available through NIH, including:

- A Web site with [A-Z health information](#) from all NIH Institutes and Centers
- “[Research Results for the Public](#),” a site that provides disease-by-disease descriptions of research progress and information to promote improved understanding of clinical research
- “[Get Involved at NIH](#),” the gateway for public participation, input, and feedback
- “[NIH & Clinical Research](#),” a health information site that features podcasts, vodcasts, and radio programs in English and Spanish on clinical research
- “[NLM Director’s Comments](#),” a prominently displayed link on the NLM Web site that features weekly podcasts by NLM’s Director. These features are now available in Spanish in an effort to reach one of America’s rapidly growing populations

Moreover, NIH continues to provide direct information to almost 900 radio stations each week. The NIH Radio News Service, more than 20 years old, is available to news and health programs nationwide and has been upgraded to improve access for those outlets. NIH programs also are broadcast to listeners on XM Satellite Radio through a radio feature called “NIH Health Matters.” Also, NIH publishes [News in Health](#), which is accessible monthly to public health workers, community centers, aging centers, voluntary health organizations, physicians, and hospitals.

The press, a major source of health information for the public, is an important transmission resource for NIH in ensuring that sound, research-based information is disseminated to the public. To help the press interpret medical information with greater ease and accuracy, NIH staff members work every day to provide background for media sources and identify key knowledgeable scientists to help reporters develop their stories. NIH also offers a free annual training course, “Medicine in the Media,” now in its sixth year. The course offers opportunities for journalists to refine their ability to evaluate and report on medical research.

In addition, the NIH Office of Communications and Public Liaison, which is responsible for coordinating NIH communications efforts, has been building a network of public information officers at grantee institutions as a way to enhance knowledge exchange and the quality of information that reaches the public regionally.

However, the Web and related media are the new frontiers for delivery of NIH-based news to the public. NIH has intensified the evaluation of its Web sites. A redesigned NIH Web site,

[www.nih.gov](http://www.nih.gov), debuted this year and reflects new technologies, including customized streaming news feeds such as Really Simple Syndication (RSS) and podcasting and vodcasting, thereby bringing NIH research to the next generation of health consumers who rely on portable electronic devices for news. Every IC has the option of using this model in redesigning Institute sites. The NIH MedlinePlus Web site has extensive health information from all NIH components. By the end of FY 2007, MedlinePlus contained trusted information on more than 740 diseases and conditions, up from just 22 when it was launched in 1998. To improve consumers' understanding of medical concepts, MedlinePlus includes a medical encyclopedia and a medical dictionary, and extensive information on prescription and nonprescription drugs. It also provides links to directories of health care professionals and information about clinical trials (<http://clinicaltrials.gov/>). MedlinePlus was voted the top government news/information Web site in the American Customer Satisfaction Index during the second quarter of 2007. A spinoff, in the form of a new quarterly magazine, *NIH MedlinePlus*, brings the latest and most authoritative information on health conditions and diseases from NIH directly to patients in physicians' offices. *NIH MedlinePlus* magazine is distributed free of charge to 40,000 physician offices and can be downloaded online as well.

The agency also seeks to take advantage of available opportunities to bring news and information to the public on regional, local, and community levels. A new feature of the MedlinePlus Web site provides more than one-third of Americans with a "Go Local" capability that puts them in touch with health resources in their communities. Go Local has links to health care information and resources in 22 States and regions; 11 of the Go Local sites were added in 2006 and 2007 and several more are in development.

## Reaching Different Audiences

The "public" is not monolithic. It includes a number of audiences divided by gender, age, race/ethnicity, susceptibility to specific diseases, and many other factors. There are patients, families, friends, scientists, health professionals, public health workers, industry, health care providers, congressional staff, and voluntary organizations, all requiring specialized information related to specific health conditions or concerns, such as aging, diabetes, or cancer. NIH responds to the requirements of specific audiences in a variety of ways.

Understanding different audiences and how to reach them is key to all public health communications programs supported by NIH. NIH develops communications programs that take into account groups that need specialized information, such as Latinas with an increased risk for diabetes, or African American males who suffer disproportionately from prostate cancer. In other cases, for example, providing parents with information about early identification programs in autism, hearing loss, or delayed language development can help them to work with their physicians to identify interventions that improve the lives of their children before a window of opportunity is lost. There must be multiple approaches and repeated messages to reach multiple audiences: NIH continues to produce science-based factsheets, checklist resources, public service announcements, podcasts and vodcasts (video podcasts), as well as other information resources concerning timely issues such as heart disease, depression, drug abuse, and eye health, each tailored for a specific audience, such as African Americans, the aging population, or teens.

NHGRI and NIDA both have sponsored major online events to provide opportunities for students and teachers in classrooms across the United States to ask real-time questions of the Nation's top scientific experts in the fields of genomics and drug abuse and addiction. The most recent event, NIDA's Drug Facts Chat Day, drew 36,000 questions. This is a format that NIH will continue to pursue.

In March 2007, the Office of Research on Women's Health began podcasting "[Pinn Point on Women's Health](#)," hosted by its Director, Dr. Vivian W. Pinn. The monthly podcast discusses the latest news in women's health research.

NIH also recently launched the Clinical Research Awareness initiative. This effort originates in the cultural shift taking place in medical care, a move away from physician referral to self-referral to clinical trials. This shift has created a different need for the public interested in participating in clinical research. As a result, there is a need for clear, easy-to-access information. NIH, with the NIH Clinical Center, has designed a Web site that includes information about (1) the nature of clinical trials, (2) what participation means, and (3) current trials and their locations, all with the goal of increasing public awareness and participation (<http://clinicalresearch.nih.gov>).

NLM supports [www.clinicaltrials.gov](http://www.clinicaltrials.gov), a database of clinical trials past and current. This is a congressionally mandated<sup>29</sup> database that is adding features to make it more user-friendly. Because of the demand for information on cancer, NCI has developed a series of materials specifically about cancer clinical trials. The [NCI Web site](#) offers a range of resources, including a guide for patients and their families; worksheets to engage the community in outreach efforts related to cancer clinical trials; online courses for health professionals; DVDs; and slide sets to assist in education programs. The goal of these efforts is to help the public—patients, families, medical professionals, and the media—gain access to information on clinical research and its benefits.

NCCAM is NIH's source of evidence-based information about complementary and alternative healing practices. Increasingly, people are investigating what alternative treatment options are available, especially for hard-to-manage conditions such as chronic back pain. A 2006 survey completed by AARP and NCCAM revealed that nearly two-thirds of adults older than age 50 are using complementary and alternative medicine, but only one-third of them are sharing that information with their physicians. Just as clinical trials are becoming an integral part of the public's knowledge base, so also is complementary and alternative medicine. To encourage an open dialogue, NCCAM launched a new patient/provider education initiative, "Time to Talk," which encourages open discussion of all health care practices to ensure safe and coordinated care.

"Time to Talk" is only one example of how NCCAM is realizing its mission of exploring complementary and alternative medicine in the context of rigorous science and then disseminating this information to the public. NCCAM's Web site received more than 2.6 million visitors in 2006 and has been cited by *Prevention* magazine for "Best Alternative Medicine

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<sup>29</sup> The original mandate, the Food and Drug Modernization Act of 1997 (Pub. L. No. 105-115), was enhanced by the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85).

Information.” In addition NCCAM has been cited by the World Health Organization as a model for evidence-based CAM.

The population is aging rapidly, and seniors are a special focus of NIH’s information dissemination efforts. As the Internet becomes an increasingly important source of information on health, seniors unfamiliar with using computers are being invited to use this new resource. NIA and NLM have joined forces to develop and maintain [www.NIHSeniorHealth.gov](http://www.NIHSeniorHealth.gov), a site with credible, aging-related health information targeted to the cognitive and visual requirements of older adults. The site covers such topics as Alzheimer’s disease, cataracts, colorectal cancer, and diabetes in a clear, easy-to-read format. Twelve NIH Institutes collaborated with NLM to develop the 33 health topics included on the site.

Print materials specially targeted to the issues of interest to older adults remain a primary way to provide information to seniors. The National Institute on Aging Information Center (NIAIC) and the Alzheimer’s Disease Education and Referral (ADEAR) Center send millions of publications to older adults each year. These cover the latest findings about Alzheimer’s disease, advice on long-distance caregiving, materials about the importance of exercise, and tips for improving communication with health care providers. The popular *Age Page* series of factsheets presents varied information tailored to seniors and these publications can be read online or downloaded. The wealth of materials specifically targeted to seniors reflects NIH’s recognition of the importance of reaching out to this expanding audience.

Ethnicity can also require targeted communication strategies. NIH recently updated its Spanish language Web site (<http://salud.nih.gov>). One of the major additions to this Web site is the inclusion of Spanish language radio programming (<http://salud.nih.gov/radio.asp>). The Spanish language radio site does not mirror the English site, but features information of particular interest and importance to Spanish-speaking communities at higher risk for specific diseases.

Some NIH communications programs target a population vulnerable to or with a specific disease. For example, NINDS developed the [Know Stroke. Know the Signs. Act in Time](#) public education campaign to help build awareness of the symptoms of stroke and the need to act quickly. New treatments are available that greatly reduce the serious losses associated with stroke. Knowing stroke symptoms, calling 911 immediately, and getting to a hospital are all essential for preventing lifelong disability. This is a dramatic example of the need for the public to know what science has learned about prevention or treatment of disease.

[The Heart Truth](#), the NIH national awareness campaign for women concerning heart disease includes locally sponsored events, dissemination of materials, and free health screenings. Additionally, the campaign reaches physicians to raise awareness of the sometimes overlooked vulnerability of women to heart disease.

The [National Kidney Disease Education Program](#), an initiative that has elements of both a campaign and a clearinghouse, disseminates educational materials tailored to minority groups at high risk and encourages dialogue about kidney disease among African American families. NIH also reaches out to specialized populations, including Native Americans, Asian Americans, those

living in Arctic regions, and the elderly, through multiple Web sites that have features designed to meet the unique needs of each group.

The audiences are not only national—NIH reaches out to international audiences through collaborative communication campaigns about global health and emerging diseases issues such as avian flu, SARS, and HIV/AIDS through Institutes such as NIAID and through FIC programs.

NIH has a special role serving the public with information about rare diseases. The NIH Office of Rare Diseases provides an informational database and a clearinghouse resource for answering questions about diseases often misunderstood and misdiagnosed.

### **Rapidly Responding to Time-Sensitive Issues**

In developing its communication programs, NIH anticipates and responds to current needs. From recognizing the physical and mental health needs of Hurricane Katrina victims to becoming aware of the growing problem of substance abuse and addiction among young people, NIH continues to respond with appropriate communications materials. Increasingly, it is becoming evident that children and adolescents are in need of tailored information resources to help them cope with health conditions, peer pressure, and life events, such as the death of a sibling or parent from disease. To address this trend, NIMH developed a number of brochures designed for parents, community members, and rescue workers that explain how to help young people through crises. These materials are readily available on the [NIMH Web site](#).

Since 2004, NIAAA has taken on the difficult challenge of underage drinking. NIAAA launched its [Underage Drinking Research Initiative](#) with the goal of obtaining a more complete and integrated scientific understanding of factors that promote initiation, maintenance, and acceleration of alcohol use among young people. The initiative also addresses variables that influence the progression to harmful use, abuse, and dependence. A unique aspect of this research is that it is framed within the context of overall psychological and neurological development. NIAAA's landmark initiative on underage drinking features Web sites tailored to teens and college students and other resources.

The initiative has already led to concrete changes. First, it provided the scientific foundation for the March [2007 Surgeon General's Call to Action to Prevent and Reduce Underage Drinking](#). It also is the basis for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking. In addition, a series of meetings focusing on diagnosing alcohol use and disorders among youth and screening for adolescent drinking have been held, and a supplement of seven developmentally focused papers covering a broad range of underage drinking topics has been accepted for publication in *Pediatrics*.

This year, NIDA and NIAAA partnered with Home Box Office (HBO) and the Robert Wood Johnson Foundation to produce the documentary *ADDICTION*, which aired in spring 2007 on HBO. The documentary's nine segments explore new thinking about addiction as a brain-based disease and the role imaging has played in enhancing our understanding of drug and alcohol use, thereby leading to new treatments. NIH-sponsored research also is playing a key role in removing the stigma that surrounds addiction, an important step in helping the 22.6 million



Americans with this disease seek and obtain treatment. *ADDICTION* was honored with a Governors Award by the Academy of Television Arts and Sciences (an Emmy), the highest honor given by the Academy, reserved for individuals or organizations committed to important social causes. More than 13 million people saw the documentary when it aired in March 2007. Millions more have accessed the content through DVDs sold in bookstores and at [HBO.com](http://HBO.com), podcasts, Web streams, a companion book, local and national outreach parties and screenings, and prominent local and national media coverage. Much of the outreach was coordinated by addiction and recovery advocacy groups, including Community Anti-Drug Coalitions of America, Join Together, and Faces and Voices of Recovery with support from the Robert Wood Johnson Foundation.

The airing of *ADDICTION* was accompanied by the release of two publications, NIAAA's *Helping Patients Who Drink Too Much* and NIDA's *Drugs, Brains, and Behavior—The Science of Addiction*. *Helping Patients Who Drink Too Much* is an update of a 2005 edition and is targeted to primary care and mental health clinicians. It includes revised screening tools and tips for managing patients with heavy drinking and alcohol use disorders. The updated edition also has new resources, including education credits for physicians and nurses (available through Medscape); support for medication-based therapy in nonspecialty settings; a new handout with strategies to help patients reduce or quit drinking; a new dedicated Web page devoted to the Guide; supporting resources for clinicians and patients; and an updated PowerPoint presentation for educators. The second publication explains in lay terms how science has revolutionized our understanding of addiction as a brain-based disease. It also identifies risk factors for developing an addiction, lists prevention strategies, and suggests new approaches to treatment.

## Recognizing Problems and Taking Action

In recent years, physicians and researchers increasingly have become aware of the issue of literacy as it relates to health. Researchers have found that almost one-half of the Nation's adults have trouble reading instructions or interpreting information from a graph or chart. As a result, many people do not understand the instructions they receive from their health care providers.<sup>30</sup> Researchers also have found that low health literacy is more common among older Americans and is linked to socioeconomic status; more than 66 percent of adults age 60 or older have marginal literacy skills, and 45 percent of all functionally illiterate adults live in poverty.<sup>31</sup>

The HHS Healthy People 2010 initiative established improving health literacy by the end of the decade as a national health objective. The term "literacy" refers to the mastery of a range of abilities, including reading, comprehending, and analyzing information; decoding instructions, symbols, charts, and diagrams; weighing risks and benefits; and, ultimately, making decisions and taking action. For example, to be considered "health literate" an individual should be able to understand instructions given by physicians; instructions on medication labels; information in health publications and on informed-consent documents; and data outlined on medical and insurance forms. A significant precept of health literacy is the ability of the individual to understand and take action. Health literacy arises from a convergence of education, health

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<sup>30</sup> Talking the Talk, Law of Averages: Casting a Wide Net in Health Literacy Efforts with Rima Rudd, Sc.D.; *Facts of Life: Issue Briefings for Health Reporters*, Vol. 8, No. 3, March 2003.

<sup>31</sup> Talking the Talk, 2003.



services, and social and cultural factors, and brings together research and practice from diverse fields. This challenge has particular relevance for health communications professionals, who must consider health literacy when developing health materials and communications strategies for different audiences, each with differing abilities, experiences, levels of knowledge, and cultural beliefs and practices. By understanding these differences, professionals can develop appropriate materials that have a greater potential for improving health and preventing disease. Through health literacy efforts designed to help both the receivers and providers of health information, NIH can improve health outcomes.

NIH has both scientific and communication initiatives in place to address the formidable challenges of health literacy. OBSSR coordinates the trans-NIH initiative of scientific grants on health literacy that is building national capacity for research on this issue. Studies under way are examining the relationship between health literacy and patient adherence, strategies such as using medical interpreters for patients with limited English proficiency, and an electronic data entry tool to help parents of children with attention deficit hyperactivity disorder communicate with health care providers, regardless of literacy levels.

NIH's Office of Communications and Public Liaison (OCPL), connecting the research with the public and serving as liaison to HHS on health literacy activities, has established the "Clear Communication," initiative that is focusing on objectives of health literacy—providing information in the form and with the content that is accessible to specific audiences based on cultural competence and incorporating such tactics as plain language and new technologies. The first phase of the "Clear Communication" program involves building upon sound research results provided by the trans-NIH initiative. OCPL is creating a number of resources to help the trans-NIH communicators and health communicators outside NIH reach audiences "where they are" and overcome health literacy barriers. One program is redevelopment of the nationally recognized resource "[Making Health Communication Programs Work](#)," which comprehensively addresses clear communication and reflects the best practices of all NIH ICs as a shared resource. OCPL maintains a [resource Web site](#) that includes synopses of research work under way and will house research results as they become available.

Sometimes health issues span Institutes and can be coordinated through offices in the Office of the Director to bring attention to identified problems. For example, an estimated 14 million American women may have vulvodynia (chronic vulvar pain) at one point in their lives, although for many women the condition remains undiagnosed. Vulvodynia can have a profound impact on a woman's quality of life. The Office of Research on Women's Health (ORWH) is addressing the needs of women in understanding the disease and physicians in recognizing it.

Health disparities for many minority populations are often further exacerbated by poor access to health information. Recognizing this problem, NIH has programs in place designed to advance the health of minorities. The National Network of Libraries of Medicine (NNLM), which has more than 5,800 full and affiliate members, is the core component of NLM's outreach programs. Partnering with community organizations, NNLM has funded many projects, such as the Consumer Health Resource Information Service, which is located in 21 churches across the State of Tennessee. The program aims to provide the congregations with health information twice a month. In addition, health screenings, such as blood pressure checks, also are made available.

NNLM continues to grow with the addition of public libraries at the community level that are joining the health sciences libraries as network members.

The Early Detection of Oral Cancer campaign is another NIH program designed to eliminate health disparities. The program is centered on developing educational materials concerning oral cancer targeted toward African American men, who have the highest risk of oral cancer and the lowest 5-year survival rate—only 35.6 percent. The first piece is a brochure called *Are You at Risk for Oral Cancer? What African American Men Need to Know* and is being pretested in Washington, D.C.; Chicago; Los Angeles; and Columbia, South Carolina. The brochure is part of a series of educational tools, including factsheets, posters, and print and audio public service announcements that will be targeted for distribution to African American community groups across the country.

In addition to developing materials, NIH reaches out to minorities by developing communications networks, such as the American Indian and Alaska Native (AI/AN) Health Communications Workgroup, established by NIAMS in 2005 with other ICs. Comprising representatives from a number of NIH ICs, the workgroup has presented two seminars: “Taking Action: Health Promotion and Outreach with American Indians and Alaska Natives” and “Cultural Competency Strategies for Indigenous Health Promotion... A Dakota Perspective.” In 2007, the workgroup finalized a literature review begun for the Taking Action seminar by experts, internal and external to NIH, and published the review to be widely distributed to the public, especially health communicators.

Eliminating health disparities is a continuing challenge requiring persistence. NICHD’s Sudden Infant Death Syndrome (SIDS) Outreach in Minority Communities campaign is a case in point. The program is in its 13th year, and death rates from SIDS have declined by 50 percent among African Americans. Nonetheless, infants from this community are still twice as likely to die from SIDS as are White infants. NIH is collaborating with national African American women’s organizations to support community and neighborhood workshops that focus on important yet easy steps to help reduce the risk of SIDS. In Mississippi, where the infant mortality and SIDS rates are among the highest in the nation, small stipends from NIH help community organizations conduct SIDS risk-reduction workshops in rural areas.

An innovative community-based program called *We Can!* (Ways to Enhance Children’s Activity and Nutrition), begun in 14 communities nationwide, including Boston, Massachusetts, and Montgomery County, Maryland, is addressing the national childhood obesity epidemic by providing educational programs and materials. *We Can!* materials include tips on how to encourage healthy eating, increase physical activity, and decrease sedentary activity, or “screen” time, such as TV watching.

## **Partnering With Health and Advocacy Organizations**

NIH ICs receive regular input from nonprofit groups, such as voluntary health agencies, and these organizations can increase the reach of NIH health communications and outreach programs. NIH interactions with health and advocacy organizations range from routine meetings to the establishment of novel programmatic initiatives and partnerships. Such programs allow for

cofunding of research, nonprofit input into the design and scope of NIH research initiatives, and the creation of new programs and collaborations. These efforts also enable NIH to receive regular input from its public constituencies and to forward research announcements, research results, agency news, and scientific press releases. Just a few examples include:

- NCI created CARRA—Consumer Advocates in Research and Related Activities—to draw on the experience of people affected by cancer to represent the views of cancer survivors and family members with respect to the agency’s daily activities.
- NIMH sponsors an Outreach Partnership Program that enlists national and State organizations in partnerships to help bridge the gap between research and clinical practice by disseminating the latest scientific findings; informing the public about mental disorders, alcoholism, and drug addiction; and reducing the stigma and discrimination associated with these illnesses.
- NIAMS is working with a coalition of professional and voluntary organizations, all concerned with the agency’s programs and findings related to diseases of bone, joints, muscle, skin, and connective tissues.
- An NIH Partners in Research Program supports 2-year pilot and/or feasibility studies of innovative activities designed to improve public understanding of biomedical and behavioral research, develop strategies for promoting collaboration between scientists and the community to improve the health of the public, and identify the conditions (e.g., settings and approaches) that will enhance the effectiveness of such activities. The long-term objectives of this initiative are (1) to study methods and strategies to engage and inform the public regarding health science in order to improve public understanding of the methods and benefits of publicly funded research and (2) to increase scientists’ understanding of and outreach to the public in their research efforts.

## **Outreach to the Scientific and Research Communities**

In addition to communicating science and health news and information, NIH reaches out to the scientific and research communities to share information and obtain input on policy issues. For example, in 2006 when NIH undertook the update of its data-sharing policies for research applications involving genome-wide association studies, NIH initiated a public consultation process to inform NIH policy development. This included a town hall meeting and, later, a formal Request for Information on the proposed policy that was issued in the *Federal Register* and publicized via press release. Currently, NIH is engaged in a profound effort to enhance its peer review system. The effort was launched in summer 2007 with a listening, or consultation phase, to ensure that NIH’s examination of the system is informed by the concerns and ideas of stakeholders. Widely publicized regional meetings with the biomedical research community, local meetings with professional societies and health advocacy groups, a Web page taking online comments, and *Federal Register* Request for Information were all part of the outreach.

In addition, in the last year and on a quarterly basis, the NIH Director has begun communicating directly to voluntary health agencies, the interested public, policy leaders, extramural grantees, administrators, and research program offices. These “[From the Desk](#)” communications have been effective in giving and soliciting information.

## Conclusion

As the paradigm for health care in the 21st century continues to evolve, NIH strives to develop appropriate communication outlets for its varied audiences. With consumers more involved in health and health care decision-making, the need for authoritative and timely information, delivered through the right conduits in the right forms, is all the more compelling. NIH is refining and reshaping its rich and varied communications program, focusing on certain topics and targeting specific populations as appropriate. It is using all the new avenues of technology—the Web, narrowcasting of television and radio, and the full range of new media—to communicate key health messages in forms and formats that resonate with the needs of diverse audiences. NIH will continue to evaluate how it reaches its audiences, always searching for innovative ways to keep the public informed about the latest developments in science and medicine in order to improve health.

### Notable Examples of NIH Activity

#### Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

COE = Supported through a congressionally mandated Center of Excellence program

GPRA = Relates to progress toward a goal tracked under the Government Performance and Results Act

## Delivering Health News and Information to the Public

**Clinical Trials Education:** Materials represent a collection of over 20 resources developed to increase awareness and participation in cancer prevention and treatment clinical trials. These materials include workbooks, a guide for community outreach, a trainer’s guide, online courses for health professionals, DVDs, and slide sets to assist in education programs.

- For more information, visit <http://cancer.gov/publications>
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NCI)

**New Publications:** In FY 2006, NIH distributed 3.1 million publications on mental disorders. During this year, NIH also released two new publications: *Anxiety Disorders* and *Schizophrenia*. In FY 2007, NIH developed a series of booklets and factsheets about what community members, parents, and rescue workers can do to help children cope after violence and disasters.

- For more information, see <http://www.nimh.nih.gov/health/publications/schizophrenia/summary.shtml>
- For more information, see <http://www.nimh.nih.gov/health/publications/anxiety-disorders/summary.shtml>
- For more information, see <http://www.nimh.nih.gov/health/publications/index.shtml>
- (E) (NIMH)

**MedlinePlus/MedlinePlus en Español:** NIH employed new methods to increase awareness of its MedlinePlus databases. Weekly podcasts by NLM’s Director were initiated to provide timely reports on health news; *NIH MedlinePlus The Magazine* was rolled out at a press event on Capitol Hill attended by members of Congress and guest celebrity Mary Tyler Moore, featured

on the cover. The magazine is distributed free to 40,000 physician offices and has covered stories on cancer, diabetes, and heart attack. NIH expanded the content and features of the English and Spanish MedlinePlus Web sites and the associated GoLocal sites that provide information on local health resources for approximately one-third of the U.S. population. MedlinePlus was one of two U.S. winners of the 2005 Award at the World Summit on the Information Society.

- For more information, see <http://www.medlineplus.gov>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (I) (NLM)

**Toxicology and Environmental Health:** To inform the general public about toxicology and environmental health, NIH developed several new tools, including ToxMystery<sup>®</sup>, an interactive learning site for 7- to 10-year-old children; and Tox Town<sup>®</sup>, which uses color, graphics, sounds, and animation to enhance learning about chemicals, the environment, and public health.

- [Hochstein C, Szczur M. \*Med Ref Serv Q\*. 2006 Fall;25:13-31](#), PMID: 16893844
- For more information, see <http://thunder1.cudenver.edu/cye/abstract.pl?n=87>
- For more information, see <http://sis.nlm.nih.gov/enviro/especialystudents.html>
- (I) (NLM)

**Medicine in the Media Course:** NIH presents a free annual training opportunity to help develop journalists' ability to evaluate and report on medical research. Now in its sixth year, the course examines the challenges and opportunities inherent in the process of communicating the results of medical research to the public. Stressing an evidence-based approach and reexamining intuitive beliefs about medicine, the course prepares participants for the crucial task of interpreting and evaluating research findings including statistics, selecting stories that hold meaningful messages for the public, and placing them in the appropriate context. Sessions are interactive, with hands-on opportunities to apply lessons learned, and incorporate journalists' special perspectives on the public's need for useful medical knowledge. The "Medicine in the Media" program was created to address a growing need to improve the reporting of scientific and medical research findings by the media. The program is highly competitive and attracts media and journalism professionals from around the country for a 3-day intensive workshop. The interactive program lays out the critical basics of differentiating strong from weak scientific information, well-designed versus poorly designed scientific studies, and "strength of opinion versus the strength of evidence." Feedback from participants indicates that the program changed their fundamental understanding of scientific news in terms of what is worthy of reporting and providing appropriate context when covering new research findings and a balanced presentation of the strength and relevance of the findings. Participants frequently recommended the program to colleagues.

- For more information, see <http://medmediacourse.nih.gov/>
- For more information, see <http://medmediacourse.nih.gov/html/MiMAgenda040907.pdf>
- (E) (OMAR)

**COPD: Learn More, Breathe Better:** Through its new education campaign, "COPD: Learn More, Breathe Better," NIH is raising public and professional awareness about chronic obstructive pulmonary disease (COPD). Launched in January 2007, the campaign is a

cooperative effort, engaging the public, health care providers, health insurers, and researchers in improving COPD diagnosis and treatment. The campaign relies upon print and radio public service announcements and on printed informational materials intended for distribution to COPD patients, to persons at risk for the disease, to health care professionals, and to community-level organizations. Joining NIH in implementing this new campaign by promoting it among their constituencies are more than 20 partners, including the American Academy of Family Physicians, the American Lung Association, the American Thoracic Society, the American College of Chest Physicians, and the U.S. COPD Coalition.

- For more information, see <http://www.nhlbi.nih.gov/health/public/lung/copd/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI)

**Disseminating Evidence-Based Health Information on Diabetes and Digestive and Kidney Diseases:** The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational material on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take “small steps” to prevent type 2 diabetes. The NKDEP encourages African American families to discuss kidney disease at family reunions. Both programs tailor materials for minority groups at high risk. Information clearinghouses also provide key health information for the public. Recent campaigns raised awareness of celiac disease and interstitial cystitis. The Weight-Control Information Network provides science-based information on topics such as obesity and nutrition.

- For more information, see <http://www2.niddk.nih.gov/HealthEducation/>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIDDK, CDC)

**Ways to Enhance Children’s Activity & Nutrition (WeCan!):** This national public education outreach program, focusing on parents and families in home and community settings, is designed to help children 8 to 13 years old achieve and maintain a healthy weight. WeCan! program materials offer tips and activities to encourage healthy eating, increase physical activity, and reduce sedentary or screen (such as television) time. Many national partners and supporting organizations are promoting the WeCan! messages and materials, and the program is being implemented in a variety of settings. In 2007, NIH began the WeCan! city program to assist towns and cities in mobilizing their communities to prevent childhood obesity. The first three cities that will participate in the new effort have pledged to offer WeCan! evidence-based obesity prevention programs to parents and youth in collaboration with community-based partners. In addition, each city will distribute WeCan! tips and information to city employees.

- For more information, see <http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/>
- For more information, see <http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=268>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NHLBI, NCI, NICHD, NIDDK)

**National Eye Health Education Program (NEHEP):** This program focuses on public and professional education programs that encourage early detection and timely treatment of glaucoma and diabetic eye disease and the appropriate treatment for low vision. A formal planning process in 2006 outlined a 5-year agenda for NEHEP that will now include programs in



age-related macular degeneration and meeting eye health needs of older adults. The travelling “EYE SITE” exhibit has toured the Nation, working with over 100 vision-related organizations to offer more than 250 public events since 2001. The NEHEP Partnership with public and private organizations coordinates development and dissemination of education programs targeted to a variety of audiences.

- For more information, see [http://www.nei.nih.gov/nehep/pdf/NEHEP\\_5\\_year\\_agenda\\_2006.pdf](http://www.nei.nih.gov/nehep/pdf/NEHEP_5_year_agenda_2006.pdf)
- (NEI)

**Alzheimer’s Disease Education and Referral (ADEAR) Center:** The ADEAR Center is the Federal government’s primary source of information for patients, caregivers, health providers, policymakers, and the general public on Alzheimer’s disease and age-related cognitive change, including diagnosis, treatment, services, and research. The Center maintains a national database of clinical trials and develops easy-to-read materials in English and some in Spanish.

- For more information, see <http://www.nia.nih.gov/Alzheimers>
- (NIA)

**NIA Information Center (NIAIC):** Through its Web site and toll-free telephone lines, the NIAIC provides information, available in English and Spanish, aimed at maintaining and improving the health of older adults by encouraging them to exercise, providing advice on long-distance caregiving, suggesting ways to improve communication with health care providers, and providing the latest information about research on aging. *Age Page* factsheets offer comprehensive, easy-to-read information on nearly 50 topics. A new Web-based newsletter will provide updates on health and NIA activities to the public, policymakers, and researchers.

- For more information, see <http://www.nia.nih.gov/HealthInformation/Publications/>
- (NIA)

**NIAID HIV Vaccine Research Education Initiative (NHVREI):** This new national initiative is designed to educate the public about HIV vaccine research, especially at-risk populations such as African Americans, Hispanics, men who have sex with men (MSM), and women at high risk of HIV infection. The goal is to increase awareness of the urgent need for an HIV vaccine within the communities that are most affected by HIV/AIDS, create a supportive environment for current and future volunteers in HIV vaccine trials, and improve the public’s perceptions and attitudes toward HIV vaccine research. The NHVREI Local Partnership Program provides support to partner organizations in targeted communities to help achieve the initiative’s goals.

- For more information, see <http://www3.niaid.nih.gov/news/newsreleases/2006/bethegeneration.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIAID)

**Information Clearinghouses:** NIAMS operates the NIAMS Information Clearinghouse and the NIH Osteoporosis and Related Bone Diseases National Resource Center. These clearinghouses produce and distribute health education materials to patient and health professionals on a variety of diseases of bone, muscle, joint, and skin. The Resource Center also manages the health

promotion plans associated with the recent Surgeon General's report on bone health and osteoporosis.

- For more information, see [http://www.niams.nih.gov/Health\\_Info/default.asp](http://www.niams.nih.gov/Health_Info/default.asp)
- For more information, see <http://www.niams.nih.gov/bone/index.htm>
- (NIAMS)

**NIDCD Information Clearinghouse:** NIDCD's Information Clearinghouse disseminates free health information in the areas of hearing, balance, smell, taste, voice, speech, and language to inquiring members of the public. For the years 2006-2007, the NIDCD Information Clearinghouse has maintained a toll-free phone and TTY number for the public and has ensured that NIDCD publications remain current and timely by adding or updating bilingual factsheets and other educational materials for dissemination to the public. In addition, Clearinghouse staff attended or provided materials for exhibits at 31 professional conferences and health fairs around the country. Clearinghouse staff also performed research to help in the planning of the new noise-induced hearing loss campaign. This included conducting focus group testing and leading a workshop seeking input from key advocacy organizations.

- (NIDCD)

**WISE EARS!®:** WISE EARS! is NIH's national public education campaign against noise-induced hearing loss (NIHL) to increase awareness among the public and workers. For the years 2006-2007, NIH distributed free bilingual WISE EARS! materials, available online and through its toll-free information clearinghouse, to health professionals, students and teachers, community organizations, government officials, and the general public. NIH also conducted an evaluation of the WISE EARS! program to determine how well the campaign is meeting its objectives and to make recommendations for the future direction of the campaign. Based on the evaluation's key findings, NIH now plans to refocus its NIHL campaign by targeting children ages 8 to 12, by forging more mutually beneficial partnerships, and by making use of delivery channels with the highest potential to attract and engage its audience.

- (NIDCD)

**Exhibitions for the Public:** NIH continues to present lively and informative exhibitions that enhance the awareness and appreciation of science, medicine, and history. *Changing the Face of Medicine: Celebrating America's Women Physicians* closed in FY 2006 after a highly successful 25-month run, but lives on in a traveling version that is touring the country. A new exhibition, *Visible Proofs: Forensic Views of the Body*, opened in February 2006 and will continue until early 2008. Scores of school and community groups visit the exhibitions at NLM.

- For more information, see <http://www.nlm.nih.gov/hmd/about/exhibition/index.html>
- (I) (NLM)

**Genetics Home Reference:** The Genetics Home Reference Web site provides basic information about genetic conditions and the genes and chromosomes related to those conditions. Created for the general public, the site was expanded to include summaries for more than 225 genetic

conditions, more than 380 genes, all the human chromosomes, and information about disorders caused by mutations in mitochondrial DNA.

- For more information, see <http://ghr.nlm.nih.gov>
- This example also appears in Chapter 3: *Genomics*.
- (I) (NLM)

**Patient and Health Professional Education and Outreach:** NIH provides comprehensive cancer information to those at risk and to patients, caregivers, and health care providers. This information ranges from prevention, through treatment, to end-of-life topics. For example, clinical sites across the country extensively utilize NIH print and Web-based materials to support their educational programs. The Cancer Information Service (CIS) effectively communicates information through a Partnership Program to help reach those with limited access to health information; an Information Service that provides cancer information by telephone, TTY, instant messaging, and e-mail; and a research program that helps advance health communication practices.

- For more information, see <http://cancer.gov/publications>, <http://www.cancer.gov/cancertopics>
- For more information, see <http://www.cancer.gov/aboutnci/epeco>
- For more information, see <http://cis.nci.nih.gov/>
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NCI)

## Reaching Different Audiences

**Podcast on Women’s Health:** In 2007, NIH began a series of podcasts entitled “Pinn Point on Women’s Health” featuring ORWH Director Dr. Vivian W. Pinn in conversation with other NIH scientists. The podcasts highlight extramural and intramural research and current topics of importance to sex/gender and women’s health.

- For more information, see [http://orwh.od.nih.gov/podcast/podcast\\_archive.html](http://orwh.od.nih.gov/podcast/podcast_archive.html)
- (E, I) (ORWH)

**Promoting Early Detection of Oral Cancer in African American Men:** NIH is developing a new series of oral cancer education materials specifically for African American men, who have the highest risk of oral cancer and the lowest 5-year survival rate (only 35.6 percent) of any population in the United States. This is the first national-level effort of its kind. The first piece in the series, “Are You at Risk for Oral Cancer? What African American Men Need to Know,” is now being pretested in Washington, DC; Chicago; Los Angeles; and Columbia, South Carolina. The brochure—along with other complimentary education tools, such as fact sheets, posters, and both print and audio public service announcements—will be distributed to African American community groups around the country.

- This example also appears in Chapter 2: *Cancer* and Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (NIDCR, NCI)

### Evidence-Based Information on CAM:

- ▷ NCCAM provides extensive sources of evidence-based information on CAM through its Web site and clearinghouse. In 2006 its Web site had more than 2.6 million visitors and was cited by *Prevention* magazine for “Best Alternative Medical Information.” It has also been cited by the World Health Organization as a model for evidence-based CAM.
- ▷ CAM on PubMed, a database developed in partnership with the National Library of Medicine, now indexes more than 467,000 scientific articles related to CAM and makes them available and accessible to health professionals and the general public.
  - For more information, see <http://nccam.nih.gov/health/>
  - (NCCAM)

**Web-Accessible List of Rare Diseases Terms: Making Research Information About Rare Diseases Available to the Public:** Each day, the Office of Rare Diseases (ORD) receives inquiries about specific rare diseases about which inquirers cannot find information. Over the years, ORD has maintained a list of rare diseases names from a number of sources. With the arrival of the Internet and increased Web sophistication by patients and their families, ORD began posting a list of rare diseases and conditions, with synonyms and links to federally funded databases. In 2000, ORD integrated into its database a similar European database, called Orphanet, and a list from the Engelhorn Foundation in Belgium. Since FY 2006 ORD has linked its rare diseases terms to the following databases: [NLM Gateway](#), [PubMed](#), [Online Mendelian Inheritance in Man \(OMIM\)](#), [Genetics Home Reference \(GHR\)](#), and [ClinicalTrials.gov](#). The “Rare Diseases Terms” on the ORD Web site represents the most comprehensive listing of rare diseases. As such, it is a resource used by many visitors to the ORD site seeking information about rare diseases. ORD will broaden the availability of information about rare diseases on the ORD Web site by connecting a database of rare diseases questions and answers with a link to the rare diseases terms. Currently, the database contains 6,827 distinct rare diseases terms. In the last 2 years, 386 diseases were deleted because information became available that showed that the prevalence was above 200,000 in the United States, 709 new terms were added, 4,177 terms were reviewed and revised, and the available information links were expanded.

- For more information, see <http://rarediseases.info.nih.gov/asp/diseases/diseases.asp>
- (ODP/ORD)

**The Heart Truth:** *The Heart Truth*, NIH’s national awareness campaign for women about heart disease, continues to extend the reach of campaign messages and promotion of the Red Dress as the national symbol for women and heart disease. Hundreds of locally sponsored *Heart Truth* events have taken place, and over a billion media impressions have been achieved. *The Heart Truth* Road Show helps participants learn about heart disease risk factors, provides free health screenings, and disseminates educational materials. In April 2006, the campaign launched the “*Heart Truth* Champions” program, to recruit health advocates and educators in local communities to increase awareness about women and heart disease. National Wear Red Day – the first Friday in February – has become an annual event when Americans wear red clothing and accessories in recognition of the importance of heart disease in women.

- For more information, see <http://www.nhlbi.nih.gov/health/hearttruth/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NHLBI)

**Never Too Early – The Milk Matters Campaign:** The risk for osteoporosis actually starts in childhood. Thus, NIH supports a public health campaign to help increase calcium consumption among children and teens, ages 11 to 15, a time of critical bone growth. Milk Matters is designed to educate parents, teachers, and health care providers about how most tweens and teens are not getting enough calcium from their diets. The campaign features materials and publications in English and Spanish.

- For more information, see <http://www.nichd.nih.gov/milk/milk.cfm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NICHD, NIDCR)

**Science Education Partnership Award (SEPA) Program:** SEPA increases the public's understanding of medical research by (1) increasing the pipeline of future scientists and clinicians, especially from minority, underserved, and rural kindergarten to grade 12 (K-12) students and (2) engaging and educating the general public on the health-related advances made possible by NIH-funded research. By creating relationships among educators, museum curators, and medical researchers, SEPA encourages the development of hands-on, inquiry-based curricula that inform participants about timely issues including obesity, diabetes, stem cells, and emerging infectious diseases. Additionally, SEPA projects are designed to enhance public trust by focusing on topics such as the clinical trials process, patient safeguards, and medical research ethics. Through SEPA exhibits at science centers and museums, the program provides educational and community outreach activities to tens of thousands of people every year. Moreover, SEPA is helping to bridge the educational gap and provide the next step in research and clinical pipelines for K-12 students interested in pursuing a career in biomedical science and providing professional development opportunities for teachers. Culturally appropriate projects have been developed to enhance the participation of African American, Hispanic, Alaska Native, American Indian, and Native Hawaiian communities. In FY 2007, SEPA supported 70 projects, with 50 targeting middle and high school students and 20 based in science centers and museums.

- For more information, see <http://www.ncrrsepa.org>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCRR)

**Cancer.gov in Español:** This Web site is designed to reach the Hispanic-Latino population – the fastest growing online audience in the country – to communicate the message that cancer can be prevented and treated and to offer information on all aspects of the disease. The site is specifically tailored for Hispanics and Latinos, with pages organized around issues of greatest concern. The site will be updated using evidence-based approaches and emerging technologies to ensure that accurate, relevant, and audience-appropriate information is provided. The site demonstrates the commitment to reducing cancer health disparities by making information readily available to underserved populations.

- For more information, see <http://www.cancer.gov/espanol>
- This example also appears in Chapter 2: *Cancer* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCI)

**NIH Senior Health Web Site:** NIHSeniorHealth.gov enables the growing number of “wired seniors” to find credible aging-related health information in an online format that is compatible with their cognitive and visual needs, as evidenced by NIH-supported research. Conceived by NIA and jointly developed with NLM, the Web site includes 33 health topics developed by 12 NIH Institutes. In 2006, 760,000 visitors viewed 1.5 million Web pages on the site. To further enable older adults to locate information and participate in their own health decisions, NIA has developed a senior-friendly curriculum for people who train older adults to use computers.

- For more information, see <http://www.NIHSeniorHealth.gov>
- (NIA)

**Underage Drinking Research Initiative:** In 2004, NIH launched this ongoing initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence, all framed within the context of overall development.

- ▷ Provided the scientific foundation for *The Surgeon General’s Call to Action to Prevent and Reduce Underage Drinking* (released March 6, 2007) and for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking.
  - ▷ Convened scientific meetings of experts including the Underage Steering Committee that met four times over a 2-year period; a Meeting on Diagnosis of Alcohol Use Disorders among Youth (April 2006); and a Meeting on Screening for Child and Adolescent Drinking and AUDs among Youth (June 2007).
  - ▷ Issued three RFAs including Underage Drinking: Building Health Care System Responses (four projects awarded FY06); Impact of Adolescent Drinking on the Developing Brain; and Alcohol, Puberty and Adolescent Brain Development.
  - ▷ Published *Alcohol Research & Health Vol. 28, Number 3 – Alcohol and Development in Youth: A Multidisciplinary Overview*.
  - ▷ Published a supplement of seven developmentally focused papers covering a broad range of underage drinking topics (accepted for the journal *Pediatrics*).
- For more information, see <http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm>
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
  - (E) (NIAAA)

**NIH Health Partnership Program and Community Health Center:** The Health Partnership Program (HPP) is a community-based, collaborative research program between NIH and Washington, D.C., area representatives. Through research with underrepresented patients affected by arthritis and other rheumatic diseases, the HPP studies health disparities and their causes and provides direction for improving the health status and outcomes of affected minority communities. Its Community Health Center (CHC) is the platform for HPP’s research, education, and training activities. The Washington, D.C., Center gives the community access to specialized care and health information, and NIH researchers access to patients most affected by



rheumatic diseases. Recently, NIH published “Exploring Perceptions About the Ethics of Clinical Research in an Urban Community.”

- [Grady C et al. \*Am J Public Health\*. 2006;96:1996-2001](#), PMID: 17018826
- For more information, see [http://www.niams.nih.gov/About\\_Us/Mission\\_and\\_Purpose/Community\\_Outreach/Health\\_Partnership/default.asp](http://www.niams.nih.gov/About_Us/Mission_and_Purpose/Community_Outreach/Health_Partnership/default.asp)
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (NIAMS)

**Know Stroke in the Community Educational Campaign:** In 2004, NIH entered a first-time partnership with the Centers for Disease Control and Prevention (CDC) to launch a new grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders called “Stroke Champions,” who worked to educate communities about the signs and symptoms of stroke. The program focuses on reaching African Americans, Hispanics, and seniors in communities that have the health care systems in place to treat stroke. In 2005-2006, the program had been implemented in 11 cities, educating 168 Stroke Champions who have conducted more than 600 community events.

- This example also appears in Chapter 2: *Minority Health and Health Disparities* and *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NINDS)

**InfoSIDA:** NIH introduced *infoSIDA*, a Spanish-language version of the *AIDSinfo* Web site, a DHHS established site that offers the latest federally approved information on HIV/AIDS clinical research, treatment and prevention, and medical practice guidelines. *InfoSIDA* features a customized home page and a search engine that locates Spanish-language resources within *AIDSinfo*. The steering group spans NIH (OAR, NIAID, NLM), FDA, HRSA, CMS, and CDC.

- For more information, see <http://aidsinfo.nih.gov/infoSIDA/>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (I) (NLM)

**Minority Health:** NIH works in a number of ways to share health information and develop the capacity of minority-serving educational institutions to access and use health information. NLM-sponsored programs focused on Historically Black Colleges and Universities (HBCUs), the National Medical Association and their more than 25,000 physicians and associated patients of African descent, health information networks for refugees, special Web sites with health information for specific populations (Asian Americans, American Indians, peoples of the Arctic), and information fellowships for representatives from American Indian tribes, Alaska Native villages, and the Native Hawaiian community.

- [Dutcher G, et al. \*J Med Libr Assoc\*. 2007;95:330-6](#), PMID: 17641769
- For more information, see <http://sis.nlm.nih.gov/outreach.html>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (I) (NLM)

**The Science of Healthy Behaviors:** The newest in a series of curriculum supplements distributed free of charge to teachers in grades K-12, this supplement introduces middle school students to the scientific study of behavior. It is a self-contained, teacher-ready guide to eight days of guided-inquiry science lessons that explore how behavioral and social factors influence health. The supplement is consistent with the National Science Education Standards and aligned to State standards for science, mathematics, English language arts, and health.

- For more information, see <http://science.education.nih.gov/customers.nsf/MSHealthy.htm>
- (E) (OBSSR, NINR, OSE)

## Rapidly Responding to Time-Sensitive Issues

**Helping Patients Who Drink Too Much: A Clinician's Guide:** In January 2007, NIH issued an update to its 2005 edition of the *Clinician's Guide*. Targeted to primary care and mental health clinicians, the *Guide* presents a user-friendly, research-based approach to screening, diagnosing, and managing patients with heavy drinking and alcohol use disorders. The updated *Guide* offers the following new resources: CME/CE credits for physicians and nurses available through Medscape; support for medication-based therapy in nonspecialty settings; a new handout with strategies to help patients reduce or quit drinking; a new dedicated Web page devoted to the *Guide* and supporting resources for clinicians and patients; and an updated PowerPoint presentation for educators and instructors. NIH has worked closely with several organizations to disseminate the *Guide* to their memberships.

- For more information, see <http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/guide.htm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIAAA)

**HBO "Addiction" Documentary:** NIH collaborated with Home Box Office (HBO) to create a 90-minute documentary, "Addiction," which aired on March 15, 2007. An NIH expert in the treatment of alcoholism was one of several principal spokespersons for the documentary and was featured in a supplementary broadcast on treatment advances. Several NIH grantees appeared in the documentary. A general-audience HBO book was produced to accompany the film.

- For more information, see <http://www.hbo.com/addiction>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIAAA, NIDA)

**Science of Dissemination and Implementation:** Relatively little is known about how to ensure that the lessons learned from research inform and improve the quality of health and human services in the population at large. The goals of the program announcement, *Dissemination and Implementation Research in Health*, and conference, *Building the Science of Dissemination and Implementation in the Service of Public Health* (September 2007), are to support innovative approaches to identifying, understanding, and overcoming barriers to the adoption, adaptation,

implementation, and maintenance of evidence-based practices by health care providers, insurers, policymakers, and the public.

- For more information see <http://grants.nih.gov/grants/guide/pa-files/PAR-07-086.html>
- For more information see <http://obssr.od.nih.gov/di2007/index.html>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCI, NHLBI, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIMH, NINR, OBSSR, ODS)

**The Rapid Response Program:** In April 2002, the Task Force on College Drinking released its seminal report “*A Call to Action: Changing the Culture of Drinking at U.S. Colleges*.” As part of its college focus, NIH initiated support of collaborations between university personnel who have responsibility for alcohol programs on various campuses and established college drinking researchers to implement and evaluate programs to reduce underage alcohol use and its consequences.

- ▷ December 2002: “Research Partnership Awards for Rapid Response to College Drinking Problems.” Five U01 (cooperative agreement) 5-year grants were awarded.
  - ▷ June 2003: “Rapid Response to College Drinking Problems.” Fifteen 3-year grants were awarded.
    - This rapid funding mechanism (U18 – cooperative agreement) supports timely research on interventions to prevent or reduce alcohol-related problems among college students. It was intended to support studies of services or interventions that could capitalize on “natural experiments” (e.g., unanticipated adverse events, policy changes, new media campaigns, campus-community coalitions, etc.)
    - Each U18 grantee was required to partner with a U01 grantee. Together, these pairs, working with NIH Scientific Staff Collaborators, jointly design, develop, implement, and evaluate college drinking projects on their campuses.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Epidemiological and Longitudinal Studies*, and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
  - (E) (NIAAA)

## Recognizing Problems and Taking Action

**National Network of Libraries of Medicine:** With more than 5,800 full and affiliate members, the Network is the core component of the National Library of Medicine’s outreach program and its efforts to reduce health disparities and to improve health information literacy. The Network also seeks to build and improve collaborations with community-based organizations as an effective means of reaching these populations. A major new initiative is the development of a nationwide emergency plan to ensure backup health library services in the aftermath of a disaster and establish librarians as key community resources in disaster planning and response. In 2006, new 5-year contracts were signed for eight Regional Medical Libraries in the Network.

- For more information, see <http://nnlm.gov/>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (I) (NLM)

**Health Disparities Research Forum:** NIH will be convening a 3-day forum in the spring of 2008. The purpose of the forum is to highlight the collective progress of NIH and its DHHS government partners, grantees/academicians, community organizations, and health care providers in implementing programs and strategies in the major priority areas, identified in the first *NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities*. The objectives of the Research Forum are to:

- ▷ Identify best practices, challenges, programs, and existing or potential gaps and practices in research initiatives, strategies, and funding,
  - ▷ Promote research partnerships by identifying opportunities to strengthen partnerships, by establishing new partnerships within NIH and across DHHS, within and between academic institutions and researchers, and within and between community organizations and health care providers, and
  - ▷ Strengthen the health disparities research collaborations at the government, academic, and community levels.
- (NCMHD)

**Blending Initiative: Bench to Bedside to Community:** Efforts to systematically move science-based interventions and practices into community settings are exemplified in the testing of drug abuse treatment approaches directly in the community settings where they will be used by drug treatment professionals trained to implement them. This work is occurring through the National Drug Abuse Treatment Clinical Trials Network (CTN) at NIH, which involves practitioners from community treatment programs (CTPs) not only in formulating research protocols, but also in providing real-world feedback on their success and feasibility. The adoption of the addiction medication buprenorphine by a growing number of CTPs treating patients with opioid addiction is an example of real culture change issuing from NIH clinical research. A similar approach is under way to enhance treatment for drug-addicted individuals involved with the criminal justice system through research supported under the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) initiative. It seeks to achieve better integration of drug abuse treatment for criminal offenders with other public health and public safety forums and is a collaborative effort by NIH and multiple Federal agencies and health and social service professionals. These initiatives are helping to change the culture of how drug abuse treatment is delivered in this country.

- For more information, see <http://www.drugabuse.gov/CTN/>
- For more information, see <http://www.cjdats.org/>
- For more information, see <http://www.drugabuse.gov/Blending/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Clinical and Translational Research*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDA) (GPRA Goal)

**Understanding and Promoting Health Literacy:** The DHHS Healthy People 2010 initiative established a national health objective to improve health literacy by the decade's end. While many diseases and conditions can be prevented or controlled, too often people with the greatest health burdens have few fact-finding skills, the least access to health information, and least effective communication with health care providers. This program announcement supports research that increases our understanding of the health literacy problem and its relationship to

health disparities as well as the development of interventions to overcome the adverse consequences of low health literacy.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-020.html>
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (OBSSR, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

## **Outreach to the Scientific and Research Communities**

**The NIMH Outreach Partnership Program:** This program is a vital element in the broad NIH outreach effort to deliver science-based information to the public, health professionals, constituency groups, and all interested stakeholders.

- For more information, see <http://www.nimh.nih.gov/outreach/partners/index.cfm>
- (E) (NIMH)

**Partners in Information Access for the Public Health Workforce (PH Partners):** PH Partners, a 12-member public-private collaboration initiated by NIH, Centers for Disease Control and Prevention, and National Network of Libraries of Medicine assists the public health workforce to make effective use of electronic information sources. The Partners Web site ([PHPartners.org](http://PHPartners.org)) provides unified access to public health information resources produced by all members of the Partnership, as well as other reputable organizations. In FY 2006, the Web site was expanded with more than 400 new links and two new categories: Fellowships and Upcoming Meetings. One of the most popular resources on the site is the Healthy People 2010 Information Access Project.

- For more information, see <http://phpartners.org/>
- (I) (NLM)

## **Chapter 4**

### **NIH Centers of Excellence**

#### **INTRODUCTION**

The National Institutes of Health (NIH) Centers of Excellence are diverse in focus, scope, and origin. In general, they facilitate and coordinate research efforts on a specific disease, a group of diseases, or an area of research. Some were created as NIH-wide initiatives, others by individual Institutes and Centers (ICs), some reflect mergers or redesignations of existing programs, and some were congressionally mandated. The NIH Centers of Excellence described in this report are a subset—those established by statutory mandate.

Some congressionally mandated Centers of Excellence focus on long-recognized, significant challenges to public health, such as Alzheimer's disease and other conditions that have a major impact on aging populations. Other centers focus attention on areas of research that might otherwise be underfunded, such as rare diseases or research on minority health and other health disparities. Depending on when they were established and how many research sites have been funded, Centers of Excellence vary in size, scope, and outcomes.

The specific research goals and activities of the centers vary according to their mandates. In general, however, Centers of Excellence help establish critical research infrastructure, foster collaboration, train physician scientists and other professional staff, and provide shared resources, often through core facilities. Shared resources include systems for data gathering and analysis, instrumentation and computing, and the development of large patient registries. Research at the centers is often multidisciplinary and designed to encourage scientists and clinicians from diverse fields to come together to focus on a common set of objectives.

NIH Centers of Excellence seek to integrate basic and translational research and to move those findings efficiently toward clinical applications, some of which are evaluated in patient populations brought together at the centers. Results from these studies may have spinoffs that increase knowledge about other areas of research. Through outreach and communication efforts, the centers inform researchers and the public of scientific advances and improvements in medical care. Research at the congressionally mandated NIH Centers of Excellence is supported by administrative and program staff at individual ICs. Centers are funded for several years and then must re compete for support.

It is important to note that the creation of Centers of Excellence should only take place after an assessment of whether there is an adequate base of knowledge or number of expert investigators; what research opportunities are being adequately supported through existing or planned funding mechanisms and initiatives; or the appropriateness of alternative funding mechanisms. Congress has recognized they should create centers of excellence only under certain circumstances and provided the NIH Director with a new authority, through the NIH Reform Act of 2006, to review and approve the establishment of all centers of excellence recommended by the agency's institutes and centers.



This chapter provides overviews, outcomes (in the form of programmatic and research accomplishments), recommendations, evaluation plans, and future directions for the six congressionally mandated NIH Centers of Excellence programs, which are described in order of their establishment:

- Alzheimer's Disease Centers (1984)
- Claude D. Pepper Older Americans Independence Centers of Excellence (1989)
- Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (2001)
- National Center on Minority Health and Health Disparities Centers of Excellence (2001)
- Rare Diseases Clinical Research Network (2002)
- New Autism Centers of Excellence (2006), which merged the previously existing Collaborative Programs of Excellence in Autism and Studies to Advance Autism Research and Treatment

Tables listing the Centers of Excellence for each program appear in the appendix at the end of this chapter.

# **ALZHEIMER'S DISEASE CENTERS**

## **Overview**

### **Why the ADCs Were Established**

In 1984 Congress directed NIH to foster further research related to Alzheimer's disease (AD). The NIH [Alzheimer's Disease Centers](#) (ADCs) program is authorized by the Public Health Service Act under section 445 (42 U.S.C. 285e-2). The first ADCs were funded in the mid-1980s in response to the congressional directive and knowledge of AD pathophysiology emerging from the work of NIH grantees and other researchers. The prospect of a medical and social crisis triggered by an explosion of AD cases in a rapidly increasing aged population also motivated their creation. The principal objectives of the ADC program are to promote research, training, and education; technology transfer; and multicenter and cooperative studies of diagnosis, treatment, and clinico-neuropathological correlations in AD, in age-related neurodegenerative diseases, and in normal aging.

### **How the ADCs Function Within the NIH Framework**

There are currently 29 ADCs funded by NIH (see Table 4-1). The centers are funded under the P30 and P50 mechanisms for 5 years and then must compete through a peer review process for additional funding. New applicants for ADCs compete with existing grantees, and if existing centers are unsuccessful in competition, new centers are funded to take their places.

### **Description of Disease or Condition**

[AD](#) is the most common form of dementia among older people. It is a neurodegenerative disease that damages the parts of the brain controlling thought, memory, and language. AD is named after Dr. Alois Alzheimer, a German doctor who, more than 100 years ago, studied the brain tissue of a woman who had died of an unusual mental illness, and found abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary tangles). Today, these plaques and tangles in the brain are considered signs of AD, as are other brain changes, including the death of nerve cells in areas of the brain that are vital to memory and other mental abilities and the disruption of functional connections, called synapses, that allow nerve cells to communicate with each other. The disease is also characterized by lower levels of some of the chemicals in the brain that carry messages between nerve cells. AD may impair thinking and memory by disrupting these messages.

There probably is no single cause of AD. The most important known risk factors are age and family history, although education, diet, and environment might also play roles. Scientists are also finding evidence that some of the risk factors for heart disease and stroke—such as high blood pressure, high cholesterol, and low levels of the vitamin folate—might increase the risk of AD. Evidence is also increasing for physical, mental, and social activities as protective factors against AD. Although scientists have learned a great deal about AD, they still do not know what causes the disease and have not identified a cure for it.

## Burden of Illness

AD is estimated to affect approximately 4.5 million older people in the United States<sup>1</sup> and 24.3 million people worldwide.<sup>2</sup> Although it is occasionally diagnosed in patients in their forties and fifties, AD most frequently is associated with advancing age. The disease doubles in prevalence with every 5 years past age 65; thus, extending life by 10 years quadruples the probability of the disease occurring. AD is the most frequent cause of institutionalization for long-term care. It destroys the active, productive lives of its victims and devastates their families financially and emotionally. It has been estimated that the United States spends as much as \$148 billion per year for the direct and indirect costs of care for patients with AD.<sup>3</sup> With the rapidly increasing percentage of the population older than 65, the number of people with AD will increase proportionately, as will the toll it takes.

## Scope of NIH Activities: Research and Programmatic

The ADC program provides an environment and core resources to enhance ongoing research by bringing together biomedical, behavioral, and clinical science investigators to study the etiology, progression, prevention, diagnosis, and treatment of AD and to improve health care delivery. ADCs also foster the development of new research approaches and provide suitable environments for research fellows and junior faculty to acquire the necessary skills and experience for interdisciplinary AD research.

All 29 ADCs are required to have an administrative core, a clinical core, a data management and statistics core, an education and information transfer core, and a neuropathology core. Some centers include other, optional cores, such as neuroimaging or genetics cores, and some have satellite diagnostic and treatment clinics to assist in the recruitment of minority research subjects. The ADC program comprises two types of centers: Alzheimer's Disease Research Centers (ADRCs) conduct research projects in addition to core resources, and the Alzheimer's Disease Core Centers (ADCCs) consist of cores only and provide access to investigators with well-characterized patients, patient and family information, and tissue and other biological specimens for use in separately funded research projects.

By pooling resources and working cooperatively, the ADCs have produced research findings and developed resources, accomplishments that could not have been achieved by individual investigators working alone. Biological samples from patients with AD have provided the materials for hundreds of non-ADC funded projects. Several major longitudinal studies on the development of dementia in particular populations rely on ADC core facilities and integrate their findings with those of the centers. Examples of shared resources are the brain and specimen banks at each center, which consist of well-characterized specimens collected under standardized protocols. Another resource is the National Cell Repository for Alzheimer's Disease (NCRAD), located at Indiana University, which collects and stores blood, well-documented phenotypic data, DNA, and cell lines from families that have multiple affected members. The repository is part of the National Institute on Aging's (NIA's) [Alzheimer's Disease Genetics Initiative](#) to identify

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<sup>1</sup> Hebert LE, et al. *Arch Neurol* 2003;60:1119-22, PMID: 12925369

<sup>2</sup> Ferri CP, et al. *Lancet* 2005;366:2112-7, PMID: 16360788

<sup>3</sup> For more information, see [http://alz.org/national/documents/PR\\_FFfactsheet.pdf](http://alz.org/national/documents/PR_FFfactsheet.pdf)

genetic risk factors for late-onset AD. The ADCs have spawned other collaborative efforts that have led to the establishment of research resource entities, such as the [Consortium to Establish a Registry for Alzheimer's Disease](#), the [National Alzheimer's Coordinating Center](#), the [Alzheimer's Disease Cooperative Study](#), and the [Alzheimer's Disease Neuroimaging Initiative](#) (see below.)

Much important progress in AD research in the United States during the past 20 years stems from research conducted at the ADCs, as well as from resources and infrastructure provided by the centers. Advances include the linkage and cloning of mutant genes on chromosomes 1, 14, and 21, the presence of which could result in early-onset, familial Alzheimer's disease, and on chromosome 17 in frontotemporal dementia, another common cause of dementia. More recent studies have revealed the importance of the abnormal processing of proteins encoded by these genes and the identification of the a specific version of a gene at a location on chromosome 19 as a risk factor for late-onset AD.

ADC scientists have conducted much of the research on protein processing related to plaque and tangle formation, including the discovery of a protein implicated in the pathogenesis of Lewy body dementia—and the recognition of the common properties of the abnormal proteins associated with several neurodegenerative diseases. Important studies relating changes in brain structure to different clinical stages of AD are being carried out in many ADCs, using patients enrolled in the clinical cores, brain imaging studies supported by imaging cores, and autopsy evaluations in neuropathology cores. In recent years, researchers have focused on evaluating cognitive changes associated with normal aging and the transitions to mild cognitive impairment and early dementia, as well as studies to identify factors that contribute to changes in cognitive abilities. Relationships and commonalities between AD and other neurodegenerative diseases are also being emphasized along with studies of contributions of non-neurological comorbid conditions.

### **NIH Funding for FY 2006 and FY 2007**

NIH funding for the ADCs was \$49.6 million in fiscal year (FY) 2006 and \$50.1 million in FY 2007.

### **Outcomes: FY 2006 and FY 2007 Progress Report**

#### **Programmatic Accomplishments**

Recent programmatic accomplishments for the ADCs include the following examples.

- [National Alzheimer's Coordinating Center \(NACC\)](#): Beginning in 1999, the NACC was established to facilitate collaborative research and to standardize procedures among the 29 ADCs. NACC developed and maintains a large relational database of standardized clinical and neuropathological research data collected from each ADC. This database provides a valuable resource to qualified research scientists for both exploratory and explanatory AD research. The data provided by NACC will permit large studies that use patient samples from diverse populations and multiple ADCs. One goal is to standardize

procedures among the ADCs in several ways: (1) the approach to diagnosis of AD; (2) the approach to followup with those who have the disease; and (3) the collection of common data elements, also known as the uniform dataset. Although the unique aspects of the individual ADCs will be preserved, a core of common elements will help promote communication among the ADCs as well as with non-ADC researchers and the public. Autopsy confirmation of many of the cases makes these aggregate data especially valuable.

- **Alzheimer's Disease Cooperative Study (ADCS)**: The ADCS is a major AD clinical trials effort that has grown out of the ADC program. This consortium was initially funded in 1991 to test the safety and efficacy of compounds of little interest to large pharmaceutical companies and to evaluate treatments for cognitive and behavioral symptoms of AD. The trials include drugs that are off-patent, were patented and marketed for another use but might be effective in AD, or novel compounds from individual investigators or small companies that lack adequate resources to conduct clinical trials. The ADCS helps to facilitate the testing of new drugs for the treatment of AD and functions as part of the AD Prevention Initiative, which was established to invigorate efforts to discover new treatments, risk factors, methods of early detection, and diagnosis of AD. The ADCS also develops strategies for improving patient care and alleviating caregiver burdens and expedites movement of promising new treatments and prevention strategies into clinical trials. The ADCs serve as performance sites for the ADCS.
- **Alzheimer's Disease Neuroimaging Initiative (ADNI)**: ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging (MRI), positron emission tomography (PET), or other biomarkers to measure earlier, and with greater sensitivity, the development and progression of mild cognitive impairment and AD. Most ADCs participate in the ADNI. Early results suggest that researchers may be able to reduce the costs associated with clinical trials by improving imaging and biomarker analysis. As part of the ADNI study, a standard physical model (i.e., a plastic phantom) was developed to monitor the performance of MRI scanners at multiple clinical sites, ensuring the accuracy of the MRI images. In another preliminary analysis, investigators compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and AD. They found that scans correlated with symptoms of each condition and that images were consistent across sites, suggesting the validity of PET scans for monitoring the effectiveness of therapies in future clinical trials. More than 200 researchers, as well as other interested individuals, have already accessed a public database containing thousands of brain images and related clinical data obtained through blood and cerebrospinal fluid analyses.
- **Late-Onset Alzheimer's Disease (LOAD) Genetics Initiative**: NIH launched the LOAD Genetics Initiative in 2002 to help advance AD-related genetics research. Eighteen ADCs participate in the initiative. The goal is to collect samples from 1,000 families having at least 2 members with late-onset AD as well as 1,000 control subjects. The Columbia University ADRC serves as the coordination center for the Genetics Initiative. As of 2007, more than 3,000 new blood samples from approximately 400 late-onset AD families have been sent to NCRAD. To complete enrollment, characterization, and followup of patients and control subjects in the Genetics Initiative, NIH awarded a

resource grant to a group of six ADCs, which formed a consortium. In 2006, the NIH Center for Inherited Disease Research performed whole-genome scans on approximately 2,500 samples from members of these families. The [data](#) are being analyzed and will be published in 2007.

- **Overlapping Dementing Diseases:** NIA and the National Institute of Neurological Disorders and Stroke (NINDS) are exploring the overlap of Parkinson's disease dementia, dementia with Lewy bodies, and AD, as well as the overlaps and contributions of cerebrovascular disease and frontotemporal dementia to the brain pathology seen in AD. Joint initiatives in these overlap areas are under way. The ADCs collaborate with the NINDS-supported Udall Parkinson's Disease Centers to further the goals of examining the overlapping scientific and clinical issues related to AD, dementia with Lewy bodies, and Parkinson's disease dementia.
- **ADCs Minority Outreach:** A major objective for the ADCs is to recruit minority and ethnically diverse research subjects for AD research. A strategy to address this goal was developed in 1990 by creating a program to add Satellite Diagnostic and Treatment Clinics linked to existing ADCs. The number of satellites has fluctuated; 23 are currently active and are recruiting African American, Hispanic, Native American, and Asian research subjects. NACC data now show that approximately 20 percent of those enrolled in the ADCs are minorities.
- **Education Outreach:** All ADCs have Education and Information Transfer Cores (EITC) that support the development of clinical and research skills related to AD for physicians and other professional staff, as well as outreach to the public, including caregivers. EITC efforts have recently been redefined to emphasize subject recruitment for projects such as the NIA Genetics Initiative, ADCS, ADNI, and other clinical trials and initiatives. Collaborations include ongoing interactions with groups such as the Alzheimer's Association and the NIA's [Alzheimer's Disease Education and Referral Center](#). The ADCs pay special attention to issues of cultural sensitivity, and, where appropriate, the information is structured so it can effectively reach minority populations, including non-English-speaking people. ADCs work with ADEAR to develop materials for broad audiences.
- **[New York Consortium for Alzheimer's Research and Education \(NYCARE\)](#):** The three New York City ADCs—at Columbia University, Mount Sinai School of Medicine, and New York University—and the New York City chapter of the Alzheimer's Association joined in 2000 to form NYCARE. The consortium provides continuing medical education programs for community physicians on AD diagnosis, management, and research opportunities.
- **The Alzheimer's Clinical Research and Training Awards Act:** This congressional initiative helps train the next generation of physician-scientists to conduct basic and clinical research on AD and associated dementias. The program provides support for promising clinicians through awards for research, study, and practice at the ADCs. Twelve awards have been made, and most of the awardees are working at ADCs.



## Research Accomplishments

Since the establishment of the ADC program in 1984, thousands of research papers have been published on all aspects of AD and related neurodegenerative disorders, ranging from the molecular biology of the disease to family and societal impact, and including many studies of diagnosis and treatment. Research accomplishments include the following important recent studies carried out by ADC scientists.

- **Amyloid-beta Protein Metabolism Studies.** Biochemical, genetic, and animal model evidence implicates amyloid-beta as a pathogenic peptide in AD that can lead to abnormal communication among nerve cells and cell death. In late-onset AD, concentrations of this peptide in brain tissue from AD patients are 100- to 200-fold higher than in control brains. Recently, investigators at the Washington University ADC reported a new method for quantifying the synthesis and clearance rates of amyloid-beta in the normal human adult central nervous system. For the first time, investigators can now accurately measure the production and clearance rates of amyloid-beta in the central nervous system of living humans, indicating that under normal circumstances it is rapidly produced and cleared from the central nervous system. This new technique may prove to be of critical importance to scientists in their efforts to address crucial questions about the underlying pathogenesis of AD, to find possible biomarkers, and to test proposed disease-modifying therapies.
- **Standards for Assessing Cognitive Status in Understudied Populations:** One difficulty in evaluating the cognitive status of people in understudied populations is that the normative values available for standard tests often are not appropriate for other populations. Cultural, linguistic, educational, and other factors differ among groups and consistently have been shown to influence neuropsychological evaluations. Recently, scientists at the Mayo Clinic ADC produced a large set of normative data on older African Americans, using several common neuropsychological assessment tools. The authors note that these normative values may be applicable only to older African Americans raised in the South, making it important to determine whether the new data can be generalized. In addition, over time, even a narrowly defined group might have different characteristics; for example, participants in this sample were educated prior to the *Brown vs. the Board of Education* decision by the U.S. Supreme Court to end segregation of public school systems. Despite some limitations in its clinical utility, this study represents the first large-scale publication of normative data for an understudied population.
- **Establishing Commonalities Between Frontotemporal Dementias and Amyotrophic Lateral Sclerosis:** Frontotemporal dementias (FTDs) are a group of neurodegenerative diseases that are sometimes misdiagnosed as AD or related dementing disorders. It is estimated that 35-50 percent of FTD cases have a family history of dementia; nearly half have been linked to a mutation on chromosome 17. In recent studies, researchers have linked some cases of FTD to another mutation on chromosome 17. In addition, a new brain protein has been identified, related to the pathogenesis of both FTD and amyotrophic lateral sclerosis (ALS), in which dementia also can occur. It is thought that changes caused by this mutation impair the ability of the cell to degrade abnormal proteins, thereby causing them to remain in the nervous system, where they contribute to the development of FTD and ALS disease processes. Investigators are continuing to study these proteins and other genetic mutations to

further identify and understand the mechanisms involved in the development of FTD, ALS, and other neurodegenerative diseases.

### **Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the ADCs**

Since their launch in 1984, the NIH ADCs have continued to grow, and many multiple-center initiatives have emerged. In 2002, NIA organized a meeting to help determine the future of the ADC program. Several recommendations were made based on this meeting and have been implemented.

The first recommendation was to create the uniform dataset, which was described earlier in this chapter (see National Alzheimer's Coordinating Center [ADCC]). Another recommendation was to encourage greater flexibility in the structure of ADCs to take better advantage of local strengths, interests, and expertise. For example, ADCs can now enroll and follow special patient populations rather than using only clinic populations, as had been required previously. ADCs also are encouraged to develop programs that change with the scientific knowledge base and to find ways to translate new knowledge into clinical applications, for example, the translation of basic research findings to measure amyloid-beta production and clearance in living patients. ADCs also are being encouraged to make better use of tissue and data resources and to share them. One example of this is the further development and expansion of NCRAD to increase its capacity to bank cell lines, DNA, and serum from all ADCs as well as other sources.

### **Evaluation Plans**

The ADCs were reviewed in great detail by an external advisory committee in 2002 and again in less detail by the National Advisory Council on Aging in 2003. The next review by the National Advisory Council on Aging will take place in May 2008.

### **Future Directions**

In the future ADCs will continue to place less emphasis on late-stage AD and instead will concentrate more on the transition from normal aging to mild cognitive impairment to full-blown AD, as well as on studies that overlap with other neurodegenerative diseases. NIH will continue to support existing ADCs and to award new grants to applicant institutions that are deemed qualified through the NIH peer-review process.

# CLAUDE D. PEPPER OLDER AMERICANS INDEPENDENCE CENTERS

## Overview

### Why the OAICs Were Established

In 1955, the U.S. Surgeon General established five Geriatric Research and Training Centers (GRTCs) to advance research on the health care problems of the elderly and to train future academic leaders in geriatrics. In 1989, Congress enacted legislation that redesignated the GRTCs as the Claude D. Pepper Older Americans Independence Centers (OAICs), in honor of former Florida Senator and Representative Claude Denson Pepper for his efforts to promote the health and well-being of older Americans. The OAICs, which are funded in 5-year periods, are authorized under Section 445A of the Public Health Service Act (42 U.S.C. 285e-3) to increase scientific knowledge leading to better ways to maintain or restore independence in older adults (see Table 4-2).

### How OAICs Function Within the NIH Framework

The OAICs are funded by NIA through a center grant mechanism (P30). The ultimate goal of the OAIC program is to enhance the translation of basic and developmental research on aging to applications and interventions that increase or maintain independence for older persons.

Each OAIC:

- Provides intellectual leadership and innovation
- Stimulates translation of basic research findings into clinical applications, e.g., research to develop or test interventions or diagnostics based on new findings from aging research or other studies of fundamental biological processes
- Facilitates and develops novel multidisciplinary and interdisciplinary research strategies
- Stimulates incorporation of emerging technologies, methods, and scientific advances into research designs, as appropriate
- Serves as a source of advice to and collaboration with other institutions regarding technology, methodology, analysis, or other expertise
- Provides career development, guidance, and training for future leaders in basic, clinical, and translational research in geriatrics and related fields

### Description of Disease or Condition

Aging research focuses on a range of conditions, including geriatric syndromes such as involuntary weight loss, dizziness, and incontinence, as well as diseases and disorders that are more common among older adults, such as cancer, cardiovascular disorders, stroke, and loss

of sensory functions such as hearing and sight. The ultimate goal is to advance the translation of basic and developmental research on aging to applications and interventions that increase or maintain independence for older adults.

## Burden of Illness

There are currently 35 million Americans older than age 65. Of these, more than 4 million are older than 85, and approximately 65,000 have attained their 100th birthday. By 2030, the number of individuals age 65 and older is likely to double to 70.3 million and comprise 20 percent of the entire population, in contrast to 13 percent today. The number of the “oldest old”—people age 85 and older—is expected to grow to at least 19.4 million by 2050.<sup>4</sup>

The ratio of older people to other age groups is important to society because older people, particularly the oldest old, may be dependent on family members, the government, or both for financial, physical, and emotional support. In addition, a large part of older people’s security depends on programs such as Social Security and Medicare, which are financed through the contributions of working-age individuals. When the entire population of “baby boomers” enters older age, around 2030, the challenge to meet their needs through social, governmental, and other health care services will expand markedly.<sup>5</sup>

Data compiled in 2003 indicate that U.S. health care expenditures totaled approximately \$1.87 trillion, more than any other industrialized country.<sup>6</sup> Researchers predict that increased longevity is likely to require more financing from Federal health care systems, including Medicare and Medicaid.<sup>7</sup> As life expectancy increases, it will be necessary to find ways to keep the additional years of life free of disease and disability. Today, for example, more than half of all Americans older than age 65 show evidence of osteoarthritis in at least one joint.<sup>8</sup> Over half of Americans older than age 50 have osteoporosis or low bone mass.<sup>9</sup> Cardiovascular disease, cancer, and diabetes remain common among older Americans.

## Scope of NIH Activity: Research and Programmatic

OAICs are designed to develop or strengthen each awardee institution’s programs to focus and sustain progress in a key area of aging research, contribute to greater independence for older persons, and offer opportunities for training and career development in aging research for young scientists. OAICs select a specific focus for their research activities from a range of topics, including:

- Specific aging-related physiologic changes, other factors, or interventions (e.g., physical activity) that affect risk for multiple conditions or disabilities in old age

<sup>4</sup> Federal Interagency Forum on Aging Related Statistics. *Older Americans 2000: Key Indicators of Well-Being*. 2000.

<sup>5</sup> U.S. Department of Health and Human Services. *65+ in the United States: 2005, Current Population Reports, Special Studies*. U.S. Department of Health and Human Services/NIH/NIA and the U.S. Department of Commerce/Economics and Statistics Administration/U.S. Census Bureau: December 2005.

<sup>6</sup> For more information, see <http://www.cdc.gov/nchs/products/pubs/pubd/hs/healthexpenditures.htm>

<sup>7</sup> Spillman BC, Lubitz J. *N Engl J Med* 2000;342:1409-15, PMID: 10805827; Feder J, et al. *Health Aff* 2000;19:40-56, PMID: 10812780

<sup>8</sup> For more information, see [http://www.niams.nih.gov/Health\\_Info/Osteoarthritis/default.asp](http://www.niams.nih.gov/Health_Info/Osteoarthritis/default.asp)

<sup>9</sup> For more information, see <http://www.nof.org/advocacy/prevalence/index.htm>

- Interactions of multiple diseases, disabilities, and interventions (e.g., medications) in older persons and their relationship to the risk of morbidity, progression of disability, and efficacy of prevention or treatment strategies
- Factors contributing to the amelioration or delay of multiple deleterious aging changes by modulating risk factors or fundamental aging mechanisms
- Causes, prevention, and treatment of a geriatric syndrome that is related to multiple pathologies or disabilities
- Causes, assessment, prevention, and treatment (including rehabilitation) of a specific type of disability in older people
- Issues related to specific conditions that contribute to a loss of independence in older persons, e.g., the role of aging changes in the etiology of debilitating physical condition(s); special problems in the diagnosis, treatment, or prevention of the condition in old age; complications, disability, or symptoms from the condition found principally in older people

### **NIH Funding for FY 2006 and FY 2007**

NIH funding for the OAICs was \$13.6 million in FY 2006 and \$13.7 million in FY 2007.

### **Outcomes: FY 2006 and FY 2007 Progress Report**

#### **Programmatic and Research Accomplishments**

- The [Duke University OAIC](#) supports studies to develop and evaluate interventions designed to help older Americans anticipate, cope with, and recover from disability arising from late-life disease and aging. An analysis of several biomarkers has linked these biomarkers to osteoarthritis; research is continuing to evaluate genes for their potential association with osteoarthritis and facioscapulohumeral dystrophy, one of the most common inherited neuromuscular disorders, which primarily affects the skeletal muscles of the face and upper arms. A Demonstration and Information Dissemination Project has helped to translate research findings from programs such as the Osteoporosis Intervention Study into clinical practice. The Genetic Ascertainment of Large African American Family for Osteoarthritis and Early Onset Cardiovascular Disease project of the Duke OAIC has analyzed the genetics of one of the largest intact extended families in the United States and is evaluating this family for evidence of osteoarthritis and early-onset heart disease.
- The **Harvard University OAIC** promotes research to help elderly individuals maintain independence well into late life by supporting a series of studies focused on the development of interventions to overcome common disabling geriatric conditions. Examples include studies of the causes and consequences of delirium after coronary bypass surgery; the relationship between cardiovascular risk factors and the development of frontal lobe dysfunction (impairments in executive function, gait, and continence) in African American elders; and the use of subsensory mechanical noise to improve

somatosensation—such as the ability to perceive pain and temperature variations—and balance in healthy older people and patients with diabetes and stroke. For example, one study indicates that caution should be used in administering isoflurane, a common inhalation anesthetic, to individuals with excessive levels of amyloid-beta protein in the brain, including AD patients, among others.<sup>10</sup>

- The **Johns Hopkins University OAIC** supports research to determine causes and potential interventions for frailty in older adults. New studies include a project to develop methods that will infer parameters to measure frailty and to test hypotheses about the causes of frailty in older adults. Another project involves compiling genetic data from several resources, including the Women’s Health and Aging I and II studies, InCHIANTI, the Baltimore Longitudinal Study of Aging, and HealthABC, to provide sufficient analytical power to detect causes of frailty. A pilot study to describe the relationship between brain-derived and peripheral cholesterol levels and cognitive and physical frailty found that high, not low, total cholesterol was associated with better psychomotor speed. The next step is to determine whether these findings also extend to physical speed and might be a predictor of physical frailty. Another pilot study to evaluate the role of glucocorticoid resistance in frail elderly people demonstrated that frailty is strongly associated with increased daytime salivary cortisol levels and that it is much more strongly related to these increases than to chronological age.
- The **University of California, Los Angeles OAIC** supports the development and testing of clinical interventions to prevent disability. Its activities include a study to refine an intervention for optimizing nursing home staff efficiency in providing feeding assistance to residents and then to test the efficacy of this model in a randomized clinical trial to determine quality of life and health outcomes. A separate, pilot, randomized clinical trial involves an intervention to improve visual functioning in older people. Information from this preliminary study will be utilized in a larger randomized clinical trial to determine whether visual and overall functioning of older people can be enhanced through a multidimensional intervention that corrects reversible causes of visual impairment, improves lighting in the home environment, and provides access to low-vision aids. Another ongoing study evaluates an age-appropriate intervention designed to improve diabetes self-care practices by enhancing the self-efficacy, empowerment, and diabetes-specific knowledge among African Americans older than age 65, a group that tends to experience substantially worse process and outcomes of care. The OAIC provides ongoing operational assistance to the new Resource Center for Minority Aging Research, one of six centers funded for the 2002-2007 cycle of this NIH initiative.
- The **University of Maryland, Baltimore OAIC** conducts mechanistic and outcome-based research in exercise rehabilitation and provides research training in gerontology and geriatrics to improve the lifestyle and functional independence of older Americans with disabilities. The center emphasizes exercise rehabilitation based on preliminary findings that exercise can improve the devastating health consequences and functional declines associated with stroke, hip fracture, and peripheral arterial occlusive disease—chronic conditions that often decrease functionality and independence in the elderly. Preliminary studies show that specific exercises such as treadmill exercise training

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<sup>10</sup> [Xie Z, et al. \*J Neurosci\* 2007;27:1247-54](#), PMID: 17287498



improves lower body strength and increases fitness reserves among gait-impaired stroke patients and that an upper body workout improves motor function in the partially paralyzed upper extremities of stroke patients who have completed conventional rehabilitation and are 1-5 years beyond the incident stroke. Evidence of improved brain function accompanying task-specific exercise provides further support to the observation that recovery not only is enhanced through exercise but also continues months and years after the stroke. Thus, task-oriented exercise programs that improve upper and lower body functional capabilities and quality of life might allow these patients to remain at home and function independently, maintaining their lifestyle, reducing caregiver burden, and lowering their utilization of health care resources.

- The **University of Texas OAIC** research focuses on age-related sarcopenia, a progressive loss of muscle mass that leads to muscle weakness, limited mobility, and increased susceptibility to injury, and the contribution of sarcopenia to loss of independence in older persons. OAIC researchers discovered in an animal model that a specific protein, UNC-45, previously demonstrated to be critical to the proper formation of muscle, acts as a chaperone for muscle proteins known as myosins and helps myosins fold into stable structures that clump together to form thicker filaments that give heart and skeletal muscle its striated appearance. Normally, electrochemical signals cause the myosin filaments to contract, producing, for example, a heartbeat or an arm movement. When myosin proteins are not yet fully stable, a cellular cleanup system, known as the ubiquitin proteasomal system, may mistake them as unstable or malfunctioning and break down the myosin. Further study of the cellular basis of muscle weakness and loss of muscle mass in aging is under way. Researchers affiliated with another study are using a porcine model to clarify the mechanisms by which amino-acid supplementation can regulate muscle protein synthesis with the goal of designing appropriate nutritional support in a variety of clinical settings. The OAIC also supports the Longitudinal Study of Mexican American Elderly Health, a population-based longitudinal study that focuses on predictors of continued physical independence among 3,000 older Mexican Americans living in five southwestern States.
- The **Wake Forest University OAIC** mission is to assess the risk factors of physical disability in older adults and to develop and test effective prevention therapies. Among the studies supported by the center is research on chronic obstructive pulmonary disease, a major cause of morbidity and mortality in the United States. Investigators are evaluating the effectiveness of a lifestyle intervention to increase physical activity to a greater extent than a traditional exercise therapy program and are comparing the impact of these two interventions on physical function, self-reported disability, health-related quality of life, and exercise capacity. The Pharmacological Intervention in the Elderly is a randomized controlled trial in older patients with diastolic heart failure to evaluate the effect of the drug enalapril on heart structure and function, exercise tolerance, and quality of life. Enalapril is one of the angiotensin-converting enzyme inhibitor drugs primarily used to treat hypertension and congestive heart failure. The goal of an observational pilot study is to examine physical function in obese individuals after a specific type of gastric bypass surgery to determine whether intensive weight loss associated with bariatric surgery will improve physical function. In addition, the Wake Forest center established

the Maya Angelou Research Center on Minority Health to address issues related to racial and ethnic health disparities.

- The **Yale University Center OAIC** focuses on causes, prevention, treatment, and disability outcomes of multifactorial geriatric conditions. Research from this OAIC has contributed significantly to understanding the extent and frequency of transitions in and out of disability by identifying factors influencing these transitions and those predicting successful recovery from disability affecting activities of daily living. Findings from the studies provide a basis for developing multifactorial interventions to prevent disability. Multifactorial interventions to prevent falls in community settings are currently supported through the Yale OAIC; injuries and fractures resulting from falls are a major cause of disability among older adults. Epidemiologists and biostatisticians at the Yale OAIC are developing new statistical approaches to analyze data from multifactorial interventions and to identify contributions from individual components and thus to guide the refinement of these interventions.
- The **University of Michigan Center OAIC** seeks to advance research on health care problems of older adults. Among their projects is one to study the loss of balance and its consequences in older adults and to utilize a wearable motion sensor to capture important parameters of this process. A pilot project on elucidating the cellular and molecular events that regulate normal epidermal growth seeks to determine how alterations in these events precipitate hyperplastic growth, particularly as it occurs in aged skin. In another pilot study, investigators are examining genetic factors in hypertension among three generations of African American women.
- The **OAIC Coordinating Center at Wake Forest University** strengthens the OAIC program by facilitating information exchange and research collaborations among individual OAICs. The Coordinating Center builds on elements that are common to individual OAIC themes and assists in the development and implementation of projects in shared areas of interest. Major activities of the Coordinating Center are the coordination and enhancement of the training programs across OAIC sites and the organization of seminars and other activities for trainees at the OAIC Annual Scientific Meeting.

## **Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the OAICs**

One recommendation of NIA's Geriatrics and Clinical Gerontology Program is to establish the Coordinating Center function as a part of the competitive OAIC Request for Applications (RFA) process. RFA AG-07-008 includes requests for applications for continuing the Coordinating Center functions. Another effort is to explore plans to expand the OAIC program.

## **Evaluation Plans**

The general progress of each OAIC is reviewed by program staff at the time of noncompeting renewal. In addition, a formal midcycle review is conducted by a panel of experts external to the OAICs at 2-3 years into the funding cycle of each OAIC. The purpose of the review is to assess the progress of individual OAICs in meeting the goals set forth in their funded applications and

to identify areas of concern that could be addressed prior to the next competing renewal. A written summary of the review is provided to each OAIC principal investigator for use in directing his or her center.

### **Future Directions**

The number of qualified applicants for OAIC sites is increasing, and NIH expects that additional centers will be added gradually to bring the total number to 12 by 2010. NIH plans to continue funding the Claude D. Pepper OAICs through a continued, competitive peer-reviewed process open to new and renewal applications.

# SENATOR PAUL D. WELLSTONE MUSCULAR DYSTROPHY COOPERATIVE RESEARCH CENTERS

## Overview

### Why the Wellstone MDCRCs Were Established

The Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Pub. L. No. 107-84) specified provisions for expanding and intensifying research on muscular dystrophy and mandated that NIH establish Centers of Excellence for research on muscular dystrophy. Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs) in the Omnibus Appropriations for FY 2004 (Pub. L. No. 108-199). Former Minnesota Senator Paul D. Wellstone, who died on October 25, 2002, was a driving force behind the Muscular Dystrophy Community Assistance Research and Education (MD-CARE) Act (see Table 3).

### How the Wellstone MDCRCs Function Within the NIH Framework

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NINDS, and the National Institute of Child Health and Human Development (NICHD) fund two Wellstone MDCRCs each, using the U54 Specialized Centers Cooperative Agreement award mechanism. A Steering Committee oversees scientific coordination of the Wellstone MDCRCs, sets goals, and makes strategic decisions about activities such as establishing collaborations. The committee consists of the directors and co-directors of each center, NIH science officers, and a public member. The External Advisory Committee, which is composed of experts in muscular dystrophy research and a patient advocate, helps inform NIH programmatic decisions regarding the Wellstone MDCRC program.

### Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of the skeletal muscles, which control movement. Some forms occur in infancy or childhood, whereas others may not appear until middle age or later. Diseases addressed by the Wellstone MDCRCs include, but are not limited to, the following conditions.

- **Duchenne and Becker muscular dystrophies:** Duchenne muscular dystrophy is the most common childhood form of muscular dystrophy. It is an X-linked recessive disease, primarily affecting males who inherit a genetic mutation from their mothers. Boys with Duchenne muscular dystrophy lack the protein dystrophin, which is essential for keeping muscle cells intact. Duchenne muscular dystrophy usually becomes evident when a child begins walking. Patients typically require a wheelchair by age 10 to 12 and die in their late teens or early twenties. Becker muscular dystrophy, a less severe disease, occurs when a partially functional form of dystrophin is produced.

- **Myotonic dystrophy:** Myotonic dystrophy is the most common adult form of muscular dystrophy, although it can strike at any age. It is marked by myotonia (an inability to relax muscles after contraction) and muscle wasting and weakness. Myotonic dystrophy varies in its severity and manifestations. It can affect other body systems in addition to skeletal muscles, including the heart, endocrine organs, eyes, and gastrointestinal tract.
- **Facioscapulohumeral muscular dystrophy:** Facioscapulohumeral muscular dystrophy initially affects muscles of the face (*facio*), shoulders (*scapulo*), and upper arms (*humeral*). Symptoms usually develop in the teenage years, and some affected individuals become severely disabled.
- **Limb-girdle muscular dystrophies:** All limb-girdle muscular dystrophies show a similar distribution of muscle weakness, affecting both upper arms and legs. Many forms of limb-girdle muscular dystrophy have been identified; some affect children, whereas others manifest in adulthood.
- **Miyoshi myopathy:** Miyoshi myopathy, one of the distal muscular dystrophies, causes initial weakness in the calf muscles. It is caused by defects in the same gene that is responsible for one form of limb-girdle muscular dystrophy, suggesting that research progress against one form of muscular dystrophy may lead to a better understanding of other forms as well.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Symptomatic treatments such as physical therapy, use of appliances for support, corrective orthopedic surgery, and drugs improve the quality of life for some individuals. However, even though some drugs, such as steroids, can slow the progression of Duchenne muscular dystrophy, there are side effects. Several therapeutic approaches, including gene therapy, cell-based treatments, and strategies to inhibit muscle degeneration, have shown promise in cell culture systems and animal models. Clinical trials of some therapies have begun, including the use of drugs to reduce muscle damage, cell-based replacement therapies, functional compensation for the lack of dystrophin by increasing the body's production of certain proteins, increasing muscle mass via inhibition of other proteins that negatively regulate muscle growth, and strategies to bypass the mutations that cause disease.

## Burden of Illness

Duchenne and Becker muscular dystrophies affect boys at a rate of 1 in 3,500 to 1 in 5,000. More than 4 million births occur annually in the United States, and about 400 to 600 boys are born with Duchenne or Becker muscular dystrophy every year.<sup>11</sup> Myotonic dystrophy affects approximately 1 in 8,000 people worldwide,<sup>12</sup> whereas facioscapulohumeral muscular dystrophy affects approximately 1 in 20,000 people and affects men and women equally.<sup>13</sup>

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<sup>11</sup> For more information, see <http://www.cdc.gov/ncbddd/duchenne/who.htm>

<sup>12</sup> For more information, see <http://ghr.nlm.nih.gov/condition=myotonicdystrophy>

<sup>13</sup> For more information, see <http://www.nlm.nih.gov/medlineplus/ency/article/000707.htm>

The MD-CARE Act called for the Centers for Disease Control and Prevention (CDC) to collect and analyze information on the number, incidence, correlates, and symptoms of individuals with muscular dystrophy. This surveillance system, once fully operational, will provide additional burden of illness data.

### **Scope of NIH Activities: Research and Programmatic**

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDCRCs are expected to promote communication and collaboration, develop and share research resources, and contribute to the training of new muscular dystrophy researchers.<sup>14</sup> Each Wellstone MDCRC includes at least one basic research project and one clinical research project, with a minimum of three individual but interrelated research projects, an administrative core, and at least one scientific resource core that serves as a resource for the national muscular dystrophy research effort.

Collectively, the Wellstone MDCRCs are engaged in research on various forms of muscular dystrophy, including some not listed above. Designed to accelerate progress toward effective treatments for muscular dystrophies through increased synergistic collaboration and coordination of research activities, they promote side-by-side basic, translational, and clinical research. Each center coordinates efforts to help bring together investigators at multiple sites.

Examples of research topics addressed at the various centers are as follows.

- The **University of Pittsburgh** center focuses on developing gene therapy techniques as well as research on muscle stem cells as potential therapies for Duchenne muscular dystrophy. The center is also preparing to conduct a clinical trial of gene therapy for limb-girdle muscular dystrophy.
- The **University of Rochester** center focuses on myotonic dystrophy and facioscapulohumeral muscular dystrophy. Researchers are examining cellular and molecular factors that contribute to these diseases and are conducting a clinical trial of the drug Iplex (mecasermin) for patients with myotonic dystrophy.
- The **University of Washington** center focuses on gene therapy techniques and has begun several new collaborative projects focused on the mechanisms underlying facioscapulohumeral muscular dystrophy.
- Researchers at the **Children's National Medical Center** are analyzing genetic and cellular factors that contribute to the progression of Duchenne muscular dystrophy and the response of patients to treatment.
- The **University of Iowa** center focuses on gene and stem cell therapeutic strategies for Duchenne, limb-girdle, and other muscular dystrophies. It provides diagnostic services

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<sup>14</sup> For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-03-001.html>; <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-04-008.html>



for physicians around the country and banks biopsy samples that can be used for research.

- The **University of Pennsylvania/Johns Hopkins University** center focuses on strategies to promote muscle growth or inhibit muscle protein degradation, approaches that could be applicable to a range of muscular dystrophies and other muscle disorders. It also provides state-of-the-art animal model physiological testing services as a resource for other researchers.

The Wellstone MDCRC program reserves funds to support new collaborative projects involving center investigators and pilot projects by non-center investigators. Center directors are also encouraged to collaborate with other muscular dystrophy researchers or representatives from voluntary health organizations to apply for Administrative Supplements to support small workshops or conferences focused on specific topics in muscular dystrophy research.<sup>15</sup>

Each of the Wellstone MDCRCs has core facilities that provide unique resources or services for the muscular dystrophy research community. Resources include repositories of research data and biologic resources from patients with various muscular dystrophies; imaging, diagnostic, bioinformatics, and computing capabilities; and viral vector development and production. The Wellstone MDCRC program also aids therapeutic development by maintaining a muscular dystrophy dog colony and providing sophisticated functional testing of mouse models.

## **NIH Funding for FY 2006 and FY 2007**

In FY 2006 and FY 2007, NIH invested a total of \$9.6 million and \$8.5 million, respectively, in the Wellstone MDCRC program. The three original Wellstone MDCRCs (Rochester, Washington, and Pittsburgh) also received up to \$500,000 per year from the Muscular Dystrophy Association. This supplemental funding ended in December 2006.

## **Outcomes: FY 2006 and FY 2007 Progress Report**

### **Programmatic Accomplishments**

Programmatic accomplishments include awards of NIH Administrative Supplements for Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships at Wellstone MDCRCs to advance the careers of four basic and clinical scientists who study muscular dystrophy.

New collaborative projects supported by the Wellstone MDCRC in FY 2006 and 2007 include the following:

- A collaborative effort between investigators at the Wellstone MDCRC at Children's National Medical Center and researchers in Japan to evaluate a gene modification technique (i.e., exon skipping) in a dystrophic dog model

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<sup>15</sup> For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-AR-05-008.html>

- Collaboration between the Iowa Wellstone MDCRC and Ohio State University to develop more effective diagnostic techniques for limb-girdle muscular dystrophy and Miyoshi myopathy
- A partnership between University of Pittsburgh and University of Pennsylvania investigators to study myostatin inhibition using the dog colony supported by the Pittsburgh Center

In 2006, the Wellstone MDCRC Administrative Supplements program to support workshops and research conferences funded a workshop entitled “High Throughput Drug Screening for the Muscular Dystrophies” at the Children’s National Medical Center. Industry, academic, and government researchers, as well as patient advocates, participated. The center is planning a second workshop, which will address the development of standard protocols for testing therapies in animal models.

The availability of Wellstone MDCRC core facilities has been publicized at national meetings, through Web sites that the centers have established, and through the [Wellstone MDCRC Web site](#). Sharing these research tools fosters collaborations across departments or schools at a single institution and among investigators and health care providers at several institutions. For example, the Muscle Tissue/Cell Culture/Diagnostics Core at the University of Iowa Wellstone MDCRC serves as both a local and a national resource for muscular dystrophy research. In addition to maintaining a muscle tissue repository of well-characterized tissues and cells representing the spectrum of muscular dystrophy diagnoses that are available for research, the center provides diagnostic services that are not readily available through clinical laboratories and is facilitating the development of new diagnostic tests.

## Research Accomplishments

The Wellstone MDCRCs conduct basic, translational, and clinical studies related to a variety of muscular dystrophies. Each center has at least three distinct but interrelated research projects. Examples of research accomplishments in FYs 2006 and 2007 are noted below.

- In the past 2 years, investigators at the University of Rochester MDCRC have begun a clinical trial to test the drug Iplex in patients with myotonic dystrophy. The dose escalation phase of this safety and feasibility trial suggests that the drug is well tolerated. The next phase of the trial will test an optimal dose in patients with myotonic dystrophy. Because Iplex improves muscle regeneration, it may be useful in many types of muscular dystrophy.
- Two other clinical trials, including one to test a gene therapy for limb-girdle muscular dystrophy, are preparing to begin recruiting patients.
- Wellstone MDCRC investigators have made numerous other advances with respect to gene therapies for other muscular dystrophies. Many strategies that 2 years ago were being tested in mice are now being evaluated in dogs. Wellstone MDCRC researchers are refining their technologies and are identifying how genes should be administered. They

also are discovering interactions between gene therapy vectors and human immune responses and have developed an immunosuppression protocol that shows promise in dogs.<sup>16</sup>

- Researchers at the University of Pennsylvania/Johns Hopkins University Wellstone MDCRC have tested a class of compounds known as protease inhibitors (i.e., Bowman-Birk inhibitors) that show promise in animal models of Duchenne muscular dystrophy and are planning to begin a clinical trial.
- The Wellstone MDCRCs are also contributing basic research findings to the understanding of muscular dystrophy. For example, during a search for stem cell traits that predict effective muscle regeneration, University of Pittsburgh researchers determined that cell sex (i.e., whether the cells originated in a male or a female donor) has a profound influence on whether muscle stem cells can produce muscle fibers in a mouse model of Duchenne muscular dystrophy.<sup>17</sup> The results could influence future research on the use of cell transplants for treating muscular dystrophy and affect the overall field of stem cell biology and regenerative medicine by prompting other investigators to consider and report the sex of the cells used in their research.
- In other basic research, investigators at the University of Rochester conducted a comprehensive genome-wide scan of biopsies from patients with early-stage facioscapulohumeral muscular dystrophy. The scan results are dispelling a widely held belief that a deletion on chromosome 4 triggers the development of facioscapulohumeral muscular dystrophy by disrupting expression of neighboring genes.<sup>18</sup> Results from this study have connected vascular abnormalities commonly observed in the retinas of patients with facioscapulohumeral muscular dystrophy who have the skeletal muscle weakness and wasting characteristics of the disease and may eventually lead to new treatments of this disease.

### **Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the Wellstone MDCRCs**

Due to NIH efforts to improve the Wellstone MDCRCs' effectiveness, efficiency, and outcomes, centers funded in FY 2008<sup>19</sup> will differ somewhat from their established counterparts in the following ways:

- Whereas the Wellstone MDCRCs established in 2003 and 2005 have three research projects, an administrative core, and a scientific research core, institutions applying for the program in FY 2008 are required to have at least one research project and specific core activities.

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<sup>16</sup> Wang Z, et al. *Mol Ther* 2007;15:1160-6, PMID: 17426713

<sup>17</sup> Deasy BM, et al. *J Cell Biol* 2007;177:73-86, PMID: 17420291

<sup>18</sup> Osborne RJ, et al. *Neurology* 2007;68:569-77, PMID: 17151338

<sup>19</sup> For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-08-002.html>

- Because the number of basic findings that are ready for translation has increased dramatically since the last competition, NIH removed the basic research requirement to allow the Wellstone MDCRCs to focus more of their efforts on translational research.
- The need for a clinical or patient-oriented project remains unchanged in the new solicitation, but because the required number of projects has been reduced from three to one, center applicants are free to propose larger, more expensive clinical research activities.
- Whereas the existing centers could apply for a training supplement to support the career development of a postdoctoral and nontenure track investigator, the training aspect of the next round of Wellstone MDCRCs will be formalized by Research Training and Education Cores that will support a predoctoral student and a postdoctoral fellow at each site. This addition was made in response to suggestions from the Steering Committee, combined with an analysis of existing training opportunities in the field of muscular dystrophy research.
- To better promote coordination of information and resources among the Wellstone Centers and throughout the muscular dystrophy research community, each applicant institution is required to provide letters documenting how one of its proposed core resources will fill a high-priority need in the muscular dystrophy research community.

As the Wellstone MDCRC program gains momentum, NIH plans to reexamine the role and composition of the External Advisory Committee to ensure that it continues to contribute to the growth and success of the program.

## **Evaluation Plans**

NIH reissued the RFA for the Wellstone MDCRCs in FY 2007. The competition was open to new applicants, and the three centers that were originally established in 2003 had to compete again for funding. Major review criteria for the Wellstone MDCRCs include the degree to which an institution demonstrates its ability to engage in substantive collaborations to address key issues in muscular dystrophy and its potential to serve as a national infrastructure and training resource.

## **Future Directions**

As noted above, the reissued RFA for Wellstone MDCRCs reflects several changes to further strengthen the program. NIAMS, NINDS, and NICHD intend to fund up to three Wellstone MDCRCs. NHLBI will participate by supporting meritorious cardiopulmonary research in successful applications. Grantees will join a network of existing Wellstone MDCRCs to foster the translation of new scientific findings and technological developments into novel treatments for the muscular dystrophies.

## **NATIONAL CENTER ON MINORITY HEALTH AND HEALTH DISPARITIES CENTERS OF EXCELLENCE PROGRAM**

### **Overview**

The National Center on Minority Health and Health Disparities (NCMHD) promotes the health of minorities as well as of other populations that experience health disparities and leads, coordinates, supports, and assesses NIH efforts to eliminate health disparities. To accomplish these goals, NCMHD:

- Conducts and supports basic, clinical, social sciences, and behavioral research
- Promotes research infrastructure and training
- Fosters emerging programs
- Disseminates information
- Reaches out to minority and other communities that experience health disparities

The Centers of Excellence program is one of several programs central to NCMHD's scientific investment strategy for addressing and ultimately eliminating health disparities.

### **Why the NCMHD Centers of Excellence Were Established**

The NCMHD Centers of Excellence were mandated by Pub. L. No. 106-525, the Minority Health and Health Disparities Research and Education Act of 2000, which also established NCMHD. Solicitations for proposals for the NCMHD Centers of Excellence were first published in the *NIH Guide* in 2001, and the first awards were made in FY 2002. When the program was launched, it was referred to as the Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT). With the FY 2007 re-competition, the program was renamed the NCMHD Centers of Excellence.

The NCMHD Centers of Excellence were established to develop novel programs across the country that would make significant advances and contributions in preventing, reducing, and ultimately eliminating health disparities in several priority diseases and conditions. The centers are helping to build the Nation's research capacity by establishing novel partnerships between different types of institutions—for example, Historically Black Colleges and Universities (HBCUs) and research-intensive institutions—and by engaging the efforts of community and faith-based organizations. The NCMHD centers provide opportunities to partner in the conduct of rigorous basic scientific research, human and animal subject-based research, and applied population and community-based research. The centers program also provides opportunities for increasing the pool of investigators from populations that experience health disparities through research training, faculty development, disseminating health information, and increasing the participation of these populations in clinical trials.

Since 2002, NCMHD has established a total of 88 centers of excellence located in 31 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. The program began using three different funding mechanisms for Resource-Related Centers, Exploratory Centers, and Comprehensive Centers. The use of these different funding mechanisms has allowed NCMHD

to help level the playing field among institutions with varying experience in biomedical research and to leverage the different skills and capabilities of the Nation’s geographically and culturally diverse institutions. Presently, 31 Exploratory Centers and 26 Comprehensive Centers are active. The Resource-Related Centers funding mechanism has been discontinued. The types of institutions are broad and include majority research institutions, medical schools, HBCUs, Hispanic-serving institutions, Tribal colleges, and liberal arts colleges.

**How the NCMHD Centers of Excellence Function Within the NIH Framework**

The NCMHD centers are managed in accordance with NIH policies and procedures for all funded research grants awarded through the R24, P20, and P60 mechanisms. Their progress is assessed annually, and updates are provided to the NCMHD Advisory Council. Like many other NIH Centers of Excellence that are supported through these mechanisms, a typical project period runs for 4-5 years. The project periods for NCMHD centers (P20s and P60s) that were established in 2002 and 2003 ended in 2007, and many of them recompleted in FY 2007.

**Description of Disease or Condition**

As described in various solicitations published in the *NIH Guide*, the NCMHD centers conduct research on the following priority diseases and conditions: cardiovascular disease, stroke (ischemic and intracerebral), cancer (all cancers, including breast, prostate, and cervical), diabetes, HIV/AIDS, infant mortality, mental health, and obesity (in men and women). In FY 2006, with the release of the new solicitations for the NCMHD centers program, research on lung disease, liver disease, psoriasis, scleroderma, and glomerular (kidney) injury was encouraged as a result of congressional interest and the fact that these diseases and conditions disproportionately affect racial and ethnic minorities but had not been widely studied.

**Burden of Illness**

Recent statistics on disparities for select diseases and conditions are provided in the following paragraphs, which highlight the need for research on minority health and health disparities.

<i>Ischemic Stroke Death Rates</i> <sup>20</sup>	
Race/Ethnicity	Rate (per 100,000)
White	73.7
African American	95.8
American Indian/Alaska Native	48.6
Asian/Pacific Islander	45.8
Hispanic	39.7

<sup>20</sup> [Ayala C. et al. Am J Epidemiol 2001;154:1057-63](#), PMID: 11724723



<b><i>Intracerebral Stroke Death Rates</i><sup>21</sup></b>	
<b>Race/Ethnicity</b>	<b>Rate (per 100,000)</b>
White	13.2
African American	22.5
Asian/Pacific Islander	20.1
American Indian/Alaska Native	10.4
Hispanic	12.0

<b><i>Breast Cancer Death Rates by Race/Ethnicity</i><sup>22</sup></b>	
<b>Race/Ethnicity</b>	<b>Rate (per 100,000 Women)</b>
All Races	25.5
White	25.0
African American	33.8
Asian/Pacific Islander	12.6
American Indian/Alaska Native	16.1
Hispanic	16.1

<b><i>Prostate Death Rates by Race/Ethnicity</i><sup>23</sup></b>	
<b>Race/Ethnicity</b>	<b>Rate (per 100,000 Men)</b>
All Races	27.9
White	25.6
African American	62.3
Asian/Pacific Islander	11.3
American Indian/Alaska Native	21.5
Hispanic	21.2

<b><i>Obesity in Men</i><sup>24</sup></b>	
<b>Group</b>	<b>Percent</b>
All	32.1
White	31.0
African American	31.2
Mexican	29.1

<b><i>Obesity in Women</i><sup>25</sup></b>	
<b>Group</b>	<b>Percent</b>
All	34.0
White	31.5
African American	51.6
Mexican	39.4

<sup>21</sup> Ibid.

<sup>22</sup> For more information, see [http://seer.cancer.gov/statfacts/html/breast.html?statfacts\\_page=breast.html&x=16&y=16](http://seer.cancer.gov/statfacts/html/breast.html?statfacts_page=breast.html&x=16&y=16)

<sup>23</sup> For more information, see [http://seer.cancer.gov/statfacts/html/prost.html?statfacts\\_page=prost.html&x=18&y=17](http://seer.cancer.gov/statfacts/html/prost.html?statfacts_page=prost.html&x=18&y=17)

<sup>24</sup> For more information, see [http://www.cdc.gov/nchs/data/06.pdf](http://www.cdc.gov/nchs/data/hus/06.pdf) - 073

<sup>25</sup> Ibid.

## **Scope of NIH Activities: Research and Programmatic**

The scope of activities at NCMHD centers includes the conduct of original and innovative basic, behavioral, clinical, or population-based research directed toward improving minority health, eliminating health disparities, or both. Support is provided for full-length research and pilot projects, research training, student and faculty development activities, and outreach and community engagement. Special emphasis has been placed on research addressing comorbidities within populations with health disparities.

## **NIH Funding for FY 2006 and FY 2007**

NIH funding for the NCMHD Centers of Excellence Program was \$53.7 million in FY 2006 and \$59.9 million in FY 2007.

## **Outcomes: FY 2006 and FY 2007 Progress Report**

### **Programmatic Accomplishments**

Significant programmatic accomplishments include increases in the number of training programs for students and junior faculty; the number of partnerships between universities and colleges and communities with health disparities; the number of senior racial and ethnic minority investigators from major research institutions, HBCUs, Hispanic-serving institutions, and Native American institutions engaged in minority health and health disparities research; and the number of individuals and community organizations from health disparity communities engaged in research. NCMHD Centers of Excellence have been successful in leveraging their NIH funding to attract new dollars from other government agencies and private foundations to support research on minority health and health disparities.

### **Research Accomplishments**

Funding of the NCMHD centers has resulted in many research accomplishments. The centers conduct research on minority health and the biologic and nonbiologic factors contributing to health disparities. For example, a review by researchers at the University of California at Los Angeles Center for Research, Education and Training and Strategic Communication on Minority Health Disparities examined the role of discrimination on health and the causes of race-based disparities. Researchers at the University of Puerto Rico-Medical Sciences Campus, in partnership with the Cambridge Health Alliance—an NCMHD-funded partnership—have developed a new theoretical mechanistic model accounting for the asthma disparities observed in minority children, particularly within subgroups of Latino children. The researchers applied a modified Institute of Medicine model to explain asthma disparities as a complex interaction among four major factors: (1) the health care system, (2) the practices and beliefs of primary care providers, (3) patient-based individual variables (i.e., physical factors such as genetic factors and sociocultural factors such as beliefs and practices), and (4) external environmental factors. This

model has been used to guide the development of the comprehensive, multilevel, community-based intervention program.<sup>26</sup>

In addition to these and other published scientific articles, NCMHD centers are also making significant gains in their communities by increasing awareness of the existence of health disparities and of the need to increase efforts to improve minority health and eliminate health disparities. The examples below highlight some of these efforts. In particular, NCMHD centers are creating new health-related messages and disseminating them to their communities through radio, public and cable TV, newsletters, Web sites, and even YouTube. Some centers produce bilingual versions of all of their messages. Many innovative approaches are being undertaken. For example, one center has produced two plays testing the role of the arts in bringing about change in health behaviors. Other centers are using immersion experiences in urban settings as a means to develop cultural competency and increase awareness and understanding of health disparities issues.

Additional examples of research accomplishments include the following:

- Researchers at the New York University NCMHD EXPORT Center for the Study of Asian American Health and the NYC Asian American Hepatitis B Program reported that approximately 15 percent of Asians living in New York City are chronically infected with the hepatitis B virus. Between January 22 and June 30, 2005, they tested 1,836 individuals for hepatitis B virus through collaborating clinics. The prevalence rate of chronic hepatitis infection was higher for males than females, higher for persons ages 20-39 years than for those age 40 years and older, and higher for those individuals born in China than for those born in other Asian countries.<sup>27</sup>
- The findings from a study conducted at the Mount Sinai NCMHD center show that the inferior survival of minority women with breast cancer is in part due to racial disparities in the use of adjuvant treatments for early-stage breast cancer (underuse for minority women). Women referred to medical oncologists were less likely to experience underuse of necessary adjuvant treatments. However, women who were minorities, lacked insurance, and had higher levels of comorbidity were at greater risk for underuse. The researchers concluded: “Minority women with early-stage breast cancer have double the risk of white women for failing to receive necessary adjuvant treatments despite rates of oncologic consultation similar to those for white women. Oncology referrals are necessary to reduce treatment disparities but are not sufficient to ensure patients’ receipt of efficacious adjuvant treatment.”<sup>28</sup>
- A recent cross-sectional survey of a community-based random sample of 230 African American and Hispanic female heads of household living in a geographically defined area (the three urban public housing communities in Los Angeles County, CA) documents significant disparity in screening for cervical cancer among underserved

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<sup>26</sup> [Canino G, et al. \*Soc Sci Med\* 2006;63:2926-37](#), PMID: 16956704

<sup>27</sup> For more information, see

<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=PubMed&Cmd=ShowDetailView&TermToSearch=16691180&>

<sup>28</sup> [Bickell NA, \*J Clin Oncol\* 2006;24:1357-62](#), PMID: 16549830

minorities, particularly Hispanic, uninsured, and older women. The continuity of obtaining medical services and receiving recommendations from physicians remains the core factor significantly associated with obtaining cervical cancer screening. The results underscore the need for continued efforts to ensure that medically underserved minority women have access to cancer screening services.<sup>29</sup>

- The [Connecticut Center for Eliminating Health Disparities among](#) Latinos, funded by NCMHD, is conducting a Diabetes Peer Counseling Study. Following are the specific aims of the study:
  1. Develop a comprehensive, culturally tailored model of diabetes management that integrates the work of community-based peer counselors and clinical specialists into a multidisciplinary health care team in order to directly respond to factors limiting successful diabetes management identified through an intensive needs assessment conducted in the Hispanic community
  2. Implement an intervention that provides education and support to Hispanic adults diagnosed with type 2 diabetes in clinical and home settings
  3. Evaluate this intervention for its impact on program adherence and improved clinical, cognitive, and behavioral outcomes sustained over time
  4. Modify the peer counseling service based on the evaluation and implement it as a best-practices model for diabetes management support of diabetic Hispanics

### **Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the NCMHD Centers of Excellence**

The NCMHD Centers of Excellence have evolved and increased in number since they were first established in 2002. In 2004, NCMHD convened a meeting of center directors and grants management staff to network, learn more about NCMHD, and share common interests and challenges in health disparities research. From this meeting emerged a number of recommendations and ideas that either have been incorporated in the NCMHD Centers of Excellence RFAs or continue to guide NCMHD in developing future program components and activities for the centers.

To improve the effectiveness of the NCMHD centers, NCMHD decreased the required number of cores (discrete components that together make up a center) from four (research, administrative, training, and community engagement) to two (research and administrative) but allowed additional cores to be added with appropriate justification. To ensure research leadership and excellence, NCMHD required the development of full research projects, provided funding for pilot projects, required that the plan for selecting pilots be peer reviewed, and allowed for the solicitation of pilot projects from health disparity researchers at other institutions. To increase outcomes contributing to minority health or the elimination of health disparities, NCMHD encouraged a multidisciplinary approach to conducting research. This approach emphasizes research on the biological, behavioral, and social determinants of health across the lifespan and includes individual, family, and population studies on factors that are relevant to one, or more,

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<sup>29</sup> [Bazargan M, et al. \*Prev Med\* 2004;39:465-73](#), PMID: 15313085

disease or condition. Each NCMHD Center of Excellence is required to develop and maintain a Web site to assist in building collaborations and in disseminating findings and information to health disparity researchers and individuals from health disparity populations.

## **Evaluation Plans**

The NCMHD Centers of Excellence will be evaluated biennially by NCMHD program and evaluation staff by examining the number and type of peer-reviewed publications, books and book chapters, and conferences and presentations on health disparities; community engagement, such as health fairs and other types of dissemination of health promotion materials; community participation in research and clinical trials (if applicable); and training of minority junior faculty, postdoctoral fellows, and graduate and undergraduate students.

## **Future Directions**

Future directions of the NCMHD centers will focus on intensifying research efforts to reduce health disparities with an emphasis on increased partnerships, as described below.

## **Scientific Knowledge To Be Gained Through the NCMHD Centers**

It is expected that new biomedical and behavioral knowledge will be discovered for improving minority health and for eliminating health disparities within and across the priority areas of cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity, as well as lung and liver diseases, psoriasis, scleroderma, and glomerular injury. An important area of emphasis is reducing comorbidities in populations that experience health disparities.

The national health program “Healthy People 2010” identified six critical determinants of health: biology, behaviors, social environment, physical environment, policies, and access to care. It is expected that research conducted at comprehensive NCMHD research centers will generate new knowledge about the interactions of significant biological factors with behavioral and social variables, how they affect each other, and how these interactions influence and contribute to minority health conditions and health disparities. This new knowledge is expected to lead to the development of biopsychosocial interventions and strategies for improving minority health and eliminating health disparities.

## ***Possible Themes for Future Research***

Themes for future research directions are the continuation of interdisciplinary minority health and health disparities research, including basic, clinical, and behavioral and social sciences research, to advance understanding of disease development and progression and the development of interventions for preventing or delaying the onset and progression of disease. Another theme is designing studies to improve approaches for disease prevention, diagnosis, and treatment. Researchers at the NCMHD centers also plan to study how disparities in health outcomes occur, including but not limited to behavioral and social factors; genetic variations; underlying biological factors; gender, ethnic, and familial factors; environmental exposures;

and policy and social factors. The latter include, for example, exposure of children or adults to abuse, discrimination, or other potential stressors. These studies would seek to identify the biological underpinnings of differential responses to stressors and to therapies (e.g., for hypertension, diabetes, renal transplantation, depression) and the differential prevalence of disease and comorbidities.

The success of future research conducted at NCMHD Centers of Excellence will depend in part on the development of improved methodological tools, measures, validated instruments, and novel research designs for disentangling the contribution to health disparities of biologic factors, behaviors, and social factors. Also important will be population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the United States, in particular, the Mississippi Delta, Appalachia, the U.S.-Mexico border region, and tribal communities. Also important will be studies to eliminate or decrease the impact of factors, including natural disasters, that contribute to the excess risks, morbidity, and mortality associated with living in such regions.



# **RARE DISEASES CLINICAL RESEARCH NETWORK**

## **Overview**

### **Why the RDCRN Was Established**

The need for Centers of Excellence for rare diseases research has been voiced since the mid-1980s. A disease is defined as rare if it has a prevalence of fewer than 200,000 people in the United States. There are almost 7,000 rare diseases known today. Approximately 80 percent of rare diseases are thought to have a genetic origin.

In 1985, the National Commission on Orphan (or rare) Diseases considered the lack of specialized centers for the diagnosis and treatment of rare diseases to be a serious barrier to the advancement of research on rare diseases. The commission found that 15 percent of patients with rare diseases did not obtain a correct diagnosis until after 5 years or more. An additional 30 percent of patients waited from 1 to 5 years before obtaining a diagnosis.

In 1999, the NIH Special Emphasis Panel on the Coordination of Rare Diseases Research endorsed the need for Centers of Excellence. The panel recommended funding for Specialized Research and Diagnostic Centers of Excellence for Rare Diseases for major categories of rare diseases. The proposal in 1999 was to establish Centers of Excellence on a graduated basis, starting with 10 regional centers in the first year and followed by incremental increases of 10 centers per year until 40 research Centers of Excellence were established. The panel also emphasized that centers should work closely with patient advocacy groups.

Some of the panel's recommendations were realized when President George W. Bush signed the Rare Diseases Act of 2002, Pub. L. No. 107-280, and when NIH established the Rare Diseases Clinical Research Network (RDCRN).

### **How the RDCRN Functions Within the NIH Framework**

The RDCRN involves collaboration among the NIH Office of Rare Diseases (ORD), National Center for Research Resources (NCRR), NICHD, NINDS, NIAMS, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and National Heart, Lung, and Blood Institute (NHLBI). In 2003, the original RDCRN, funded through a U54 cooperative agreement, consisted of seven consortia and a Data and Technology Coordinating Center (DTCC). In 2004, three additional centers were funded (see Table 4-5). During the first 2 years of operation, each consortium focused on developing clinical protocols for a subset of related rare diseases. RDCRN incorporated standards across centers and developed and instituted an adverse event reporting system.

The RDCRN contains more than 70 sites distributed across the United States and in other countries. The goals of the sites are to make investigational studies and treatments more accessible to patients with rare diseases and to facilitate the recruitment of patients for clinical trials.

The RDCRN Steering Committee consists of the principal investigator of each center, NIH representatives, and a patient advocacy representative. The committee meets on a monthly basis via teleconferencing and two times per year in person.

Other cross-network committees ensure collaboration, cooperation, efficiency, and quality for RDCRN research. They include the Human Subjects Committee, the Participant/Community Liaison Committee, the Standards Committee, the Web Site Committee, the Training Committee, a project managers committee, and the Coalition of Patient Advocacy Groups. Since 2006, 17 training modules on individual protocols and important issues of common interest have been developed and are available to RDCRN participants through the Network Media Center.

## **Description of Disease or Condition**

Rare diseases affect many tissues, organs, and organ systems. Researchers affiliated with the RDCRN study more than 40 rare diseases. These include Angelman, Rett, and Prader-Willi syndromes; myelodysplastic syndrome and other bone marrow failure conditions; lymphangi leiomyomatosis, rare genetic disorders of the airways, and other rare lung diseases; episodic ataxia, Andersen-Tawil syndrome, and nondystrophic myotonias; several vasculitides; urea cycle disorders; antiphospholipid syndrome and other rare thrombotic diseases; rare pediatric liver diseases; and rare genetic steroid defects.

## **Burden of Illness**

The burden of illness for rare diseases is difficult to estimate because of the large number of these disorders and the limited availability of prevalence and incidence statistics for each disease. Estimates of prevalence or incidence exist for only a minority of rare diseases, and the burden of illness and associated costs are complex. Occasionally, estimates have been produced by patient advocacy organizations or principal investigators applying for funding either to NIH or the U.S. Food and Drug Administration's Office of Orphan Products Development. The National Organization for Rare Disorders estimates that 20-25 million people are affected by a rare disease.

Overall, rare diseases are devastating because of their severity and because diagnosis may take a long time, well after symptoms have appeared. Additionally, there may be no available treatment once the disease is diagnosed.

## **Scope of NIH Activities: Research and Programmatic**

The RDCRN brings together health care researchers who are skilled in diagnosing and treating particular groups of rare diseases. Additionally, the centers gather groups of patients with similar or related disorders, foster basic scientific investigation, encourage synergy in translational research, and enhance opportunities for collaborative clinical investigation.

The DTCC is designed to enable sharing of study results nationally and internationally in a timely and uniform way. Although data and technology coordination is primarily the

responsibility of the DTCC, each center as well as NIH IC program officers also participate in overall coordination.

More than 30 patient advocacy groups are affiliated with the RDCRN and have formed the Coalition of Patient Advocacy Groups to support outreach efforts to patients with rare diseases, their families, and the public. A representative of the group serves on the RDCRN Steering Committee and acts as a liaison between the committee and participating advocacy groups.

### **NIH Funding for FY 2006 and FY 2007**

As the Rare Diseases Act of 2002 stipulated, each center award has been made for 5 years. Total funding in FY 2006 was \$14.1 million and \$9.4 million in FY 2007.

## **Outcomes: FY 2006 and FY 2007 Progress Report**

### **Programmatic and Research Accomplishments**

To date, the network has produced 25 publications, posters, and abstracts. In 2006, NIH launched the first [clinical studies of the RDCRN](#), and, by September 20, 2007, 26 clinical protocols had been approved, of which 24 were recruiting patients. Twenty more protocols are under development. To date, 2,357 subjects have been enrolled in research studies.

Many centers participating in the RDCRN have developed longitudinal studies as well as clinical trials to test the safety and efficacy of new therapeutic agents. The centers have established training programs for clinical investigators who are interested in rare diseases and have developed a [Web site](#) to inform the public, physicians, patients, and investigators about rare diseases.

The DTCC has developed and enabled new technology, tools, and services for the RDCRN, including electronic data entry, remote direct laboratory transfer, vocabulary and laboratory standards, statistical support, Web site development and maintenance, and database querying tools. The DTCC, in collaboration with each center, has also implemented a patient contact registry that allows individuals to register to receive information about new or ongoing clinical studies in addition to periodic educational updates.

To facilitate patients' transportation needs, Angel Flight NIH has widened its services to include the RDCRN. Volunteer pilots donate their time, planes, fuel, and operating expenses to transport patients and family members free of charge to and from medical and research facilities in the RDCRN so that no patient is denied medical access to ongoing research projects because of lack of air transportation.

## **Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the RDCRN**

In anticipation of the completion of the first 5 years of the network, ORD and the participating NIH ICs assessed the current design of the RDCRN and published a [Notice of Intent](#) to announce that an RFA would be published in December 2007. The new [RFA](#), which will be open to the current participating centers as well as to new applicants, builds on lessons learned during the initial 5 years. With the completion of the first 5 years of the network, the re-issuance of the RFA, and a probable increase in the number of participating NIH ICs, NIH continues to respond to the needs of the rare diseases community and the legislative mandate of the Rare Diseases Act of 2002.

### **Evaluation Plans**

Because the RDCRN was established so recently, it has not been formally evaluated. The ORD estimates that it takes approximately 3 years for a clinical study on a rare disease to be developed, fulfill requirements for approval, and enroll patients. Another 10 years are required to assess the overall impact of the research conducted within the RDCRN.

Eventually, the contribution of the RDCRN to rare diseases research will be determined by the following criteria:

- Completion and outcomes of the 45-50 studies
- Successful recruitment of adequate patient populations
- Number of trainees who complete their training programs
- Seminal impact of scientific publications on future rare diseases research
- Contribution of the DTCC to research in terms of a coordinated data management system, the ability to capture and integrate many different forms of data, and the development and broad acceptance of novel technological approaches to distributed computing, federated databases, and data mining

Although no formal evaluation of the RDCRN is planned soon, a review of the consortia and the DTCC will occur in 2008/2009, when applications of currently participating centers are peer reviewed along with new applicants. New awards will be made in 2009.

### **Future Directions**

ORD and the partner ICs will continue to coordinate the network's clinical research and encourage the training of new rare diseases researchers. Depending on IC interest in applications, the RDCRN may be expanded to comprise more than the current 10 centers, thereby encompassing a larger number of rare sites across the United States and in other countries with additional research protocols as well as rare diseases under study.

# AUTISM CENTERS OF EXCELLENCE

## Overview

### Why the ACE Were Established

Recent studies suggest that autism spectrum disorders (ASD) may affect approximately 1 in 150 children in the United States.<sup>30</sup> Because of the urgent need to better understand the causes of ASD and develop treatments for these serious and disabling disorders, Congress passed the Combating Autism Act of 2006 (Pub. L. No. 109-416), which emphasized the need for expanding research and improving coordination among NIH Centers of Excellence focused on ASD. The new Autism Centers of Excellence (ACE), scheduled for funding in fiscal years 2007 and 2008, will focus on identifying the causes of ASD and developing new and improved treatments.

Under the new ACE program, NIH will consolidate two existing programs in autism research, the [Collaborative Programs of Excellence in Autism](#) (CPEA) and [Studies to Advance Autism Research and Treatment](#) (STAART). NIH launched the CPEA program in 1997 to support significant, collaborative research on the possible causes of autism, including genetic, immunological, and environmental factors. In 2000, Congress passed the Children's Health Act (Pub. L. No. 106-310), which called on NIH to expand, intensify, and coordinate autism research activities, and to establish at least five Centers of Excellence for autism research. In response, the five NIH institutes participating in the NIH Autism Coordinating Committee (NIH ACC)—NICHD, the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Mental Health (NIMH), and NINDS—launched the STAART Centers Program to unite expertise, infrastructure, and resources focused on major questions about autism, including treatment research.

Although the CPEA and STAART programs collaborate extensively and will be consolidated under the new ACE program, the CPEA is not congressionally mandated. Therefore, this report will focus on the goals, activities, and accomplishments of the congressionally mandated NIH Centers of Excellence for autism research, namely the STAART and ACE Programs (see Tables 4-6 and 4-7).

### How the Centers Function Within the NIH Framework

The Children's Health Act of 2000 also established an Interagency Autism Coordinating Committee (IACC), which includes Federal agencies and members of the public appointed by the Secretary of the U.S. Department of Health and Human Services (DHHS). At the request of Congress, the IACC developed an [Autism Research Matrix](#) in 2003. The matrix serves as a guiding framework for directing autism research funded by NIH. ACE grantees will focus on the goals of the Autism Research Matrix, particularly in the areas of identifying causes of ASD and developing treatments.

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<sup>30</sup> For more information, see <http://www.cdc.gov/MMWR/preview/mmwrhtml/ss5601a2.htm>

The NIH ACC conceptualized the program goals of the STAART and ACE programs, and the ICs share responsibilities for administration and oversight. For example, NIMH administers the individual STAART centers, and NICHD administers the Data Coordinating Center (DCC). Thus, there is input from multiple ICs in managing these programs, which are funded through cooperative agreements. Grants that support centers affiliated with the ACE program are administered through a program officer and grants management officer at the awarding IC. The STAART and ACE programs represent less than a quarter of the total NIH commitment to autism research. The rest is distributed across contracts, grants of many types, and cooperative agreements.

## **Description of Disease or Condition**

Autism was first described in 1943 by Leo Kanner as a disorder “characterized by extreme aloneness and a desire for the preservation of sameness, with a variety of behavioral (cognitive, affective) symptoms derived from them.”<sup>31</sup> Over time, the description of this complex neurodevelopmental disorder has broadened. ASD includes a group of developmental disorders of early childhood that vary in severity, share common clinical features, and persist throughout the lifetime of the individual. These disorders share the core clinical characteristics of impairment in verbal and nonverbal communication skills and social interactions, and restricted, repetitive, and stereotyped patterns of behavior. ASD ranges in severity; “classic” autistic disorder is the most disabling, whereas others, such as Asperger’s disorder, have fewer or milder symptoms. Among children at the more severe end of this spectrum, mental retardation, seizures, and self-injurious behaviors are common.

Symptoms of ASD often are first identified by a child’s primary caregivers. There may be delays or plateaus in a child’s attainment of developmental milestones, such as the onset of speech. In some cases, the first signs of an ASD occur in young children who appear to regress after they seem to have been developing normally. For most children, the diagnosis of an ASD can be reliably made by age 3. The current diagnostic criteria and classifications of ASD represent progress in identifying a core set of developmental symptoms that, in the past, might have been diagnosed differently because the criteria were more narrowly defined than they are today.

## **Burden of Illness**

ASD causes tremendous economic and social burdens for families and society at large. Although ASD varies greatly in character and severity, it occurs in all ethnic and socioeconomic groups and affects every age group. Currently, there is no coherent and comprehensive system of care for affected individuals. People with autism may receive private and public services in special education settings, hospitals and university medical centers, and residential treatment facilities, among others.

Some scientists and economists have estimated that the combined direct and indirect costs to care for all Americans with ASD during their lifetimes exceed \$34 billion and that each individual accrues approximately \$3 million in costs over his or her lifetime.<sup>32</sup> Families often incur large

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<sup>31</sup> [Kanner L. Autistic disturbances of affective contact. \*Nervous Child\* 1943;2:217-50.](#)

<sup>32</sup> [Ganz ML. \*Arch Pediatr Adolesc Med.\* 2007;161:343-9.](#) PMID: 17404130



debts related to medical and educational services not covered through public programs or medical insurance. In addition to financial challenges, autism often leads to profound emotional hardships for patients and their families.

Current CDC estimates of the prevalence rate of ASD are as high as 6.7 children per 1,000.<sup>33</sup> The total number of individuals in the United States with an ASD diagnosis is unknown. However, CDC estimates that up to 560,000 individuals age 21 and younger have an ASD (assuming a prevalence rate of 1 in 150, a birth rate of 4 million children per year in the United States, and a constant prevalence rate over the past 20 years). Prevalence estimates, which refer to the number of affected individuals at a given point in time, have increased markedly since the early 1990s, but it is unclear whether there is also an increase in incidence, a measure of the number of new cases across time in the same population. It is also unclear whether the rise in prevalence is due to factors such as the use of the broader category of ASD or earlier and better diagnosis of ASD. A similar increase in ASD prevalence has occurred in other countries. Boys are approximately four times as likely as girls to have an ASD.<sup>34</sup>

### **Scope of NIH Activities: Research and Programmatic**

The primary goals of the STAART Centers Program are to support cohesive teams of accomplished biomedical, behavioral, and clinical investigators to pursue common objectives in ASD research, and to establish a research network that is capable of implementing large treatment, diagnostic, genetic, neuroscientific, and other studies of ASD that were previously not feasible. The new ACE program will improve the efficiency of administering the STAART and CPEA centers by consolidating them into one program and will broaden the pool of researchers involved in ASD research.

Each STAART center supports clinical and basic studies, including at least one study focused on treatment. The centers provide core resources that enhance ongoing research by providing critical infrastructure, including centralized patient recruitment and tracking, with standardization of clinical data. The centers are multidisciplinary and include outstanding investigators in related disciplines.

Although the Children's Health Act of 2000 required a minimum of five centers, NIH funded eight centers because of the exceptional quality of the applications. Scientific investigations of the STAART Centers Program focus on genetics, neurobiology, behavioral interventions, drug therapies, and diagnosis, in accord with the legislation. Each center conducts a unique set of studies, including investigations to determine how parents can better assist children with ASD, research on the neurobiological causes of ASD and the impact of early intervention, and projects to examine the possible role of serotonin in ASD, including a neuroimaging study of serotonin pathways and receptors comparing people with Asperger's disorder to people with more typical development.

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<sup>33</sup> CDC, 2007.

<sup>34</sup> [Fombonne E. \*J Clin Psychiatry\*. 2005;66 Suppl 10:3-8](#), PMID: 16401144

To identify genes that confer susceptibility to the development of autism, STAART centers use and contribute to the [NIMH Center for Collaborative Genetic Studies](#), a repository of DNA, cell cultures, and clinical data that serves as a national resource for researchers studying the genetics of complex mental disorders. This collaborative program, established partly through an innovative public-private partnership, provides a major resource for qualified investigators.

Another important resource for studies on ASD is the DCC, which provides data management and statistical support for autism research activities, including those conducted at the STAART centers. The DCC supports pharmacologic, multisite, randomized control trials and works with the data collection and analysis personnel at each center to standardize data forms and formats so that centralized data storage can be accessed.

### **NIH Funding for FY 2006 and FY 2007**

The total funding for autism COEs—STAART Centers (U54s), DCC (U01), and the ACE program, which includes centers (P50s) and networks (R01s)—was \$12.8 million and \$25.5 million in FY 2006 and FY 2007, respectively.

## **Outcomes: FY 2006 and FY 2007 Progress Report**

### **Programmatic and Research Accomplishments**

The STAART program is contributing to the understanding of ASD by investigating areas such as early detection, efficacy of early behavioral interventions, neural bases of core features, efficacy trials for pharmacotherapy, genotypic and phenotypic responses to treatment, and identification of susceptibility genes. A few accomplishments of the STAART program are highlighted briefly below.

- **Early Detection:** The Kennedy Krieger Institute of Johns Hopkins University has conducted a prospective longitudinal study of children who are at high risk for autism because they are younger siblings of children with an ASD. Important implications of this study are that autism screening could be usefully implemented near the first birthday, but screening would need to be repeated near the second birthday to detect children whose development becomes atypical during this interval.<sup>35</sup>
- **Neurological Characteristics:** Researchers at other STAART centers are evaluating specific neural mechanisms that perform atypically in people with autism. For example, teams at the University of Washington, Boston University, and the University of Wisconsin have used functional MRI to study face perception, which is altered in people with autism. The researchers found that the integration of perceptual and emotional processing mediated by the fusiform cortex and the amygdala, a specific brain pathway, is altered, which may explain the atypical visual scanning of faces that is characteristic of

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<sup>35</sup> [Landa RJ, et al. Arch Gen Psychiatry 2007;64:853-64](#), PMID: 17606819

- autism.<sup>36</sup> Research suggests that other brain pathways, such as those of the basal ganglia, may also contribute to repetitive behaviors, a core symptom of autism.<sup>37</sup>
- **Finding Effective Treatments:** To identify a treatment for autism, STAART investigators have collaborated in a multisite study to evaluate the efficacy of a drug that selectively inhibits the activity of serotonin, a neurotransmitter in the brain that may play a role in the repetitive behaviors associated with autism. The study subjects have completed the treatment phase of the trial and preparation for data analysis is under way. A manuscript with results is expected to be submitted for publication in 2008.

## Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of ASD Research

To improve the effectiveness, efficiency, and outcomes of ASD research, the NIH ACC planned the ACE program to address the need for the following:

- **Enhanced coordination of ASD Research:** Coordination of ASD research is an important priority for all stakeholders. This effort has been spearheaded by the IACC, which facilitates information exchange among the member Federal agencies and patient advocacy groups and coordinates autism-related programs and initiatives.
- **More collaborative studies:** Collaborative studies allow ASD researchers to combine data from their diverse samples and increase statistical power for detecting many types of experimental effects.
- **Improved data standardization and sharing:** In the past, data gathering in autism-related research was separated by format, location, and method of analysis, which makes cross-site data comparisons difficult. The [National Database for Autism Research](#) (NDAR) is building on the gains made by the DCC by creating a common data platform for data gathering and analysis. The NDAR will make it easier and faster for researchers to gather, evaluate, and share autism research data from a variety of sources and will allow the seamless integration of data, research tools, and institutions across the United States and internationally. All ACE Centers and Networks will make data contributions to NDAR.

## Evaluation Plans

The Combating Autism Act of 2006 expanded the scope of the IACC. In accordance with the new law, the IACC will develop and update annually a summary of research advances in ASD, as well as a strategic plan, and will monitor and make recommendations about Federal ASD-

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<sup>36</sup> [Hadjikhani N, et al. \*Hum Brain Mapp\* 2007;28:441-9](#), PMID: 17133386; [van Reekum CM, et al. \*Neuroimage\* 2007;36:1041-55](#), PMID: 17493834; [Nacewicz BM, et al. \*Arch Gen Psychiatry\* 2006;63:1417-28](#), PMID: 17146016; [Dalton KM, et al. \*Biol Psychiatry\* 2007;61:512-20](#), PMID: 17069771; [Webb SJ, et al. \*J Autism Dev Disord\* 2006;36:881-90](#), PMID: 16897400; [Kleinhans NM, et al. \*Neuroreport\* 2007;18:987-91](#), PMID: 17558282

<sup>37</sup> [Hollander E, et al. \*Biol Psychiatry\* 2005;58:226-32](#), PMID: 15939406

related activities. The priorities and progress of the ACE program will be an integral component of these annual activities.

In 2010, DHHS will provide Congress with a progress report on activities related to ASD, to include contributions from the ACE program. The report will discuss information about the incidence of ASD, average age for diagnosis, average age for intervention, effectiveness and outcomes of interventions by subtypes, and effectiveness and outcomes of newly developed intervention strategies for individuals with an ASD. In addition, NIH will consider how best to assess the effectiveness of the ACE Program and will identify ways to improve implementation of the program.

## **Future Directions**

The strategic plan for autism research to be prepared by the IACC will be developed with broad representation from Federal agencies as well as members of the public. In addition, private organizations that support autism research will be invited to participate in the planning process so that coordination will occur across autism funding groups, both public and private.

NIH created the ACE program to maximize coordination and cohesion of NIH-sponsored ASD research efforts and to broaden the pool of researchers involved in ASD research. Early in 2006, NIH solicited proposals for the ACE centers and networks with an application deadline of August 2006. NIH instructed grantees to direct their research projects toward the goals of the Autism Research Matrix, particularly in the areas of etiology and treatment. NIH made seven ACE awards in 2007 and anticipates making four additional awards in 2008.

The NDAR will be needed to achieve several of the goals of the IACC Autism Research Matrix, such as “establish[ing] resources for genotype/phenotype studies (i.e., bioinformatics, genetic repository).” NDAR also will coordinate data with other Federal databases, such as the [NIMH Center for Collaborative Genetic Studies](#), which stores DNA, cell cultures, and clinical data, and serves as a national resource for researchers who study the genetics of complex mental disorders, including autism.

## APPENDIX Centers of Excellence

**Table 4-1. Alzheimer’s Disease Centers of Excellence**

Institution and Location	Year Established
University of California, San Diego	1984
Massachusetts General Hospital, Boston	1984
Mount Sinai School of Medicine, New York	1984
University of Southern California, Los Angeles	1984
Johns Hopkins University, Baltimore	1984
Duke University, Durham	1985
University of Kentucky, Lexington	1985
University of Pittsburgh, Pittsburgh	1985
University of Washington, Seattle	1985
Washington University in St. Louis	1985
University of Texas Southwestern Medical Center, Dallas	1988
University of Michigan, Ann Arbor	1989
Columbia University Health Sciences, New York	1989
Oregon Health & Science University, Portland	1990
New York University School of Medicine, New York	1990
Mayo Clinic College of Medicine, Rochester	1990
University of Pennsylvania, Philadelphia	1991
University of California Davis School of Medicine, Sacramento	1991
Indiana University-Purdue University, Indianapolis	1991
Rush University Medical Center, Chicago	1991
University of California, Los Angeles	1991
Boston University Medical Campus, Boston	1996
Northwestern University, Chicago	1996
University of Alabama, Birmingham	1999
University of California, Irvine	2000
Arizona Alzheimer’s Center, Phoenix	2001
University of California, San Francisco	2004
Emory University, Atlanta	2005
University of South Florida, Tampa	2005

**Table 4-2. Claude D. Pepper Older Americans Independence Centers (OAICs)**

<b>Institution and Location</b>	<b>Year Established</b>
Duke University, Durham	1955 <sup>38</sup>
University of Michigan, Ann Arbor	1989
Harvard University, Boston, MA	1990
University of California, Los Angeles	1991
Wake Forest University, Boston, MA	1991
Yale University, New Haven	1992
University of Maryland, Baltimore	1994
University of Texas Medical Branch, Galveston	1999
Johns Hopkins University, Baltimore	2003
University of Pittsburgh, Pittsburgh	2004
University of Florida	2007

A Coordinating Center was added to the OAIC program in 2005 to promote scientific collaborations among Pepper Center investigators and to facilitate the sharing of unique resources across all sites. The Coordinating Center is currently located at Wake Forest University.

**Table 4-3. Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers**

<b>Institution and Location</b>	<b>Year Established</b>
University of Pittsburgh	2003
University of Rochester, Rochester	2003
University of Washington, Seattle	2003
Children’s National Medical Center, Washington, DC	2005
University of Iowa, Iowa City	2005
University of Pennsylvania/Johns Hopkins University, Philadelphia, PA, and Baltimore, MD	2005

<sup>38</sup> The only remaining Geriatric Research and Training Center.



**Table 4-4. List of NCMHD Centers of Excellence Funded in FY 2002-2007**

Institution and Location	Year Established
Arizona State University-Tempe Campus, AZ	2007
Case Western Reserve University, OH	2007
Charles R. Drew University of Med. & Sci., CA	2002
Clark Atlanta University, GA	2007
Florida International University, FL	2007
Henry M. Jackson Fdn. for the Adv. Mil./Med., MD	2003
Howard University, DC	2002
Johns Hopkins University, MD	2002
Meharry Medical College, TN	2003
Montana State University (Bozeman), MT	2007
Morehouse School of Medicine, GA	2002
Mount Sinai School of Medicine of NYU, NY	2002
New York University School of Medicine, NY	2003
North Carolina Central University, NC	2002
San Diego State University, CA	2002
Texas A&M University System, TX	2003
Tuskegee University, AL	2002
University of Alabama at Birmingham, AL	2003
University of Arkansas Med. Scis. Ltl., AR	2007
University of California, San Diego, CA	2002
University of Colorado, Denver/HSC Aurora, CO	2003
University of Hawaii at Manoa, HI	2002
University of Maryland, Baltimore, MD	2003
University of Massachusetts, Boston, MA	2007
University of Miami, Coral Gables, FL	2007
University of Michigan at Ann Arbor, MI	2007
University of North Carolina, Chapel Hill, NC	2002
University of North Carolina, Greensboro, NC	2007
University of Oklahoma Hlth. Sciences Ctr., OK	2003

<b>Institution and Location</b>	<b>Year Established</b>
University of Pennsylvania, PA	2002
University of Pittsburgh at Pittsburgh, PA	2002
University of Puerto Rico Med. Sciences, PR	2003
University of South Alabama, AL	2004
University of Southern California, CA	2007
University of Texas, El Paso, TX	2007
University of Texas M.D. Anderson Can. Ctr., TX	2003
University of the Virgin Islands, VI	2004
Virginia Commonwealth University, VA	2007
Winston-Salem State University, NC	2007
Yeshiva University, NY	2003

**Table 4-5. Rare Diseases Clinical Research Network Sites**

<b>Institution and Location</b>	<b>Year Established</b>
Children’s National Medical Center, Washington, DC	2003
Baylor College of Medicine, Houston	2003
University of Rochester School of Medicine, Rochester	2003
Cleveland Clinic Foundation, Cleveland	2003
The Children’s Hospital, Denver	2004
Boston University Medical Center, Boston	2003
Mount Sinai School of Medicine, New York City	2003
Duke University Medical Center, Durham	2004
Cincinnati Children’s Hospital Medical Center	2003
University of North Carolina School of Medicine, Chapel Hill	2004
University of South Florida, Tampa	2003

**Table 4-6. Autism Centers of Excellence**

<b>Institution and Location</b>	<b>Year Established</b>
University of California, Davis	2007
University of California, Los Angeles	2007
University of California, San Diego	2007
University of Illinois, Chicago	2007
University of North Carolina, Chapel Hill	2007
University of Pittsburgh, Pittsburgh	2007
University of Washington, Seattle	2007

**Table 4-7. Studies to Advance Autism Research and Treatment (STAART) Centers**

<b>Institution and Location</b>	<b>Year Established</b>
University of North Carolina, Chapel Hill	2002
Yale University, New Haven	2002
Boston University, Boston	2003
Kennedy Krieger Institute, Baltimore	2003
Mt. Sinai Medical School, New York	2003
University of California, Los Angeles	2003
University of Rochester, Rochester	2003
University of Washington, Seattle	2003

Appendix A

**Public Law 109-482: The National Institutes of Health  
Reform Act of 2006 (Relevant Passages)**

Institutes of  
Health Reform  
Act of 2006.  
42 USC 201 note.

PUBLIC LAW 109-482—JAN. 15, 2007

120 STAT. 3675

Public Law 109-482  
109th Congress

**An Act**

To amend title IV of the Public Health Service Act to revise and extend the authorities of the National Institutes of Health, and for other purposes.

*Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,*

**SECTION 1. SHORT TITLE.**

This Act may be cited as the "National Institutes of Health Reform Act of 2006".

**TITLE I—NIH REFORM**

**SEC. 101. ORGANIZATION OF NATIONAL INSTITUTES OF HEALTH.**

(a) IN GENERAL.—Section 401 of the Public Health Service Act (42 U.S.C. 281) is amended to read as follows:

(1) shall be carried out by regulation in accordance with the procedures for substantive rules under section 553 of title 5, United States Code. A rule under the preceding sentence shall be considered a major rule for purposes of chapter 8 of such title (relating to congressional review of agency rulemaking).

“(g) DEFINITIONS.—For purposes of this title:

“(1) The term ‘Director of NIH’ means the Director of the National Institutes of Health.

“(2) The terms ‘national research institute’ and ‘national center’ mean an agency of the National Institutes of Health that is—

“(A) listed in subsection (b) and not terminated under subsection (d)(2)(A); or

“(B) established by the Director of NIH under such subsection.

“(h) REFERENCES TO NIH.—For purposes of this title, a reference to the National Institutes of Health includes its agencies.”.

(c) CONFORMING AMENDMENTS.—Title IV of the Public Health Service Act (42 U.S.C. 281 et seq.) is amended—

(1) by redesignating subpart 3 of part E as subpart 19; 42 USC 287c.

(2) by transferring subpart 19, as so redesignated, to part C of such title IV;

(3) by inserting subpart 19, as so redesignated, after subpart 18 of such part C; and

(4) in subpart 19, as so redesignated—

(A) by redesignating section 485B as section 464z– 42 USC 287c, 285s.

(B) by striking “National Center for Human Genome Research” each place such term appears and inserting “National Human Genome Research Institute”; and 42 USC 285s.

(C) by striking “Center” each place such term appears and inserting “Institute”.

**SEC. 102. AUTHORITY OF DIRECTOR OF NIH.**

(a) SECRETARY ACTING THROUGH THE DIRECTOR.—Section 402(b) of the Public Health Service Act (42 U.S.C. 282(b)) is amended—

(1) by redesignating paragraph (14) as paragraph (22);

(2) by striking paragraphs (12) and (13);

(3) by redesignating paragraphs (4) through (11) as paragraphs (14) through (21);

(4) in paragraph (21) (as so redesignated), by inserting “and” after the semicolon at the end;

(5) in the matter after and below paragraph (22) (as so redesignated), by striking “paragraph (6)” and inserting “paragraph (16)”; and

(6) by striking “the Secretary” in the matter preceding paragraph (1) and all that follows through paragraph (1) and inserting the following: “the Secretary, acting through the Director of NIH—

“(1) shall carry out this title, including being responsible for the overall direction of the National Institutes of Health and for the establishment and implementation of general policies respecting the management and operation of programs and activities within the National Institutes of Health.”.

(b) ADDITIONAL AUTHORITIES.—Section 402(b) of the Public Health Service Act, as amended by subsection (a) of this section,

120 STAT. 3682

PUBLIC LAW 109–482—JAN. 15, 2007

is amended by striking paragraphs (2) and (3) and inserting the following:

“(2) shall coordinate and oversee the operation of the national research institutes, national centers, and administrative entities within the National Institutes of Health;

“(3) shall, in consultation with the heads of the national research institutes and national centers, be responsible for program coordination across the national research institutes and national centers, including conducting priority-setting reviews, to ensure that the research portfolio of the National Institutes of Health is balanced and free of unnecessary duplication, and takes advantage of collaborative, cross-cutting research;

“(4) shall assemble accurate data to be used to assess research priorities, including information to better evaluate scientific opportunity, public health burdens, and progress in reducing health disparities;

“(5) shall ensure that scientifically based strategic planning is implemented in support of research priorities as determined by the agencies of the National Institutes of Health;

“(6) shall ensure that the resources of the National Institutes of Health are sufficiently allocated for research projects identified in strategic plans;

“(7)(A) shall, through the Division of Program Coordination, Planning, and Strategic Initiatives—

“(i) identify research that represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that deserve special emphasis and would benefit from conducting or supporting additional research that involves collaboration between 2 or more national research institutes or national centers, or would otherwise benefit from strategic coordination and planning;

“(ii) include information on such research in reports under section 403; and

“(iii) in the case of such research supported with funds referred to in subparagraph (B)—

“(I) require as appropriate that proposals include milestones and goals for the research;

“(II) require that the proposals include timeframes for funding of the research; and

“(III) ensure appropriate consideration of proposals for which the principal investigator is an individual who has not previously served as the principal investigator of research conducted or supported by the National Institutes of Health;

“(B) may, with respect to funds reserved under section 402A(c)(1) for the Common Fund, allocate such funds to the national research institutes and national centers for conducting and supporting research that is identified under subparagraph (A); and

“(C) may assign additional functions to the Division in support of responsibilities identified in subparagraph (A), as determined appropriate by the Director;

“(8) shall, in coordination with the heads of the national research institutes and national centers, ensure that such institutes and centers—



PUBLIC LAW 109–482—JAN. 15, 2007

120 STAT. 3689

(49) by striking subsection (c) in the section 487F that relates to a loan repayment program regarding clinical researchers. 42 USC 288–5a.

(c) RULE OF CONSTRUCTION REGARDING CONTINUATION OF PROGRAMS.—The amendment of a program by a provision of subsection (b) may not be construed as terminating the authority of the Federal agency involved to carry out the program. 42 USC 282 note.

**SEC. 104. REPORTS.**

(a) REPORT OF DIRECTOR OF NIH.—The Public Health Service Act (42 U.S.C. 201 et seq.), as amended by section 103(a) of this Act, is amended—

- (1) by redesignating section 403A as section 403C; 42 USC 283a,
- (2) in section 1710(a), by striking “section 403A” and inserting “section 403C”; and 283a–3,
- (3) by striking section 403 and inserting the following sections: 42 USC 300a–9.

(3) by striking section 403 and inserting the following sections: 42 USC 283.

**“SEC. 402B. ELECTRONIC CODING OF GRANTS AND ACTIVITIES.** 42 USC 282b.

“The Secretary, acting through the Director of NIH, shall establish an electronic system to uniformly code research grants and activities of the Office of the Director and of all the national research institutes and national centers. The electronic system shall be searchable by a variety of codes, such as the type of research grant, the research entity managing the grant, and the public health area of interest. When permissible, the Secretary, acting through the Director of NIH, shall provide information on relevant literature and patents that are associated with research activities of the National Institutes of Health.

**“SEC. 403. BIENNIAL REPORTS OF DIRECTOR OF NIH.** 42 USC 283.

“(a) IN GENERAL.—The Director of NIH shall submit to the Congress on a biennial basis a report in accordance with this section. The first report shall be submitted not later than 1 year after the date of the enactment of the National Institutes of Health Reform Act of 2006. Each such report shall include the following information:

“(1) An assessment of the state of biomedical and behavioral research.

“(2) A description of the activities conducted or supported by the agencies of the National Institutes of Health and policies respecting the programs of such agencies.

“(3) Classification and justification for the priorities established by the agencies, including a strategic plan and recommendations for future research initiatives to be carried out under section 402(b)(7) through the Division of Program Coordination, Planning, and Strategic Initiatives.

“(4) A catalog of all the research activities of the agencies, prepared in accordance with the following:

“(A) The catalog shall, for each such activity—

“(i) identify the agency or agencies involved;

“(ii) state whether the activity was carried out directly by the agencies or was supported by the agencies and describe to what extent the agency was involved; and

“(iii) identify whether the activity was carried out through a center of excellence.

120 STAT. 3690

PUBLIC LAW 109–482—JAN. 15, 2007

“(B) In the case of clinical research, the catalog shall, as appropriate, identify study populations by demographic variables and other variables that contribute to research on minority health and health disparities.

“(C) Research activities listed in the catalog shall include, where applicable, the following:

“(i) Epidemiological studies and longitudinal studies.

“(ii) Disease registries, information clearinghouses, and other data systems.

“(iii) Public education and information campaigns.

“(iv) Training activities, including—

“(I) National Research Service Awards and Clinical Transformation Science Awards;

“(II) graduate medical education programs, including information on the number and type of graduate degrees awarded during the period in which the programs received funding under this title;

“(III) investigator-initiated awards for postdoctoral training;

“(IV) a breakdown by demographic variables and other appropriate categories; and

“(V) an evaluation and comparison of outcomes and effectiveness of various training programs.

“(v) Clinical trials, including a breakdown of participation by study populations and demographic variables and such other information as may be necessary to demonstrate compliance with section 492B (regarding inclusion of women and minorities in clinical research).

“(vi) Translational research activities with other agencies of the Public Health Service.

“(5) A summary of the research activities throughout the agencies, which summary shall be organized by the following categories, where applicable:

“(A) Cancer.

“(B) Neurosciences.

“(C) Life stages, human development, and rehabilitation.

“(D) Organ systems.

“(E) Autoimmune diseases.

“(F) Genomics.

“(G) Molecular biology and basic science.

“(H) Technology development.

“(I) Chronic diseases, including pain and palliative care.

“(J) Infectious diseases and bioterrorism.

“(K) Minority health and health disparities.

“(L) Such additional categories as the Director determines to be appropriate.

“(6) A review of each entity receiving funding under this title in its capacity as a center of excellence (in this paragraph referred to as a ‘center of excellence’), including the following:

“(A) An evaluation of the performance and research outcomes of each center of excellence.

“(B) Recommendations for promoting coordination of information among the centers of excellence.

“(C) Recommendations for improving the effectiveness, efficiency, and outcomes of the centers of excellence.

“(D) If no additional centers of excellence have been funded under this title since the previous report under this section, an explanation of the reasons for not funding any additional centers.

“(b) REQUIREMENT REGARDING DISEASE-SPECIFIC RESEARCH ACTIVITIES.—In a report under subsection (a), the Director of NIH, when reporting on research activities relating to a specific disease, disorder, or other adverse health condition, shall—

“(1) present information in a standardized format;

“(2) identify the actual dollar amounts obligated for such activities; and

“(3) include a plan for research on the specific disease, disorder, or other adverse health condition, including a statement of objectives regarding the research, the means for achieving the objectives, a date by which the objectives are expected to be achieved, and justifications for revisions to the plan.

“(c) ADDITIONAL REPORTS.—In addition to reports required by subsections (a) and (b), the Director of NIH or the head of a national research institute or national center may submit to the Congress such additional reports as the Director or the head of such institute or center determines to be appropriate.

“SEC. 403A. ANNUAL REPORTING TO INCREASE INTERAGENCY COLLABORATION AND COORDINATION. 42 USC 283a.

“(a) COLLABORATION WITH OTHER HHS AGENCIES.—On an annual basis, the Director of NIH shall submit to the Secretary a report on the activities of the National Institutes of Health involving collaboration with other agencies of the Department of Health and Human Services.

“(b) CLINICAL TRIALS.—Each calendar year, the Director of NIH shall submit to the Commissioner of Food and Drugs a report that identifies each clinical trial that is registered during such calendar year in the databank of information established under section 402(i).

“(c) HUMAN TISSUE SAMPLES.—On an annual basis, the Director of NIH shall submit to the Congress a report that describes how the National Institutes of Health and its agencies store and track human tissue samples.

“(d) FIRST REPORT.—The first report under subsections (a), (b), and (c) shall be submitted not later than 1 year after the date of the enactment of the National Institutes of Health Reform Act of 2006.

“SEC. 403B. ANNUAL REPORTING TO PREVENT FRAUD AND ABUSE. 42 USC 283a–1.

“(a) WHISTLEBLOWER COMPLAINTS.—

“(1) IN GENERAL.—On an annual basis, the Director of NIH shall submit to the Inspector General of the Department of Health and Human Services, the Secretary, the Committee on Energy and Commerce and the Committee on Appropriations of the House of Representatives, and the Committee on Health, Education, Labor, and Pensions and the Committee on Appropriations of the Senate a report summarizing the activities

120 STAT. 3696

PUBLIC LAW 109–482—JAN. 15, 2007

42 USC 284 note.

**SEC. 106. ENHANCING THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD.**

(a) **IN GENERAL.**—In administering the Clinical and Translational Science Award, the Director of NIH shall establish a mechanism to preserve independent funding and infrastructure for pediatric clinical research centers by—

(1) allowing the appointment of a secondary principal investigator under a single Clinical and Translational Science Award, such that a pediatric principal investigator may be appointed with direct authority over a separate budget and infrastructure for pediatric clinical research; or

(2) otherwise securing institutional independence of pediatric clinical research centers with respect to finances, infrastructure, resources, and research agenda.

(b) **REPORT.**—As part of the biennial report under section 403 of the Public Health Service Act, the Director of NIH shall provide an evaluation and comparison of outcomes and effectiveness of training programs under subsection (a).

(c) **DEFINITION.**—For purposes of this section, the term “Director of NIH” has the meaning given such term in section 401 of the Public Health Service Act.

**SEC. 107. FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH.**

Section 499 of the Public Health Service Act (42 U.S.C. 290b) is amended—

(1) in subsection (d)—

(A) in paragraph (1)—

(i) by amending subparagraph (D)(ii) to read as follows:

“(ii) Upon the appointment of the appointed members of the Board under clause (i)(II), the terms of service as members of the Board of the ex officio members of the Board described in clauses (i) and (ii) of subparagraph (B) shall terminate. The ex officio members of the Board described in clauses (iii) and (iv) of subparagraph (B) shall continue to serve as ex officio members of the Board.”; and

(ii) in subparagraph (G), by inserting “appointed” after “that the number of”;

(B) by amending paragraph (3)(B) to read as follows:

“(B) Any vacancy in the membership of the appointed members of the Board shall be filled in accordance with the bylaws of the Foundation established in accordance with paragraph (6), and shall not affect the power of the remaining appointed members to execute the duties of the Board.”; and

(C) in paragraph (5), by inserting “appointed” after “majority of the”;

(2) in subsection (j)—

(A) in paragraph (2), by striking “(d)(2)(B)(i)(II)” and inserting “(d)(6)”;

(B) in paragraph (4)—

(i) in subparagraph (A), by inserting “, including an accounting of the use of amounts transferred under subsection (l)” before the period at the end; and

(ii) by striking subparagraph (C) and inserting the following:

Termination.



## Appendix B

### **Priorities and Plans of the Institutes and Centers and the Program Offices in the Office of the Director**

This appendix provides brief descriptions of the missions of the NIH Institutes and Centers (ICs) and program offices in the Office of the Director. Links to strategic plans (or strategic planning Web sites) are embedded in the names of the ICs and offices. The ICs are presented in the order in which they appear on the appropriation table in the Congressional Justification. This compilation of mission statements and strategic plans both classifies and justifies NIH priorities.

#### **NIH Institutes and Centers**

[National Cancer Institute \(NCI\)](#). NCI leads a national effort to reduce the burden of cancer. The National Cancer Act of 1971 broadened the scope and responsibilities of NCI and created the National Cancer Program, which conducts and supports basic and clinical biomedical research; training; health information dissemination; and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer and HIV/AIDS; rehabilitation from cancer; and the continuing care of cancer patients and their families. NCI aims for a future in which we can prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

[National Heart, Lung, and Blood Institute \(NHLBI\)](#). NHLBI provides leadership for a national research program in diseases of the heart, blood vessels, lung, and blood; sleep disorders; and blood resources management. The Institute plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigations and trials, observational studies, and demonstration and education projects. In addition, NHLBI plans and directs research in the development and evaluation of interventions and devices related to the prevention of diseases and disorders within its purview and the treatment and rehabilitation of patients who suffer from them. Also, the NHLBI oversees management of the NIH Women's Health Initiative.

[National Institute of Dental and Craniofacial Research \(NIDCR\)](#). NIDCR's mission is to improve oral, dental, and craniofacial health through research, research training, and the dissemination of health information. The Institute accomplishes its mission through basic and clinical research; training and career development programs that ensure an adequate number of talented, well-prepared, and diverse investigators; coordination across all sectors of the research community; and the timely transfer of knowledge gained from research and its implications for health to the public, health professionals, researchers, and policymakers.



**National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**. NIDDK conducts and supports basic and applied research and provides leadership for national programs in diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Several of these diseases are among the leading causes of disability and death and all can seriously affect the quality of life of those who have them.

**National Institute of Neurological Disorders and Stroke (NINDS)**. NINDS aims to reduce the burden of neurological diseases and disorders. To accomplish this goal, the Institute conducts and supports basic, translational, and clinical research on the normal and diseased nervous system, fosters the training of investigators in the neurosciences, and seeks to better understand, diagnose, treat, and prevent neurological disorders. The NINDS research portfolio encompasses hundreds of neurological disorders, from diseases such as stroke that affect millions of people and are among the leading causes of death and disability, to rare disorders that individually affect a few people but collectively have an enormous impact on patients and families.

**National Institute of Allergy and Infectious Diseases (NIAID)**. NIAID's mission is to conduct and support research to understand, treat, and prevent infectious and immune-related diseases. Infectious diseases include well-known killers such as HIV/AIDS, tuberculosis, and malaria; emerging or reemerging threats such as influenza and extensively drug-resistant tuberculosis (XDR-TB); and "deliberately emerging" threats from potential agents of bioterrorism. Immune-related disorders include autoimmune diseases such as rheumatoid arthritis as well as asthma, allergies, and problems associated with transplantation.

**National Institute of General Medical Sciences (NIGMS)**. NIGMS supports basic biomedical research that increases the understanding of life processes and lays the foundation for advances in disease diagnosis, treatment, and prevention. The Institute's programs encompass the areas of [cell biology](#), [biophysics](#), [genetics](#), [developmental biology](#), [pharmacology](#), [physiology](#), [biological chemistry](#), [bioinformatics](#), [computational biology](#), and [minority biomedical research and training](#).

**National Institute of Child Health and Human Development (NICHD)**. NICHD conducts and supports research on all stages of human development, from preconception to adulthood, to better understand the health of children, adults, families, and communities. This includes research on fertility, pregnancy, growth, developmental disabilities, and medical rehabilitation.

**National Eye Institute (NEI)**. NEI conducts and supports research that helps prevent and treat eye diseases and other disorders of vision. This research leads to sight-saving treatments, reduces visual impairment and blindness, and improves the quality of life for people of all ages. NEI-supported research has advanced our knowledge of how the eye functions in health and disease.

**National Institute of Environmental Health Sciences (NIEHS)**. The mission of NIEHS is to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease.

**National Institute on Aging (NIA)**. NIA leads a broad scientific effort to understand the nature of aging and to extend the healthy, active years of life. The Institute provides leadership in aging research, training, health information dissemination, and other programs relevant to aging and older people and serves as the primary Federal agency on Alzheimer's disease research.

**National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**. NIAMS supports research to address the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of basic and clinical scientists to carry out this research; and the dissemination of information on research progress in these diseases.

**National Institute on Deafness and Other Communication Disorders (NIDCD)**. NIDCD conducts and supports biomedical research and research training on normal mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. In addition, NIDCD conducts and supports research and research training related to disease prevention and health promotion; addresses special biomedical and behavioral problems associated with persons who have communication impairments or disorders; and supports efforts to create devices that substitute for lost and impaired sensory and communication function.

**National Institute of Mental Health (NIMH)**. NIMH's mission is to reduce the burden of mental illness and behavioral disorders through research on the mind, brain, and behavior. Mental disorders are brain disorders and that means that achieving progress requires a deeper understanding of the brain and behavior. To fulfill its mission, NIMH conducts and supports research and training on advancing the integrative science of brain and behavior; developing more reliable, valid diagnostic tests and biomarkers; defining the genetic and environmental risk architecture for mental disorders; developing interventions to prevent occurrence and/or reduce relapse of mental disorders; developing more effective, safer, and equitable treatment; conducting clinical trials that will provide treatment options to deliver more effective personalized care across diverse populations and settings; and creating improved pathways for rapid dissemination of science to mental health care and service efforts.

**National Institute on Drug Abuse (NIDA)**. NIDA's mission is to lead the Nation in bringing the power of science to bear on drug abuse and addiction. This charge has two critical components. The first is the strategic support and conduct of research across a broad range of disciplines. The second is ensuring the rapid and effective dissemination and use of the results of that research to significantly improve prevention and treatment, and to inform policy as it relates to drug abuse and addiction.

**National Institute on Alcohol Abuse and Alcoholism (NIAAA)**. NIAAA supports and conducts research focused on improving the treatment and prevention of alcoholism and alcohol-related problems to reduce the enormous health, social, and economic

consequences of this disease. NIAAA conducts and supports research in a wide range of scientific areas including genetics, neuroscience, epidemiology, health risks and benefits of alcohol consumption, prevention, and treatment; coordinates and collaborates with international, national, State, and local institutions, organizations, agencies, and programs engaged in alcohol-related work; and communicates research findings to health care providers, researchers, policymakers, and the public.

**National Institute of Nursing Research (NINR)**. NINR promotes and improves the health of individuals, families, communities, and populations through nursing research and research training. NINR's research foci encompass health promotion and disease prevention, quality of life, health disparities, and end-of-life care. NINR seeks to extend nursing science by integrating the biological and behavioral sciences, applying new technologies to research questions, improving research methods, and developing the nurse scientists of the future.

**National Human Genome Research Institute (NHGRI)**. NHGRI's mission has expanded since the initiation of the International Human Genome Project to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease. A critical part of the NHGRI mission continues to be the study of the ethical, legal, and social implications of genome research. NHGRI also supports the training of investigators and the dissemination of genome-related information to the public and health professionals.

**National Institute of Biomedical Imaging and Bioengineering (NIBIB)**. NIBIB's mission is to improve health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating the physical and engineering sciences with the life sciences to advance research and medical care.

**National Center for Research Resources (NCRR)**. NCRR provides laboratory scientists and clinical researchers with the environments and tools needed to make biomedical discoveries, translate these findings to animal-based studies, and then apply them to patient-oriented research. NCRR connects researchers with one another and with patients and communities across the Nation. These connections bring together innovative research teams and the power of shared resources, multiplying the opportunities to improve human health. Together, NCRR's four integrated and complementary divisions—biomedical technology, clinical and translational research, comparative medicine, and research infrastructure—accelerate and enhance research along the entire continuum of biomedical science.

**National Center for Complementary and Alternative Medicine (NCCAM)**. NCCAM is dedicated to exploring complementary and alternative healing practices in the context of rigorous science; training complementary and alternative medicine researchers; and disseminating authoritative information to the public and professionals. To fulfill its mission, NCCAM supports a broad-based portfolio of research, research training, and educational grants and contracts, as well as various outreach mechanisms to disseminate information.

**National Center on Minority Health and Health Disparities (NCMHD)**. NCMHD promotes minority health and leads, coordinates, supports, and assesses NIH efforts to reduce and ultimately eliminate health disparities. In this effort, NCMHD supports and partners with other ICs to support basic, clinical, social, and behavioral research, promote research infrastructure and training, foster emerging programs, disseminate health information, and reach out to minority and other communities that suffer from disparities in health.

**John E. Fogarty International Center (FIC)**. FIC strengthens human and institutional capacity to confront complex global health challenges through innovative and collaborative research and training programs. It builds the knowledge and skills of developing country foreign scientists, identifies crucial gaps in global health research, and supports and advances the NIH mission through international partnerships.

**National Library of Medicine (NLM)**<sup>1</sup>. NLM is the world's largest research library of the health sciences, serving scientists, health professionals, and the public by collecting, organizing, and providing access to biomedical information. NLM also carries out programs designed to strengthen existing and develop new medical library services in the United States. It conducts research in health communications, supports medical informatics, and provides information services and sophisticated tools in the areas of molecular biology and toxicology/environmental health. NLM creates Web-based services for the general public containing information from NIH and other reliable sources. (Also see “The Library” in the section on “Providing the Platform for Discovery,” in Chapter 1.)

**NIH Clinical Center**. The Clinical Center is the NIH facility that provides the patient care, medical services, and environment necessary for NIH scientists to conduct clinical research. Clinical and laboratory research is conducted shoulder-to-shoulder at the Clinical Center and this tandem approach drives all aspects of its operations. (Also see “The Clinical Center” in the section on “Providing the Platform for Discovery” in Chapter 1)

**Center for Information Technology (CIT)**. CIT incorporates the power of modern computers into NIH’s biomedical and behavioral research programs and administrative procedures by focusing on three primary activities: conducting computational biosciences research, developing computer systems, and providing computer facilities. (Also see “Information Technology” in the section on “Providing the Platform for Discovery” in Chapter 1.)

**Center for Scientific Review (CSR)**. CSR carries out peer review of the majority of research and research training applications submitted to NIH; serves as the central receipt point for all such Public Health Service applications; makes referrals to scientific review groups for scientific and technical merit review of applications and to funding components for potential award; and develops and implements innovative, flexible ways

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<sup>1</sup> The NIH Health Disparities Strategic Plan for 2004-2008 has been approved by the National Advisory Council on Minority Health and Health Disparities, but is awaiting formal clearance.

to conduct referral and review for all aspects of science. (Also see “NIH Peer Review Process” under the section on “The Extramural Research Program” In Chapter 1.)

## Office of the Director

### ***Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI).***

DPCPSI is a new structure within the NIH OD, mandated by the NIH Reform Act of 2006. DPCPSI incorporates functions of the Office of Portfolio Analysis and Strategic Initiatives (which has primary responsibility for trans-NIH research initiatives based on NIH-wide portfolio assessment, strategic planning, evaluation, and assessment) and most responsibilities of the four OD Program Offices (which are responsible for stimulating and coordinating specific areas of research across NIH). See “Strategic Planning and Roadmap 1.5,” in Chapter 1, for further information on DPCPSI, the Office of Portfolio Analysis and Strategic Initiatives, and the activities they support. See Appendix C for the Common Fund Strategic Planning Report, FY 2008.

The four OD Program Offices are in the areas of disease prevention; behavioral and social sciences research; women's health; and AIDS research.

***Office of Disease Prevention (ODP).*** ODP fosters, coordinates, and assesses research in prevention research that seeks to improve public health in the Nation and throughout the world. ODP collaborates with other Federal agencies, academic institutions, the private sector, nongovernmental organizations, and international organizations in the formulation of research initiatives and policies that promote public health, and advises the NIH Director on these topics. There are three offices within ODP: Office of Rare Diseases (ORD), Office of Dietary Supplements (ODS), and Office of Medical Applications of Research (OMAR):

- ORD stimulates and coordinates research on rare diseases to respond to the needs of approximately 25 million patients who have one of the 7,000 known rare diseases. (Also see the section on the Rare Diseases Clinical Research Network in Chapter 4, which addresses NIH Centers of Excellence.)
- [ODS](#) promotes and supports, through collaboration with the ICs, basic and clinical research to increase understanding of the impact of dietary supplements (e.g., plant extracts, enzymes, vitamins, minerals, amino acids, hormonal extracts) on disease prevention and health maintenance.
- OMAR is the focal point for evidence-based assessments of medical practice and state-of-the-science conferences—key mechanisms for translating and disseminating the results of biomedical research to improve the delivery of health services to the public.

***Office of Behavioral and Social Sciences Research (OBSSR).*** OBSSR coordinates and stimulates behavioral and social sciences research throughout the NIH and integrates it more fully into the NIH research enterprise. The Office provides leadership on matters relating to research on the roles of human behavior and the social environment in the development of health, prevention of disease, and

therapeutic intervention, as well as in training, continuing education, and dissemination of research findings to the broader scientific community and the general public.

[Office of Research on Women's Health \(ORWH\)](#). ORWH serves as a focal point for women's health research at NIH. ORWH promotes, stimulates, and supports efforts to improve the health of women through biomedical and behavioral research. The Office works in partnership with the NIH ICs to ensure that women's health research is part of the scientific framework at NIH and throughout the broader scientific community.

[Office of AIDS Research \(OAR\)](#). OAR is responsible for the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. This includes responsibility for developing an annual comprehensive plan and budget for all NIH AIDS research and supporting trans-NIH Coordinating Committees to assist in these efforts.





## **Appendix C**

# **Common Fund Strategic Planning Report, FY 2008**

**National Institutes of Health  
Department of Health and Human Services**

**March 2008**

### **Common Fund Strategic Planning Report, 2008**

Scientific staff of the National Institutes of Health (NIH) are implementing new initiatives that have been approved for support through the Common Fund starting in FY 2008. The staff have consulted with experts inside and outside NIH to identify and refine initiatives that will most efficiently and directly meet the scientific need and criteria established for use of the Common Fund. This updated report describes the strategic process that guides the use of the Common Fund, new initiatives that have been chosen for implementation, additional concepts that remain in development, and plans for ongoing identification and development of Common Fund initiatives.

#### **I. Background and Budget of the Roadmap/Common Fund**

In FY 2003, Dr. Elias Zerhouni established the NIH Roadmap as a defined, centralized pool of funds to provide virtual “incubator space” or venture capital to support innovative research initiatives that address grand challenges in basic, clinical, and translational research. With funding beginning in FY 2004, the NIH Roadmap became the foundation for the Common Fund. In January 2007, President Bush signed into law the National Institutes of Health Reform Act of 2006, Pub. L. No. 109-482, which reauthorized the NIH, affirming its vital role in advancing biomedical research, and codified the Common Fund.

In FY 2004–FY 2006, the Common Fund was composed of contributions from each of the NIH Institutes and Centers as well as the NIH Office of the Director (OD). In FY 2007 and FY 2008 appropriations action, the Congress directly appropriated resources for the Common Fund to the OD. The following table shows Roadmap/Common Fund dollars and their percentage of NIH Labor/HHS budget authority by fiscal year:

	FY 2004 Actual B.A.	FY 2005 Actual B.A.	FY 2006 Actual B.A.	FY 2007 Joint Resolution	FY 2008 Appropriation
Dollars in Millions					
Institute or Center Roadmap/Common Fund Contribution	\$93.5	\$175.7	\$247.3	\$0.0	\$0.0
OD Roadmap/Common Fund Contribution	\$38.4	\$64.0	\$85.3	\$483.0	\$495.6
<b>Roadmap/Common Fund</b>	<b>\$131.9</b>	<b>\$239.7</b>	<b>\$332.6</b>	<b>\$483.0</b>	<b>\$495.6</b>
Roadmap/Common Fund Percent of NIH Labor/HHS Budget Authority <sup>1</sup>	0.5%	0.8%	1.2%	1.7%	1.7%

<sup>1</sup> Adjusted for Type I Diabetes, Global Fund for AIDS, Superfund, Secretary’s transfer authority for NLM.

The OD appropriation for FY 2008 included \$495.6 million for the Common Fund. The NIH is using those funds to support:

- a) The cohort of NIH Roadmap/Common Fund research initiatives that began between FY 2004 and FY 2007. The estimated funding for these initiatives (summarized in Section III) in FY 2008 is \$464 million.
- b) The Human Microbiome Project and the Epigenomics program, which have been added to the Common Fund in FY 2008 to support the development of novel research tools, technologies, and resources for research on microbes associated with the human body and epigenetic changes linked to human disease. The Common Fund is providing \$32 million to launch these programs in FY 2008 (described in Sections III and IV).

## II. Strategic Planning for the Roadmap/Common Fund

Planning and implementation of the Roadmap/Common Fund are highly dynamic processes that are intended to afford NIH the flexibility to quickly respond to new ideas, challenges, gaps, and advances in biomedical research. Nonetheless, decisions on the use of the Common Fund are based on strategic principles that defined the challenges and goals during the creation of the Roadmap and that guide the identification of new initiatives that receive support through this program.

## **A. Challenges Faced by NIH and the Biomedical Research Enterprise**

The evolution of biomedical research in recent decades has led to an explosion of knowledge and technology that has revolutionized our understanding of basic biological systems and transformed the practice of medicine. Many of these advances, such as the Human Genome Project (HGP) and the state-of-the-art research technologies that were developed to complete that project, have created the means to compile vast amounts of biologically-relevant data and the corresponding need for new tools to effectively mine that data for new knowledge. In contrast, some research fields, such as fundamental research to characterize the microbes that live in and affect the human body, have lagged behind because they fall into “gaps” in traditional NIH programmatic approaches and funding mechanisms. The NIH recognized an opportunity to address these challenges by devising a new approach that would meet the research and training needs of biomedical research in the 21<sup>st</sup> century and accelerate the transformation of scientific knowledge into real benefits for public health.

## **B. Goals of the Roadmap/Common Fund**

To respond to new opportunities and fill important research gaps, the NIH developed the Roadmap program (funded through the Common Fund) in consultation with leading experts from academia, industry, government, and the public. The NIH Roadmap/Common Fund supports wide-ranging and ambitious initiatives related to emerging opportunities and challenges. These activities focus on fundamental barriers to basic, clinical, and translational research that often require new multidisciplinary approaches, collaborations, synergies between basic science, clinical research, and informatics, as well as new training approaches for scientists. The Common Fund facilitates transformative research or technology development with cross-cutting relevance to many research disciplines, diseases or conditions, and biological questions.

Three broad categories of research have been identified that encompass the goals of the Roadmap/Common Fund: New Pathways to Discovery; Research Teams of the Future; and Reengineering the Clinical Research Enterprise. Initiatives funded through the first and second cohorts fit into one of these major themes, which will continue to be primary focus areas for the foreseeable future. Specific elements within each theme area will evolve as programs transition out of the Common Fund and new ideas are developed. (Section III lists the current programs that address the goals of the three overarching themes.)

## **C. Identification of Ideas and Criteria for Use of the Common Fund**

NIH is committed to a broad, representative process for proposing, reviewing, and selecting concepts for new initiatives to be developed and implemented through the Common Fund. Ideas can be submitted by members of the extramural or intramural scientific community, health professionals, patient advocates, or the general public. After a public comment period, current initiatives were chosen for inclusion in the Common Fund by Institute and Center (IC) Directors and the NIH Director in consultation with the

Advisory Council to the Director. For FY 2009 and future years, the newly-formed Council of Councils, which includes representation from each of the individual IC advisory councils, will participate in the prioritization of Common Fund projects, among other activities.

Specific criteria have been established to guide the ongoing development of Common Fund initiatives. Projects chosen for support must meet all five criteria:

- The proposed initiative must be truly transforming. It must have high potential to dramatically affect how biomedical and/or behavioral research is conducted over the next decade.
- The outcomes from the proposed initiative must synergistically promote and advance the individual missions of NIH ICs to benefit health.
- The proposed initiative must require participation from NIH as a whole and/or address an area(s) of science that does not clearly fall within the mission of any one IC or OD program office.
- The proposed initiative must be something that no other entity is likely or able to do.
- There must be a public health benefit to having the results of the research in the public domain.

#### **D. Transition of Common Fund Initiatives**

As a virtual incubator space for trans-NIH research initiatives, the Common Fund supports initiatives for a limited amount of time (5-10 years). This defined period of funding is intended to be catalytic—that is, the Roadmap initiatives are designed to establish new resources, tools, and technologies that will then be available for the broad scientific community to incorporate into research efforts funded through more typical mechanisms. Likewise, fundamental knowledge gaps that are filled through Roadmap projects will stimulate research proposals in many fields that can be submitted for review and funding by appropriate Institutes or Centers. The Roadmap is also intended to catalyze the development of critical research services that benefit the mission of all the Institutes and Centers and that, once developed, can be supported through the Institutes and Centers. Thus, the rigorous selection processes allow innovative initiatives to enter the incubator space for short-term support to prove their value to the research community.

At the end of the defined funding term, each initiative will have one of several possible outcomes. Programs that were designed from the outset to achieve their goals within the timeframe of support by the Common Fund will end. Other programs may end due to unmet objectives. Innovation often requires risk, and a fundamental goal of Roadmap programs is to foster innovative approaches to complex problems. Therefore the NIH encourages risk taking in the Roadmap and expects that some Roadmap programs may not be successful. Finally, many initiatives are expected to transition to other sources of support once the Roadmap “incubation” period has ended. If the programs have proven utility to the research missions of the Institutes and Centers, the Institutes and Centers either individually or via joint funding mechanisms will provide continued support. Alternatively, programs may continue to be funded via private foundations or research

institutions. From the beginning of the funding period, each initiative has a transition plan that describes the anticipated path after Common Fund goals are achieved. Advanced planning for the strategic transition or termination of all initiatives selected for Common Fund support ensures that the program remains nimble and capable of responding to high-priority opportunities in a timely manner.

The majority of the first cohort of initiatives funded through the NIH Roadmap/Common Fund continues to receive support in FY 2008 through the Common Fund. In general, these research initiatives are expected to transition out of the Common Fund by 2013. In the meantime, each of these initiatives and all new initiatives are subject to objective reviews to ensure high quality research and to monitor progress. Continuation of support by the Common Fund is based in part on the outcome of these evaluations.

### **III. Implementation of the NIH Roadmap/Common Fund Strategic Plan, FY 2004–2008**

FY 2008 funding continues support for the first cohort of NIH Roadmap/Common Fund initiatives. To take advantage of new opportunities, the NIH maintains a degree of flexibility in the allocation of funds. Emerging opportunities that have been identified and prioritized by the NIH for support by the Common Fund include the NIH Director's New Innovator Awards, which were first awarded in FY 2007, and the Human Microbiome Project and the Epigenomics program, which began implementation in FY 2008.

**A. New Pathways to Discovery:** Facilitates the development of research tools and/or methodologies that are of use to wide swaths of the scientific community; fills fundamental knowledge gaps to result in new scientific paradigms. Seven components comprise this theme, including two new initiatives for FY 2008.

- 1) *Molecular Libraries and Molecular Imaging*  
Establishes a national network of Centers and various supporting technologies for the discovery and development of small molecule probes to interrogate biological pathways.
- 2) *Building Blocks, Pathways, and Networks*  
Focuses on new technologies that are necessary to accelerate the process of scientific discovery and the understanding of biological pathways.
- 3) *Bioinformatics and Computational Biology*  
Develops informatics and computational tools tailored to handle the large amount of scientific data generated using cutting-edge discovery technologies.
- 4) *Nanomedicine*  
Establishes a network of Nanomedicine Centers at academic institutions, to study how molecular structures are constructed and how they function.



5) *Structural Biology*

Establishes Centers for Innovation in Membrane Protein Production that aim to formulate new methods and techniques for producing ample quantities of cellular membrane proteins that are of a quality suitable for structural and functional studies.

6) *Human Microbiome Project* (new for FY 2008, see section IV)

Develops tools and generates resources to facilitate characterization of the human microbiome and analysis of its role in human health and disease.

7) *Epigenomics* (new for FY 2008, see section IV)

Develops comprehensive reference maps of the human epigenome and new technologies for epigenomic analysis to define the relationship between the epigenome and human health and disease.

**B. Research Teams of the Future:** Supports investigators in new ways, encouraging team approaches to complex problems and highly innovative research.

1) *Interdisciplinary Research*

Overcomes barriers to interdisciplinary research by building teams, training scientists in multiple disciplines, and changing academic research culture.

2) *Director's Pioneer Award*

Supports visionary scientists to carry out extensive, high-risk, highly innovative research. These investigators perform research that is broad in its scope and may contribute to a transformation of new, fundamental principles within that research niche.

3) *Public-Private Partnerships*

Provides a point of leadership and coordination for the harmonization, streamlining, and optimization of the NIH partnership activities.

4) *NIH Director's New Innovator Awards* (new in FY 2007)

Stimulates highly innovative research and supports promising new investigators who propose exceptionally creative approaches that have the potential to produce an unusually high impact on the research enterprise.

**C. Reengineering the Clinical Research Enterprise:** Changes clinical research infrastructure to improve the ability to systematically leverage medical resources. This includes proposals and policy decisions that affect the culture and manner in which research is conducted.

1) *Clinical Translational Science Awards (CTSAs)*

Transforms how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments more efficiently and quickly to patients.

2) *Patient-Reported Outcomes Measurement Information System (PROMIS)*

PROMIS is a revolutionary effort to enhance the precision of measures of patient-reported symptoms and function.

3) *Translational Research Core Services*

Makes available, on a competitive basis, certain critical resources needed for the development of therapeutic agents and to bridge the gap between discovery and clinical testing so that more efficient translation of promising discoveries may take place.

4) *Clinical Research Policy Analysis and Coordination*

Serves as a focal point for the ongoing coordination, streamlining, and optimization of policies and requirements concerning the conduct and oversight of clinical research.

5) *The National Electronics Clinical Trials and Research Network (NECTAR)*

Addresses the growing role of informatics in the medical field, particularly in conducting clinical trials. This initiative supports pilot studies that will provide the basis for a unified informatics system. This program has merged with the CTSAs for FY 2008 and beyond.

6) *The National Clinical Research Associates (NCRA)*

Establishes and trains cadres of community-based health practitioners to conduct clinical research in collaboration with academic researchers. This program has merged with the CTSAs for FY 2008 and beyond.

#### **IV. Ongoing Development of Common Fund Initiatives**

To plan for the use of new funds expected to become available in FY 2008, the NIH undertook an intensive, wide-ranging, and transparent planning process that solicited input from NIH staff and scientists, extramural researchers, and the broader stakeholder community on gaps in knowledge or tools that impede certain types of research from moving forward. After reviewing and prioritizing more than 300 ideas for new initiatives, the NIH selected two major programs for implementation beginning in FY 2008 with resources from the Common Fund. Each of these multicomponent programs represents the integration of several original ideas submitted for review. Other concepts remain under consideration for future implementation. The process of solicitation, review, and prioritization of concept proposals that could advance the mission of the NIH as a whole and that meet the criteria for Common Fund support will continue in FY 2008 and will be repeated each year to allow emerging opportunities to be identified.

##### **A. New Common Fund Initiatives for Implementation in FY 2008**

The two initiatives being launched in FY 2008—the Human Microbiome Project and the Epigenomics program—are associated with the general theme of “New Pathways to Discovery.” These programs each respond to the Common Fund goals of advancing basic knowledge and developing new tools or resources that will be broadly applicable to many research fields. In FY 2008, the NIH is spending a combined \$32 million from the Common Fund on the first year of funding for these initiatives.

**Human Microbiome Project:** The human body contains ten times as many microbial cells—bacteria and other micro-organisms—as it does human cells.

These microbes, which are found in locations throughout the body, are thought to have a profound influence on many biological processes, including development, immunity, and nutrition. However, technical difficulties in isolating and studying many of these organisms have limited our ability to fully understand the effects of the microbiome on human health and disease. The Human Microbiome Project will generate resources and support the development of new technologies and computational approaches to facilitate the characterization of the highly complex human microbiome. This project will improve our knowledge of how changes in the microbiome correlate with changes in human health.

**Epigenomics:** The human epigenome is the collection of all stable, “epigenetic,” modifications of the human genome structure that do not change the DNA sequence. Some human diseases are known to be associated with epigenetic changes, but little is known about the factors that cause these changes. Moreover, new tools are needed to more efficiently detect epigenetic changes and correlate them with specific diseases or health conditions. The Epigenomics program will support efforts to map all common epigenetic changes in the human genome and to develop new technologies and data analysis tools for detecting and studying epigenetic modifications. Public databases will be made available to the broad research community to facilitate progress in epigenomics research.

## **B. Concepts in Development for Future Implementation**

Two additional programs are being refined for possible future implementation. Each of these initiatives, if chosen for funding, also represents the synthesis of multiple ideas submitted through the proposal review and prioritization process. The process of soliciting, reviewing, and developing new concepts that meet the criteria for Common Fund support will continue in FY 2008 and future years to ensure that the Roadmap/Common Fund rapidly identifies and responds to emerging scientific opportunities.

The **Protein Capture Tools/Proteome Tools** project will develop and disseminate high quality probes that can be synthesized reproducibly for the detection and analysis of proteins. Such tools would enable researchers to characterize protein function in health and disease and would reveal new targets for disease prevention and therapy. This initiative, if implemented, would address the general theme of “New Pathways to Discovery.”

The **Phenotyping Services and Tools** project will develop resources for the systematic characterization of human phenotypes—the total physical appearance and constitution of an individual—to facilitate the study of complex diseases. If funded, this initiative would be part of the “Reengineering the Clinical Research Enterprise” theme area.

Appendix D

**Research Training and Graduate Medical Education Data**

**National Research Service Award (NRSA) and National Library of Medicine (NLM) Research Training Programs**

**Ph.D.s Awarded to NIH Trainees and Fellows**

Field of Study*	FY 2005	FY 2006
<b>Life Sciences</b>	<b>2,053</b>	<b>1,650</b>
<i>Biological/Biomedical Sciences</i>	<i>1,850</i>	<i>1,465</i>
Biochemistry	195	166
Biomedical Sciences	71	56
Biophysics	60	51
Biotechnology	5	4
Bacteriology	3	1
Plant Genetics	10	6
Plant Pathology/Phytopathology	1	1
Plant Physiology	1	3
Botany/Plant Biology	1	2
Anatomy	3	1
Biometrics & Biostatistics	34	18
Cell/Cellular Biology and Histology	109	105
Ecology	5	2
Developmental Biology/Embryology	70	48
Endocrinology	8	2

<b>Field of Study*</b>	<b>FY 2005</b>	<b>FY 2006</b>
Entomology	2	3
Immunology	150	120
Molecular Biology	226	194
Microbiology	148	107
Neuroscience	292	259
Nutritional Sciences	22	9
Parasitology	2	10
Toxicology	33	23
Genetics, Human & Animal	124	82
Pathology, Human & Animal	30	24
Pharmacology, Human & Animal	117	80
Physiology, Human & Animal	55	42
Zoology, Other	2	6
Biology/Biological Sciences, General	27	21
Biology/Biomedical Sciences, Other	44	19
<i><u>Health Sciences</u></i>	<i><u>197</u></i>	<i><u>180</u></i>
Speech-Language Pathology & Audiology	20	11
Environmental Health	2	6
Environmental Toxicology	7	8
Health Systems/Service Administration	2	1
Public Health	24	34
Epidemiology	58	39

<b>Field of Study*</b>	<b>FY 2005</b>	<b>FY 2006</b>
Kinesiology/Exercise Sciences	9	7
Nursing Science	46	56
Pharmacy	7	1
Rehabilitation/Therapeutic Services	2	2
Veterinary Medicine	1	1
Health Sciences, General	3	6
Health Sciences, Other	16	8
<i><u>Agricultural Sciences/Natural Resources</u></i>	<u>6</u>	<u>5</u>
Agricultural Economics	1	0
Poultry Science	1	1
Animal Science, Other	3	1
Plant Pathology/Phytopathology	1	1
Plant Sciences, Other	0	1
Environmental Science	0	1
<b>Social Sciences</b>	<b>396</b>	<b>259</b>
<i><u>Psychology</u></i>	<u>321</u>	<u>201</u>
Clinical	137	57
Cognitive & Psycholinguistics	25	27
Counseling	7	3
Developmental & Child	45	25
Human Development & Family Studies	11	4
Family Psychology	0	1



<b>Field of Study*</b>	<b>FY 2005</b>	<b>FY 2006</b>
Experimental	18	9
Educational	2	1
Industrial & Organizational	1	2
Personality	4	2
Physiological/Psychobiology	28	18
Psychometrics & Quantitative	4	2
School	1	0
Social	23	25
Psychology, General	7	13
Psychology, Other	8	12
<i><u>Social Sciences</u></i>	<u>75</u>	<u>58</u>
Anthropology	13	4
Criminology	1	1
Demography/Population Studies	5	3
Economics	16	16
Econometrics	1	0
Geography	0	1
Political Science & Government	0	1
Public Policy Analysis	8	3
Sociology	26	25
Social Sciences, Other	5	4

<b>Physical Sciences</b>	<b>150</b>	<b>129</b>
<i>Chemistry</i>	<u>108</u>	<u>88</u>
Analytical	10	13
Inorganic	9	5
Organic	37	22
Medicinal/Pharmaceutical	15	18
Physical	7	10
Polymer	3	2
Theoretical	0	3
Chemistry, General	14	9
Chemistry, Other	13	6
<i>Computer Sciences</i>	<u>10</u>	<u>11</u>
Computer Science	8	5
Information Science & Systems	0	3
Computer & Information Sciences, Other	2	3
<i>Geological &amp; Earth Sciences</i>	<u>3</u>	<u>1</u>
Geology	1	0
Geochemistry	1	1
Geophysics & Seismology	1	0
<i>Mathematics</i>	<u>10</u>	<u>10</u>
Applied Mathematics	4	2
Geometry/Geometric Analysis	0	1
Statistics	5	4

Mathematics/Statistics, General	0	2
Mathematics/Statistics, Other	1	1
<i>Ocean/Marine Sciences</i>	<u>1</u>	<u>0</u>
Marine Sciences	1	0
<i>Physics</i>	<u>18</u>	<u>19</u>
Elementary Particle	0	1
Biophysics	9	11
Optics/Phototonics	1	1
Polymer Physics	0	1
Applied Physics	0	3
Plasma/Fusion	1	0
Condensed Matter/Low Temperature	1	0
Physics, General	2	0
Physics, Other	4	2
<b>Engineering</b>	<b>94</b>	<b>97</b>
<b>Education</b>	<b>8</b>	<b>9</b>
<b>Humanities</b>	<b>7</b>	<b>6</b>
<b>Other Fields</b>	<b>19</b>	<b>19</b>
<b>TOTAL</b>	<b>2,727</b>	<b>2,169</b>

**Note:** Detailed field data are provided only for broad (i.e., shaded) fields with  $\geq 100$  Ph.D. recipients.

**Sources:** NIH Trainee and Fellow File, IMPAC II, and the Doctorate Records File.

**Demographic Characteristics\* of NRSA Participants**

<b>Demographic Characteristic</b>	<b>FY 2005</b>	<b>FY 2006</b>
<u>Sex</u>		
Female	50.8%	52.1%
Male	47.4%	46.0%
Unreported	1.8%	1.9%
<u>Race/Ethnicity</u>		
White	69.3%	66.2%
Asian	15.3%	14.4%
Hispanic	6.1%	6.4%
African American	10.2%	9.1%
Native American	1.1%	1.1%
Native Hawaiian/Pacific Islander	.06%	0.6%
Unreported	4.3%	8.1%

**Source:** IMPAC II

\* Reporting personal information such as sex, race, and ethnicity is voluntary.

**Graduate Medical Education:**  
**NIH-sponsored, ACGME-Accredited, Residency and Subspecialty Training Programs**

**Successfully Completed Residency and Subspecialty Training By Academic Year**

NIH Clinical Center Program Specialty	Successfully Completed	
	2005/2006	2006/2007
Allergy and Immunology	4	3
Dermatology	0	2
Medical Genetics	3	2
Critical Care Medicine	5	3
Endocrinology, Diabetes, and Metabolism	5	6
Hematology	3	3
Infectious Disease	3	3
Oncology	10	12
Rheumatology	2	1
Pathology-Anatomic and Clinical	1	3
Blood Banking/Transfusion Medicine	1	3
Cytopathology	1	1
Hematology (Pathology)	1	1
NICHD/Georgetown University Hospital Program / Pediatric Endocrinology*	2	2
Psychiatry	1	1
<b>Total</b>	<b>42</b>	<b>46</b>

\*Cosponsored by NICHD and Georgetown University Hospital

Source: AAMC GME Track Database

**Appendix E**

**Monitoring Adherence to the NIH Policy on Inclusion of Women and  
Minorities as Subjects in Clinical Research**

Comprehensive Report: Tracking of Human Subjects Research As Reported in Fiscal Year 2005  
and Fiscal Year 2006

Following is an excerpt of the report—all of the report except for the appendices. The full report  
can be found at:

<http://orwh.od.nih.gov/inclusion/2007%20Annual%20Comprehensive%20Report%20-%20Web%20Version%20Rev%208-22-07.pdf>



Department of Health and Human Services  
National Institutes of Health

MONITORING ADHERENCE TO THE  
NIH POLICY ON THE INCLUSION  
OF WOMEN AND MINORITIES  
AS SUBJECTS IN CLINICAL RESEARCH

Comprehensive Report: Tracking of Human Subjects Research  
As Reported in Fiscal Year 2005 and Fiscal Year 2006

**NIH Tracking/Inclusion Committee**

*Vivian W. Pinn, M.D., Co-Chair*  
Office of Research on Women's Health

*Carl Roth, Ph.D., LL.M., Co-Chair*  
National Heart, Lung, and Blood Institute

*Angela C. Bates, M.B.A.*  
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*Kim Jarema*  
Liaison, NIH Clinical Center

**Spring 2007**

**Table of Contents**

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	<u>Page</u>
<b><u>Historical Summary and Current Activities</u></b>	
Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research	1
Data Analyses and Report of NIH Inclusion Data	9
<b><u>Summary Data Tables: FY2006 and Twelve-Year Trend Reports</u></b>	
<b><u>NIH Wide Clinical Research Performed in 2005 and Reported in FY2006</u></b>	
Table 1. Summary of NIH Clinical Research Reported in FY2006: Total Number of Protocols and Enrollment by Sex and Domestic versus Foreign Protocols	19
Table 2. Overview of NIH Extramural and Intramural Clinical Research Reported in FY2006: Number of Sex- Specific Protocols and enrollment, and Domestic versus Foreign Protocols	21
Table 3. Summary of NIH Phase III Clinical Research Reported in FY2006: Total Number of Protocols and Enrollment by Sex, and Domestic versus Foreign Protocols	23
Table 4. Overview of NIH Phase III Extramural and Intramural Clinical Research Reported in FY2006: Number of Sex-Specific Protocols and Enrollment, and Domestic versus Foreign Protocols	25
<b><u>Trend Summary Reports: FY1995-2006</u></b>	
Table 5. Twelve-Year Trend for Protocol and Enrollment Data	27
Table 6. Twelve-Year Minority Trend Summary of NIH Extramural and Intramural Clinical Research reported in FY1995-2006: Enrollment by Race and Ethnicity	30
Table 7. Twelve-Year Minority Trend Summary of NIH Phase III Extramural and Intramural Clinical Research Reported in FY1995-2006: Enrollment by Race and Ethnicity	33
<b><u>Domestic and Foreign Clinical Research: Trend Reports FY2002-2005</u></b>	
Table 8. DOMESTIC PROTOCOLS: Summary of NIH Extramural and Intramural Clinical Research Reported in FY2002-2006: Enrollment Using U.S. Race and Ethnicity Categories	36
Table 9. DOMESTIC PROTOCOLS: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY2002-2006: Enrollment Using U.S. Race and Ethnicity Categories	38
Table 10. FOREIGN PROTOCOLS: Summary of NIH Extramural and Intramural	

	Clinical Research Reported in FY2002-2006: Enrollment Using U.S. Race and Ethnicity Categories	40
Table 11.	FOREIGN PROTOCOLS: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY2002-2006: Enrollment Using U.S. Race and Ethnicity Categories	42

**APPENDICES**

<b>Appendix A</b>	Historical Narrative on the Implementation of the NIH Inclusion Policy .....	47
<b>Appendix B</b>	Explanation of Gender and Minority Codes .....	58
<b>Appendix C</b>	NIH Tracking and Inclusion Committee Member List .....	61
<b>Appendix D</b>	Internet Homepage: Inclusion of Women and Minorities Policy Implementation.....	67
<b>Appendix E</b>	NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001 .....	71
<b>Appendix F</b>	NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research .....	87
<b>Appendix G</b>	NIH Inclusion Tables for Target and Enrollment Data .....	99
<b>Appendix H</b>	Comparison of 1977 and 1997 OMB Classifications for Reporting Race and Ethnicity .....	105
<b>Appendix I</b>	FY2006 Aggregate Extramural and Intramural Data Tables .....	109

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### Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

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The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by the National Institutes of Health (NIH) has its origins in the women's health movement. Following the issuance of the report of the Public Health Service Task Force on Women's Health in 1985, the NIH established a policy in 1986 for the inclusion of women in clinical research. This policy, which *urged* the inclusion of women, was first published in the NIH Guide to Grants and Contracts in 1987. Later that year, minority and other scientists at the NIH recognized the need to address the inclusion of minority populations. Therefore, in a later 1987 version of the NIH guide, a policy *encouraging* the inclusion of minorities in clinical studies was first published.

In order to ensure that the policies for inclusion were firmly implemented by NIH, the Congress made what had previously been policy into Public Law, through a section in the NIH Revitalization Act of 1993 (PL 103-43)<sup>1</sup>, entitled *Women and Minorities as Subjects in Clinical Research*. In 1994, the NIH revised its inclusion policy to meet this mandate that women and minorities must be included in all of its clinical research studies. The Revitalization Act essentially reinforced the existing NIH policies, but with four major differences:

- ▶ that NIH ensure that women and minorities and their subpopulations be included in all clinical research;
- ▶ that women and minorities and their subpopulations be included in Phase III clinical trials in numbers adequate to allow for valid analyses of differences in intervention effect;
- ▶ that cost is not allowed as an acceptable reason for excluding these groups; and,
- ▶ that NIH initiate programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as participants in clinical studies

Revised inclusion guidelines developed in response to this law were published in the *Federal Register*<sup>2</sup> in March 1994, and they became effective in September 1994. The result was that NIH could not and would not fund any grant, cooperative agreement or contract or support any intramural project to be conducted or funded in Fiscal Year 1995 and thereafter which did not comply with this policy.

Strategies to ensure uniform implementation of the revised guidelines across the NIH were developed through the establishment and deliberations of an NIH Tracking and Inclusion Committee made up of representatives of the directors of each of the ICs. This trans-NIH committee, convened by the Office of Research on Women's Health (ORWH) and co-chaired with a senior IC official, meets on a regular basis, focusing on consistent and widespread adherence to the NIH guidelines by all the ICs. Working in collaboration with the Office of Extramural Research (OER), the Office of Intramural Research (OIR), and other components of the NIH, the ORWH coordinates the activity of developing and establishing data collection and reporting methodologies to ensure uniform standards and definitions in the reporting of data on women and minority participants in NIH-funded clinical research.

To ensure NIH-wide adherence to the revised inclusion guidelines, in 1994 NIH conducted extensive training on the revised inclusion guidelines. In June 1994, the ORWH convened a meeting of Institutional Review Board (IRB) chairs to discuss their role in implementing the revised policy. Training was especially important in light of 1990 GAO findings that an earlier policy was inconsistently applied and had not been well communicated or understood within the NIH or in the research community. A variety of outreach activities were initiated to explain the revised policy to the scientific research community and to clear up common misunderstandings about the new requirements.

### **Continuing Implementation and Monitoring Activities**

Following a Congressional request for an assessment of NIH's progress in implementing the 1994 guidelines on including women in clinical research, the GAO issued another report in May, 2000, entitled *Women's Health - NIH Has Increased Its Efforts to Include Women in Research*.<sup>3</sup> It concluded that in the past decade, NIH has made significant progress in implementing a strengthened policy on including women in clinical research.

The GAO report also included two specific recommendations to the Director of NIH to ensure the following:

- ▶ that the requirement be implemented that Phase III clinical trials be designed and carried out to allow for the valid analysis of differences between women and men and communicate this requirement to applicants as well as requiring peer review groups to determine whether each proposed Phase III clinical trial is required to have such a study design, and that summary statements document the decision of the initial reviewers; and
- ▶ that the NIH staff who transmit data to the inclusion tracking data system receive ongoing training on the requirements and purpose of the system.

Immediately following the release of this report, an *NIH Subcommittee Reviewing Inclusion Issues* was formed, consisting of representatives from several ICs, ORWH, OER, and OIR, to reexamine NIH's system for tracking data on the inclusion of women and minorities in clinical research, recommend any necessary changes to improve its accuracy and performance, and reiterate the NIH policy. Several actions resulted to clarify the requirement for NIH-defined Phase III clinical trials to include women and minority groups, if scientifically appropriate, and for analysis of sex/gender and/or racial/ethnic differences to be planned and conducted by investigators engaged in NIH-funded research. Significant actions in 2001 included:

- ▶ **Updating the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research** and posting it on the ORWH home page <http://orwh.od.nih.gov/inclusion.html> and NIH web page, *Inclusion of Women and Minorities Policy Implementation* at: [http://grants.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants.nih.gov/grants/funding/women_min/women_min.htm).
- ▶ **Developing a new term and condition of award** statement for awards made after October 1, 2000 that have NIH-defined Phase III clinical trials.
- ▶ **Incorporating language in the NIH solicitations for grant applications and contract proposals to clarify the submission requirement for NIH-defined Phase III clinical trials**, a description of plans for sex/gender and/or race/ethnicity analysis including subgroups, if applicable, and reporting accrual annually and results of analyses, as appropriate.
- ▶ **Guidelines and instructions for reviewers and Scientific Review Administrators (SRAs) were developed** to emphasize and clarify the need to review research proposals that are classified as NIH-defined Phase III clinical trials for both inclusion requirements and issues related to analyses by sex/gender and/or race/ethnicity. Instructions were developed for the proper documentation to include in summary statements to address adherence to these policies.

Training to ensure compliance with this policy was provided to NIH program and review officials, grants and contracts management staff, and current and prospective research investigators. Several initiatives

were implemented for review, grants management and program staff since 2000, including specific topics addressing revisions to the NIH Inclusion policy, a grants policy update and Scientific Review Administrator (SRA) orientation on specific issues related to review meetings and proceedings.

The PHS 398 Grant Application was significantly revised to provide additional instructions about the Women and Minorities Inclusion Policy and the revised form became mandatory as of May 10, 2005. These PHS 398 instructions about the Women and Minorities Inclusion Policy have also been included in the new federal application form SF-424 (R&R) for NIH grants using the federal Grants.gov system (see <http://era.nih.gov/ElectronicReceipt/>). The application instructions included two significant changes in definitions. First, the NIH required use of a revised definition of clinical research that was reported in the 1997 Report of the NIH Director's Panel on Clinical research and adopted by NIH. Secondly, the Office of Management and Budget (OMB) Directive 15, "Race and Ethnic Standards for Federal Statistics and Administrative Reporting", revised the definitions for the racial and ethnic categories to be used when reporting population data (see: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>). In addition, NIH policy reemphasized that that NIH-defined Phase III clinical trials must be designed and conducted in a manner to allow for a valid analysis of whether the variables being studied affect women or members of minority groups differently than other subjects.

Many of the training sessions are available electronically for all NIH staff, and the Office of Extramural Research (OER) has made available existing training materials on the Population tracking system website on the NIH Intranet. A training subcommittee of the full NIH Tracking and Inclusion committee has been established to develop new training documents and methods of training for NIH staff and the extramural research community. Further information regarding training initiatives since the 2000 GAO report is discussed in the background section of the Appendices (See Appendix A)

#### **Communication and Outreach Efforts to the Scientific Community**

NIH staff provides outreach to the scientific community to help increase understanding of the revised inclusion policy and OMB requirements. These training and outreach efforts are designed to improve understanding of the sex/gender and minority inclusion policy and assist investigators and NIH staff to appropriately address these issues throughout the research grant and contract process. Investigators are instructed to address women and minority inclusion issues in the development of their applications and proposals for clinical research.

Reference documents such as the *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research* (<http://orwh.od.nih.gov/inclusion/outreach.pdf>) and the *Frequently Asked Questions (FAQs) for the Inclusion, Recruitment and Retention of Women and Minority Subjects in Clinical Research* (<http://orwh.od.nih.gov/inclusion/outreachFAQ.pdf>) have been published and distributed for investigators and NIH staff. These publications discuss the elements of recruitment and retention, the NIH inclusion policy, 1997 OMB requirements for reporting race and ethnicity data, as well as information for application submission, peer review, and funding. Both are posted on the ORWH website <http://orwh.od.nih.gov> as well as on the NIH website for the inclusion of women and minorities policy implementation at: [http://grants1.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants1.nih.gov/grants/funding/women_min/women_min.htm). The revised Outreach Notebook and FAQs continue to be available to the research community to further explore the inclusion policy and its intent. Additionally, a slide show available electronically and in hard copy, "Sex/Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know!" was developed for NIH staff to assist them in working with the extramural community.



#### **Monitoring Compliance: Extramural and Intramural Population Data Analysis**

***When assessing inclusion data, enrollment figures should not be directly compared to the national census figures.*** The goal of the NIH policy is not to satisfy any quotas for proportional representation, but rather to conduct biomedical and behavioral research in such a manner that the scientific knowledge acquired will be generalizable to the entire population of the United States. The numbers of women or minority subgroups included in a particular study depends upon the scientific question addressed in the study and the prevalence among women and minority subpopulations of the disease, disorder, or condition under investigation.

Scientific Review Groups are instructed to focus on scientific considerations when assessing the planned enrollment for a particular study. The Scientific Review Group (SRG) determines if the implementation plan for an application is unacceptable if it: 1) fails to provide sufficient information about target enrollment; 2) does not adequately justify limited or lack of inclusion of women or minorities; or 3) does not realistically address recruitment and retention. For NIH-defined Phase III clinical trials, the Scientific Review Group (SRG) also evaluates the description of plans to conduct analyses, as appropriate, to address differences in the intervention effect by sex/gender and/or racial/ethnic groups. Applications with unacceptable inclusion plans cannot be funded until NIH staff is assured that revised inclusion plans from the investigators meet the inclusion policy requirements. Research awards covered by this policy require the grantee to report annually on enrollment of women and men, and on the race and ethnicity of research participants so that accrual can be monitored.

NIH has monitored aggregate demographic data for study populations through the evolving NIH computerized tracking system since fiscal year 1994, and tracking the inclusion of women and minorities in clinical studies is well established in all ICs. Members of the NIH Tracking and Inclusion Committee continuously work on ways to refine and improve data collection methods and the quality of the data entered by each IC into this system. In May 2002, the NIH successfully deployed a new population tracking system for monitoring the inclusion of women and minorities in clinical research. This system provides easier data entry and project monitoring of investigator data reporting for NIH staff. An *eRA Population Tracking User Group* consisting of representatives from several ICs provides continuous feedback related to system use.

The aggregate data enable the NIH to measure inclusion in order to formulate more specific questions about gaps in enrollment and to design studies to respond to those questions. Data compiled in future years allows for longitudinal examination of trends and continued monitoring of compliance, although this will be more difficult for minority trends because of a change in how these data are collected (see next section).

A review of intramural inclusion data indicates that the intramural research program continues to be compliant with the reporting requirements adhered to by the extramural community and outlined in the NIH Implementation Guidelines on the Inclusion of Women and Minority Subjects in Research Studies. The Clinical Center Medical Executive Committee (MEC) has taken a leading role in assuring that investigators conducting clinical research protocols in the Clinical Center are trained and competent in the conduct of clinical research. The MEC designed and endorsed the Standards for Clinical Research within the NIH Intramural Research Program which set forth guidelines for the infrastructure, training, education, and monitoring required for safe and effective conduct of clinical research.

#### Format Changes for Reporting Race and Ethnicity Data

Beginning in FY2002, NIH changed how data are reported based on the 1997 Office of Management and Budget (OMB) Directive 15 minimum standards for maintaining, collecting and reporting data on race and ethnicity. Implementation of the 1997 OMB standards involved a number of changes including collecting and reporting information on race and ethnicity separately, whereas the 1977 OMB standards used a combined race and ethnicity format. NIH aggregate population data tables describe data using both the 1997 and 1977 OMB standards for reporting data on race and ethnicity. Since 2002, the number of studies reporting data using the 1997 format (NEW FORM) has steadily increased, while the number of studies using the 1977 format (OLD FORM) has steadily decreased as the studies funded prior to FY2002 are completed.

The 1997 OMB reporting format (NEW FORM) and standards does not allow direct comparison of ethnic and racial data with similar data collected under the 1977 OMB reporting format (OLD FORM) and standards because the categories and methods for collecting the data are fundamentally different. Changes in the standardization of definitions and business rules across the NIH for improving the data entered in the population tracking system are reflected in data reported beginning in FY2002. While implementation of these changes will improve the consistency and comparability for future reporting, comparisons with prior FY 2002 data are difficult.

As demonstrated below, the primary differences are: (1) the Hispanic population is considered an ethnic category and reported separately from racial data; (2) there is a separate racial category for Asian population data and Hawaiian and Pacific Islander population data; and 3) respondents are given the option of selecting more than one race. (See Appendix H)

Race and ethnicity data from the OLD and NEW Forms are combined differently as described below for purposes of reporting on the minority population enrolled in NIH clinical research:

- the OLD FORM uses the 1977 OMB combined Race and Ethnicity Format, which has mutually exclusive categories, and allows Hispanics to be reported as either "Hispanic, Not White" or "White".
- the NEW FORM uses the 1997 OMB Race and Ethnicity Categories, with separate reporting for Ethnicity (Hispanic or Latino; Not Hispanic or Latino) and Race (Part A); in this format, an individual is classified both by Ethnic Category and by Race Category. Part B of the NEW FORM therefore provides a distribution of only "Hispanics or Latinos" by the five main Race categories. Since minority categories are defined to include both "Hispanic or Latino ethnicity" and non-white racial categories when providing summary totals of minorities, it is necessary to add "White Hispanics" and "Unknown/Other Hispanics" based on their ethnicity to the non-white racial categories.
- Hispanics are defined by country of origin, and may be identified as belonging to any one, or more than one, race category.

Appendix E: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

<b>OLD FORM (1977) versus NEW FORM (1997)</b>		
<b>Race/Ethnicity Category</b>	<b>Minority Total</b>	
	<b>Old Form</b>	<b>New Form</b>
<b>OLD FORM: Combined 1977 OMB Race/Ethnicity Categories</b>		
American Indian/Alaska Native	X	
Asian/Pacific Islander	X	
Black or African American	X	
Hispanic, Not White	X	
White		
Unknown/Other		

<b>NEW FORM: Separate 1997 OMB Race/Ethnicity Categories</b>		
<b>Part A: Total Enrollment Report</b>		
<b>Ethnic Category</b>		
Hispanic or Latino**		
Not Hispanic or Latino		
Unknown (ethnicity not reported)		
Ethnic Category Total of All Subjects*		
<b>Racial Categories</b>		
American Indian/Alaska Native		X
Asian		X
Black or African American		X
Hawaiian/Pacific Islander		X
White		
More Than One Race		X
Unknown/Other		
Racial Categories: Total of all Subjects*		
<b>Part B: Hispanic Enrollment by RACE</b>		
American Indian/Alaska Native		
Asian		
Black or African American		
Hawaiian/Pacific Islander		
White (Hispanic)		X
More Than One Race		
Unknown/Other (Hispanic)		X
<b>Racial Categories: Total of Hispanics or Latinos**</b>		

\* The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects"

\*\* The "Hispanic or Latino"(Part A) must be equal to "Racial Categories: Total of Hispanics or Latinos"(Part B).

DEFINITIONS:

**Clinical Research as defined by the 1997 Report of the NIH Director's Panel on Clinical Research, <http://www.nih.gov/news/crp/97report/execsum.htm>**

- (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies;
- (2) Epidemiologic and behavioral studies; and
- (3) Outcomes research and health services research

**NIH-Defined Phase III Clinical Study**

For the purpose of these guidelines, an NIH-defined "clinical trial" is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

**Valid Analysis**

The term "valid analysis" means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:

- ▶ allocation of study participants of both sexes/genders (males and females) and different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization,
- ▶ unbiased evaluation of the outcome(s) of study participants, and
- ▶ use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups.

**Significant Difference**

For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

**Domestic organization**

A public (including a State or other governmental agency) or private non-profit or for-profit organization that is located in the United States or its territories, is subject to U.S. laws, and assumes legal and financial accountability for awarded funds and for the performance of the grant-supported activities

**Foreign institution**

An organization located in a country other than the United States and its territories that is subject to the laws of that country, regardless of the citizenship of the proposed PI.

#### CONCLUSION AND CURRENT STATUS

NIH staff continues to monitor, document, and work with grantees and contractors to ensure compliance with the inclusion policy. Program Officials provide technical assistance to investigators as they develop their applications and proposals throughout the application process. Review Officials introduce and discuss with reviewers the Guidelines/Instructions for reviewing the Inclusion of Women and Minorities in Clinical Research as well as the instructions and requirements for designing Phase III Clinical Trials in order that valid analyses can be conducted for sex/gender and ethnic/racial differences. At the time of award and submission of progress reports, program officials monitor and verify that inclusion policy requirements are met. When new and competing continuation applications that are selected for payment are deficient in meeting policy requirements, grants management staff and program officials are required to withhold funding until the principal investigator has satisfactorily addressed the policy requirements.

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#### References

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1. Public Law 103-43. National Institutes of Health Revitalization Act of 1993. 42 USC 289 (a)(1).
2. NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14508-14513 (1994).
3. *Women's Health: NIH Has Increased Its Efforts to Include Women in Research* (GAO/HEHS-00-96, May, 2000).
4. NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, NIH Guide for Grants and Contracts, Amended 2001.

For Additional Information on the implementation of the inclusion policy, please visit:

NIH Office of Extramural Research Inclusion of Women and Minorities Policy Implementation Website:  
[http://grants.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants.nih.gov/grants/funding/women_min/women_min.htm)

Revitalization Act of 1993, 42 USC 289 (a)(1): <http://grants.nih.gov/grants/guide/notice-files/not94-100.html>

NIH Policy on Reporting Racial and Ethnicity Data: Subjects in Clinical Research, NIH Guide for Grants and Contracts Web page: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>

Office of Research on Women's Health Website: <http://orwh.od.nih.gov/inclusion.html>

**Aggregate Enrollment Data Tables  
For Extramural and Intramural  
Research Protocols**

*Fiscal Year 2006 Summary Reports  
Twelve -year Trend Summary Reports*

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## Summary Report of NIH Inclusion Data

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### NIH AGGREGATE POPULATION DATA REPORTED IN FY2005 and FY2006

The following section is provided in order to guide consideration of the data especially in trend of human subjects participation in NIH-funded extramural and intramural clinical research. Because new studies are added each year and other studies are ending, it is not appropriate to compare data over time or to compare data with census population data. Looking at the trend data represents the best interpretation of the aggregate data. Data on inclusion is tabulated from human subject populations in NIH-defined Phase III clinical trials and other human subject research studies. NIH clinical research studies are determined in accordance with the NIH definition of clinical research to include, for example, non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, and database studies.

Analysis of aggregate NIH data on inclusion for FY2005 and FY2006 document that substantial numbers of women and men, especially non-minority men, and minorities have been included as research subjects in NIH-defined Phase III clinical trials and other human subject research studies during these fiscal years. Because the data included in the tables are aggregate data from across NIH, it does provide documentation of the tracking and inclusion across the NIH, and some degree of analysis of the data. But caution should be utilized in not over-interpreting the figures that are provided. The NIH Tracking and Inclusion committee has provided for the reader's interest, conclusions that can be reasonably drawn from the data.

Previous inclusion reports and aggregate enrollment figures for women, men and minority groups for FY1994 to the present can be found on the ORWH website at <http://orwh.od.nih.gov/inclusion.html>. For this report, the FY2005 and FY2006 data tables have been reformatted and some tables may vary slightly or differ from prior reported summary data in an effort to better clarify reporting.

### NIH CLINICAL RESEARCH: Fiscal Years 2005 and 2006

In FY2005, there were 14,798 extramural and intramural clinical research protocols, including Phase III and other clinical studies, of which 10,233 protocols reported human subject participation. Of these, 96.4% were domestic protocols and 3.6% were foreign protocols. Approximately 15.7 million participants were enrolled in extramural and intramural research protocols of which 80.6% were domestic participants and 19.4% were foreign participants. Of the 15.7 million participants, 60.4% were women, 37.8% were men and 1.8% did not provide sex identification. Further, 39.7% of the total participants, and 27.4% of the Domestic-only participants, were reported as minorities following the OMB categories for race and ethnicity. (Table 6)

Correspondingly, in FY2006 there were 15,320 extramural and intramural clinical research protocols, including Phase III and other clinical studies, of which 10,758 protocols reported human subject participation as noted in this report's trend summary tables. Of these, 95.7% were domestic protocols and 4.3% were foreign protocols. Approximately 14.8 million participants were enrolled in extramural and intramural research protocols of which 77.0% were domestic participants and 23.0% were foreign participants. Of the 14.8 million participants, 63.9% were women, 34.9% were men and 1.3% did not provide sex identification. Further, 43.1% of the total participants, and 28.9% of the Domestic-only participants, were reported as minorities following the OMB categories for race and ethnicity. (Table 1)



While the number of participants in all extramural and intramural clinical research decreased (15.7M in FY2005 and 14.8M in FY2006), there was no significant change in the ratio of women and men (60.4%F and 37.8%M in FY2005; and 63.9%F and 34.9%M in FY2006). One large study involving approximately 1.6M participants that ended in FY2005 and therefore was not included in the FY2005 figures, accounted for the net decreased number of participants reported.

#### NIH Defined Phase III Clinical Research: FY2005 and FY2006

In FY2005, there were 665 extramural and intramural Phase III clinical research protocols, of which 547 protocols reported human subject participation. Of these, 94.5% were domestic protocols and 5.5% were foreign protocols. Approximately 493,000 participants were enrolled in extramural and intramural Phase III research protocols of which 88.8% were domestic participants and 11.2% were foreign participants. Of the 493,000 participants, 59% were women, 40% were men and 1% did not provide sex identification. Further, 31.3% of the total participants, and 25.1% of the Domestic-only participants, in Phase III clinical research were reported as minorities following the 1997 OMB categories for race and ethnicity. (Table 7)

According to the trend summaries in this report, of the 210 extramural and intramural Phase III research protocols that report following the 1977 OMB standards, minority representation was highest for Blacks (not Hispanic) at 12.5% and lowest for American Indian/Alaska Natives at 0.4%. Hispanics represented approximately 6.9%, Asian/Pacific Islanders were 5.6% and Whites (not Hispanic) 73.2% of the participants. The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations with the 1977 OMB standards. (Table 7)

Furthermore, in FY2005, there were 337 extramural and intramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting by both race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 28.5% and lowest for Hawaiian/Pacific Islanders 0.3%. Asians represented 5.2%, American Indian/Alaska Natives 1.2% and Whites 57.3% of participants. Participants identifying as *More Than One Race* were 1.7% of the total number of participants. In addition, 5.8% did not identify a race category. Of the 337 extramural and intramural Phase III research protocols designating an ethnicity in FY2005, 88.6% of total participants identified as "Not Hispanic", 5.9% of the total participants identified as "Hispanic or Latino" and 5.5% of the total participants did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately. (Table 7)

Correspondingly, in FY2006 there were 760 extramural and intramural Phase III clinical research protocols, of which 624 protocols reported human subject participation as noted in this report's trend summary tables. Of these, 90.4% were domestic protocols and 9.6% were foreign protocols. Approximately 499,430 participants were enrolled in extramural and intramural Phase III research protocols of which 80.2% were domestic participants and 19.8% were foreign participants. Of the 499,430 participants, 62.9% were women, 36.0% were men and 1.1% did not provide sex identification. Further, 33.5% of the total participants, and 20.7% of Domestic-only participants, in Phase III clinical research were reported as minorities following the OMB categories for race and ethnicity. (Table 3)

According to the trend summaries in this report, of the 215 extramural and intramural Phase III research protocols that report following the 1977 OMB standards in FY2006, minority representation was highest for Blacks (not Hispanic) at 8.9% and lowest for American Indian/Alaska Natives at 0.4%. Hispanics represented approximately 4.1%, Asian/Pacific Islanders were 7.3% and Whites (not Hispanic) 76.5% of the participants. The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations with the 1977 OMB standards. (Table 7)

Moreover, in FY 2006, there were 409 extramural and intramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting by both race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 18.8% and lowest for Hawaiian/Pacific Islanders 0.2%. Asians represented 12.0%, American Indian/Alaska Natives 1.7% and Whites 47.0% of participants. Participants identifying as *More Than One Race* were 1.6% of the total number of participants. In addition, 18.7% did not identify a race category. Of the 409 extramural and intramural Phase III research protocols designating an ethnicity in FY2006, 75.0 % of total participants identified as “Not Hispanic”, 11.5 % of the total participants identified as “Hispanic or Latino”, and 13.5% of the total participants did not identify an ethnicity category. The racial distribution of the “Hispanic or Latino” participants is also provided separately. (Table 7)

While the number of participants in Phase III extramural and intramural clinical research slightly increased (493,000 in FY2005 and 499,430 in FY2006), there was no significant change in the ratio of women and men (59.0% F and 40.0%M in FY2005; and 62.9%F and 36.0%M in FY2006).

The following sections provide data on extramural research and intramural research separately.

#### **EXTRAMURAL CLINICAL RESEARCH: Fiscal Years 2005 and 2006**

In FY2005, there were 13,003 extramural clinical research protocols, including Phase III and other clinical studies, of which 8,763 protocols reported human subject participation as noted in this report’s trend summary tables. Approximately 13.8 million participants were enrolled in extramural research protocols of which 62.1% were women, 36.1% were men and 1.9% did not provide sex identification. (See 2006 Report, Table 2 and Appendix table 3A)

Correspondingly, in FY2006, there were 13,522 extramural clinical research protocols, including Phase III and other clinical studies, of which 9,235 protocols reported human subject participation. Of these, 95.7% were domestic protocols and 4.3% were foreign protocols. Approximately 13.02 million participants were enrolled in extramural research protocols of which 76.6% of the total enrollment is domestic participants and 23.4% of the total enrollment is foreign participants. Of the 13.02 million participants, 65% were women, 33.8% were men and 1.2% did not provide sex identification. Further, 45.9% of the total participants were reported as minorities following the OMB categories for race and ethnicity. (Table 2 and Appendix Table 3A)

While the number of participants in all extramural clinical research decreased (13.8 million in FY2005 and 13.02 million in FY2006), there was no significant change in the ratio of women and men (62%F and 36%M in FY2005 and 65%F and 34%M). However, when sex-specific studies were excluded, the proportions of women and men in all extramural clinical research were proportional to the percentages of the general population. (52.4%F and 45.8 % M)

#### NIH Defined Phase III Extramural Clinical Research: FY2005 and FY2006

In FY2005 of the 273 extramural Phase III research protocols that report following the 1977 OMB standards, minority representation was highest for Blacks (not Hispanic) at 12.9% and lowest for American Indian/Alaska Natives at 0.4%. Hispanics represented approximately 7%, Asian/Pacific Islanders were 1.9% and Whites (not Hispanic) 76% of the participants. The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations with the 1977 OMB standards. (See 2006 Report)

In FY2006 there were 707 extramural Phase III clinical research protocols, of which 580 protocols reported human subject participation as noted in this report’s trend summary tables. Approximately

467,954 participants were enrolled in extramural Phase III research protocols of which 63.5% were women, 35.4% were men and 1% did not provide sex identification. (Table 4 and Appendix Table 5A)

According to trend summaries in the 2006 report, in FY2005, there were 621 extramural Phase III clinical research protocols, of which 511 protocols reported human subject participation. Of these, 88.5% were domestic protocols and 4.9% were foreign protocols. Approximately 465,956 participants were enrolled in extramural Phase III research protocols of which 86% of total enrollment is domestic participants and 8.6% of total enrollment is foreign participants. Of the 465,956 participants, 59.5% were women, 39.5% were men and 1% did not provide sex identification. Further, 29.9% of the total participants in Phase III clinical research were reported as minorities following the OMB categories for race and ethnicity. (See 2006 Report, Table 4 and Appendix Table 5A)

Correspondingly, in FY2006, there were 382 extramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 19.7% and lowest for Hawaiian/Pacific Islanders 0.2%. Asians represented 12.67%, American Indian/Alaska Natives 1.8% and Whites 46.32% of participants. Participants identifying as *More Than One Race* were 15% of the total number of participants. In addition, 17.8 % did not identify a race category. Of the 382 extramural Phase III research protocols designating an ethnicity in FY 2006, 75.8 % of total participants identified as “Not Hispanic”, 11.14 % of the total participants identified as “Hispanic or Latino”, and 13.1 % of the total participants did not identify an ethnicity category. The racial distribution of the “Hispanic or Latino” participants is also provided separately. (Appendix Table 5A)

In FY 2005, there were 319 extramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 30.00 % and lowest for Hawaiian/Pacific Islanders 0.28%. Asians represented 5.44%, American Indian/Alaska Natives 1.30% and Whites 55.75% of participants. Participants identifying as *More Than One Race* were 1.56% of the total number of participants. In addition, 5.66 % did not identify a race category. Of the 319 extramural Phase III research protocols designating an ethnicity in FY2005, 88.7 % of total participants identified as “Not Hispanic”, 5.98 % of the total participants identified as “Hispanic or Latino”, and 5.32 % of the total participants did not identify an ethnicity category. The racial distribution of the “Hispanic or Latino” participants is also provided separately. (See 2006 Report, Appendix Table 5A)

Of the 192 extramural Phase III research protocols that report following the 1977 OMB standards, minority representation was highest for Blacks (not Hispanic) at 13.03 and lowest for American Indian/Alaska Natives at 0.4%. Hispanics represented approximately 7.23%, Asian/Pacific Islanders were 1.81% and Whites (not Hispanic) 76.1% of the participants. The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations with the 1977 OMB standards. (See 2006 Report, Appendix Table 5A)

While the number of participants in Phase III extramural clinical research protocols slightly increased, there was also some change in the ratio of women and men (59.5%F and 39.5%M in FY2005 and 63.5 %F and 35.4% M in FY2006).

#### **INTRAMURAL CLINICAL RESEARCH: Fiscal Years 2005 and 2006**

Substantial numbers of women and minorities were included in NIH intramural studies in FY 2005 and FY2006.

In FY2005, there were 1,795 intramural clinical research protocols, including Phase III and other clinical studies, of which 1,470 protocols reported human subject participation. Of these, 13.7% of the total protocols were domestic protocols and 0.7% of the total protocols were foreign protocols. Approximately 1.94 million participants were enrolled in intramural research protocols of which 10.4% of the total enrollment is domestic participation and 1.9% of the total enrollment is foreign participation. Of the 1.94 million participants, 48.7% were women, 50.5% were men and 0.79% did not provide sex identification. (See 2006 Report, Table 2 and Appendix Table 7A)

In FY2005, approximately 1.94 million participants were reported in all intramural research including Phase III clinical trials, and other clinical studies. Of the 733 intramural research protocols that report data following the 1977 OMB standards, minority representation was highest for Asian/Pacific Islanders at 17.8% and lowest for American Indian/Alaska Natives at 1.8%. Blacks (not-Hispanic) represented 7.5%, Hispanics 4.7%; and Whites (not Hispanic) 60.9% of the intramural research study population. The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations with the 1977 OMB standards. (See 2006 Report, Appendix Table 7A)

For the 737 intramural clinical research studies that reported data following the current 1997 OMB standards in FY 2005 the largest racial minority group was Blacks at 4.74% and the smallest racial minority group was Hawaiian/Pacific Islanders at 0.19%. Asians represented 3.1%, American Indian/Alaska Natives 0.42% and Whites 86.2% of participants in all intramural clinical research. Approximately 1% of participants reported *More Than One Race* as their racial category. In addition, 4.42 % did not identify a race category. Of the 737 intramural research protocols following the current 1997 OMB standards designating an ethnicity in FY 2005, 95.58 % of total participants identified as “Not Hispanic”, 2.10 % of the total participants identified as “Hispanic or Latino”, and 2.32 % of the total participants did not identify an ethnicity category. The racial distribution of the “Hispanic or Latino” participants is also provided separately. (See 2006 Report, Appendix 7A)

Correspondingly, in FY2006 there were 1,798 intramural clinical research protocols, including Phase III and other clinical studies, of which 1,523 protocols reported human subject participation. Approximately 1.8 million participants were enrolled in intramural research protocols of which 55.4% were women, 43.0% were men and 1.6% did not provide sex identification. (See Table 2 and Appendix Table 7A)

In FY 2006, approximately 1.8 million participants were reported in all intramural research including Phase III clinical trials, and other clinical studies. Of the 590 intramural research protocols that report data following the 1977 OMB standards, minority representation was highest for Asian/Pacific Islanders at 19.9% and lowest for American Indian/Alaska Natives at 3.3%. Blacks (not-Hispanic) represented 7.2%, Hispanics 3.5%; and Whites (not Hispanic) 62.0% of the intramural research study population. The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations with the 1977 OMB standards. (See Appendix Table 7A)

For 933 intramural clinical research studies that reported data following the current 1997 OMB standards in FY 2006, the largest racial minority group was Asian at 8.6 % and the smallest racial minority group was Hawaiian/Pacific Islanders at 0.07%. Blacks represented 5.0%, American Indian/Alaska Natives 0.4% and Whites 79.1% of participants in all intramural clinical research. Approximately 0.8% of participants reported *More Than One Race* as their racial category. In addition, 6.0 % did not identify a race category. Of the 933 intramural research protocols following the current 1997 OMB standards designating an ethnicity in FY2006, 91.3 % of total participants identified as “Not Hispanic”, 4.1 % of the total participants identified as “Hispanic or Latino”, and 4.6 % of the total participants did not identify an ethnicity category. The racial distribution of the “Hispanic or Latino” participants is also provided separately. (See Appendix Table 7A)

There was an increase in female participants from 48.7% to 55.4% and a corresponding decrease in male participants from 50.5% to 43.0%. The number of participants in all intramural clinical research decreased slightly from 1.9M to 1.8M from FY2005 to FY2006.

NIH Defined Phase III Intramural Clinical Research: FY2005 and FY2006

In FY2005, there were 44 intramural Phase III clinical research protocols, of which 36 protocols reported human subject participation. Of these, 6% of the total protocols is domestic protocols and 0.5% of the total protocols is foreign protocols. Approximately 27,044 participants were enrolled in intramural Phase III research protocols of which 2.86% of total enrollment is domestic participation and 2.6% of total enrollment is foreign participation. Of the 27,044 participants, 50.5% were women, 49.5% were men and 0% did not provide sex identification. Further, 54.5% of the total participants in Phase III clinical research were reported as minorities following the OMB categories for race and ethnicity. (See 2006 Report, Table 4 and Appendix Table 9A)

Correspondingly, in FY2006 there were 53 intramural Phase III clinical research protocols, of which 44 protocols reported human subject participation. Of these, 6.3% of the total number of protocols is domestic and 0.7% of the total number of protocols is foreign. Approximately 31,476 participants were enrolled in intramural Phase III research protocols of which 2.34% of the total enrollment is domestic participants and 3.5% are foreign participants. Of the 31,476 participants, 54% were women, 46% were men and 0% did not provide sex identification. Further, 54% of total participants in Phase III clinical research protocols were reported as minorities following the OMB categories for race and ethnicity. (Table 4 and Appendix Table 9A)

There was a small increase in women (50.5% to 54.0%) and corresponding decrease in men (49.5% to 46.0%). The number of participants in Phase III intramural clinical research increased from 27,044 to 31,476.

#### TREND REPORT ON NIH AGGREGATE POPULATION DATA: FY1995 – FY2006

The following section is a new addition to the Annual Comprehensive report. Tables 5-11 provide trend data on the collection and reporting of human subject participation in NIH funded clinical research, which includes Phase III clinical studies; trend data are also provided in terms of foreign and domestic participation. Trend data vary over time because the data for each year represent the net total of data resulting from: (1) studies continuing from the prior year; (2) the addition of new studies reported; and (3) the subtraction of studies that are no longer reported.

Table 5 is a twelve year summary report showing a steady increase in the number of protocols and enrollment. The number of protocols with enrollment increased from 3,188 in FY1995 to 10,758 in FY2006 – a 3.4 fold increase. Reported enrollment increased from approximately 1.0 million (FY1995) to 14.8 million (FY2006) – a 14.5 fold increase; minority enrollment increased from approximately 0.4 million (FY2002) to 6.4 million (FY2006) – a 17.1 increase in minority representation in NIH clinical research. Over the last five years, the total number of protocols reported with enrollment data has leveled off at about 10,000 protocols per year.

With the deployment of a new population tracking system in 2002 and the requirement to report data using a new format, NIH was able to report domestic and foreign data in a better way. Thus, trend data are now available for domestic and foreign protocols and participation beginning in FY2002. Domestic enrollment increased from 10.2 million (FY2002) to 11.4 million (FY2006) – a 1.1 fold increase. Foreign enrollment increased from 0.9 million (FY2002) to 3.4 million (FY2006) – a 3.6 fold increase. Overall, the total enrollment has increased with domestic participation averaging between 75.9-91.5% and foreign participation averaging between 8.5-24.1%. In FY2006, domestic and foreign enrollment was 77.0% and 23.0% respectively.

Table 6 is a summary report of all extramural and intramural clinical research by sex/gender and minority representation following the old and new data formats for domestic and foreign studies. The report demonstrates that female participation in all extramural and intramural research generally averaged between 51.7% and 63.9%, male participation in all extramural and intramural research averaged between 34.9% and 45.0%. Overall minority participation in all extramural and intramural clinical research averaged between 31% and 43%. Table 6E provides a comparison of domestic and foreign participation between FY2002 and FY2006. The vast majority of protocols are domestic (~94%-96%) of the total clinical research protocols. While the number of foreign protocols has increased, they incorporate only about 4%-6% of the total clinical research protocols with enrollment. Table 6F shows domestic and foreign enrollment for the five-year period. Domestic minority enrollment varied between 24.1% and 28.9% of total domestic participation, while foreign minority enrollment varied between 82.2% and 90.9% of total foreign participation.

Table 7 is a summary report of NIH-funded Phase III extramural and intramural clinical research by sex/gender and minority representation following the old and new data reporting formats for domestic and foreign studies. The report demonstrates that female participation in NIH funded Phase III extramural and intramural clinical research generally averaged between 54.1% and 74.8% and male participation in NIH-funded Phase III extramural and intramural clinical research averaged between 24.3% and 44.6%. Overall minority participation in NIH-funded Phase III extramural and intramural clinical research increased from 26.9% to 33.5%. Table 7E provides a comparison of domestic and foreign participation between FY2002 and FY2006. The vast majority of protocols are domestic (75.5% and 95.8%) of the total clinical research protocols. While the number of foreign protocols has decreased, they incorporate only about 4.2%-9.6% of the total clinical research protocols with enrollment in the last three years. Table 7F shows domestic and foreign enrollment for the five-year period. Domestic minority enrollment varied between 20.7% and

25.4% of total domestic participation, while foreign minority enrollment in NIH-funded Phase III clinical research varied between 48.4% and 85.2% of total foreign participation. Comparing both domestic and foreign Phase III enrollment over the five year period shows that the small percentage of foreign protocols (9.6%) in FY2006 account for a significant proportion (19.8%) of the total enrollment.

Tables 8-11 provide summary reports of domestic and foreign participation for NIH funded clinical research and NIH-funded Phase III clinical research. For extramural and intramural clinical research, domestic participants enrolled in domestic protocols, female participation averaged between 61.8 and 67.3% while male participation averaged between 31.2 and 36.9%. (*Table 8*) For NIH-funded Phase III extramural and intramural clinical research, domestic participants enrolled in domestic protocols, female participation averaged between 54.8 and 64.6% while male participation averaged between 34.4 and 44.8%. (*Table 9*) For all extramural and intramural clinical research, foreign participants enrolled in foreign protocols, female participation varied from 39.2% to 58.5% while male participation varied from 40.1% to 60.4%. (*Table 10*) For NIH-funded Phase III extramural and intramural clinical research, foreign participants enrolled in foreign protocols, female participation varied from 47.4% to 56.7% while male participation varied from 42.0% to 52.5%. (*Table 11*)



**Table 1. Summary of NIH Clinical Research Reported In FY2006: Total Number of Protocols and Enrollment By Sex and Domestic versus Foreign Protocols**

<b>1A. PROTOCOLS REPORTED</b>	<b>Total All Clinical Studies*</b>	<b>Domestic</b>	<b>%</b>	<b>Foreign</b>	<b>%</b>
Protocols with Enrollment	10,758	10,294	95.7%	464	4.3%
%	70.2%	70.3%		69.3%	
Protocols with zero enrollment. Enrollment data has not yet been submitted	4,562	4,356	95.5%	206	4.5%
	29.8%	29.7%		30.7%	
<b>Total Number of Protocols</b>	<b>15,320</b>	<b>14,650</b>	<b>95.6%</b>	<b>670</b>	<b>4.4%</b>
%	100.0%	100.0%		100.0%	

See Table 1A comments on next page.

<b>1B. ENROLLMENT REPORTED</b>	<b>Total All Clinical Studies*</b>	<b>Domestic</b>	<b>%</b>	<b>Foreign</b>	<b>%</b>
Females Enrolled	9,473,273	7,684,453	81.1%	1,788,820	18.9%
%	63.9%	67.3%		52.5%	
Males Enrolled	5,172,205	3,566,577	69.0%	1,605,628	31.0%
%	34.9%	31.2%		47.2%	
Sex of Subjects is Unknown	185,452	174,671	94.2%	10,781	5.8%
%	1.3%	1.5%		0.3%	
<b>Total Subjects Enrolled</b>	<b>14,830,930</b>	<b>11,425,701</b>	<b>77.0%</b>	<b>3,405,229</b>	<b>23.0%</b>
%	100.0%	100.0%		100.0%	

See Table 1B comments on next page.

<b>1C. MINORITY ENROLLMENT REPORTED</b>	<b>Total All Clinical Studies*</b>	<b>Domestic</b>	<b>%</b>	<b>Foreign</b>	<b>%</b>
<b>Minority Total**</b>	<b>6,388,316</b>	<b>3,301,135</b>	<b>51.7%</b>	<b>3,087,181</b>	<b>48.3%</b>
<b>% Minority Enrollment</b>	<b>43.1%</b>	<b>28.9%</b>		<b>90.7%</b>	

See Table 1C omments on next page.

\* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. "Total All Clinical Studies" includes NIH Defined Phase III Clinical Trials.

\*\* See Appendix H for the Race and Ethnicity categories included in Minority Enrollment Data from the 1977 and 1997U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

NOTE: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

**COMMENTS**

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**Table 1. Summary of NIH Clinical Research Reported In FY2006: Total Number of Protocols and Enrollment By Sex and Domestic versus Foreign Protocols**

**Table 1A: Total Number of Protocols**

1. The total number of protocols reported in the NIH database in FY2006 was 15,320; of these, 10,758 (70.2%) reported subject enrollment.
2. Subsequent Tables reporting "Enrollment Reported" are based on the 10,758 protocols reporting subject enrollment, or a defined subset.
3. Protocols with zero enrollment (data not yet submitted) are not included in subsequent tables reporting "Enrollment reported."

**Total Domestic Protocols**

4. Domestic protocols made up the vast majority of protocols (14,650; 95.6%); of these, 10,294 (70.3%) reported domestic subject enrollment.
5. Clinical Research involving both domestic and foreign sites are reported as separate domestic and foreign protocols in subsequent tables.

**Table 1B: Total Enrollment Reported**

1. The total "Enrollment Reported" in the NIH database in FY2006 was 14,830,930 subjects in 10,758 protocols with enrollment.
2. Females made up 63.9% (9.5M) of the total subjects enrolled, while Males made up 31.2%(5.2M), with 1.3% unknown.

**Total Domestic Enrollment Reported**

3. The total Domestic Enrollment reported was 11,425,701 (77%).
4. Females made up 67.3%(7.7M) of the domestic subjects enrolled, while Males made up 31.2%(3.56M), with 1.5%(.17M) unknown.

**Table 1C Comments: Minority Enrollment Reported**

1. Minorities made up 43.1% (6.4M) of the total subjects enrolled.
2. Minorities made up 28.9%(3.3M) of the Domestic Enrollment.
3. The Total Minority Enrollment was made up of 51.7% Domestic and 48.3% Foreign enrollment The small percentage of foreign protocols (4.0%) account for a significant proportion (48.3%) of the total minority enrollment.

**Table 2: Overview of NIH Extramural and Intramural Clinical Research Reported in FY2006: Number of Sex-Specific Protocols, and Domestic versus Foreign Protocols**

2A. PROTOCOLS REPORTED	Total All Clinical Studies	Domestic				Foreign			
		Extramural	%	Intramural	%	Extramural	%	Intramural	%
Number of Protocols reporting females only	1,338	1,162	86.8%	124	9.3%	46	3.4%	6	0.4%
%	8.7%	9.0%		7.3%		8.1%		6.1%	
Number of Protocols reporting males only	581	468	80.6%	93	16.0%	17	2.9%	3	0.5%
%	3.8%	3.6%		5.5%		3.0%		3.0%	
Number of Protocols with Both Female and Male Enrollment (excluding sex-specific protocols)	8,839	7,221	81.7%	1,226	13.9%	321	3.6%	71	0.8%
%	57.7%	55.8%		72.2%		56.2%		71.7%	
<b>Total Number of Protocols with Enrollment</b>	<b>10,758</b>	<b>8,851</b>	<b>82.3%</b>	<b>1,443</b>	<b>13.4%</b>	<b>384</b>	<b>3.6%</b>	<b>80</b>	<b>0.7%</b>
%	70.2%	68%		84.9%		67.3%		80.8%	
Number of Protocols with zero enrollment. Enrollment data has not yet been submitted.	4,562	4,100	89.9%	256	5.6%	187	4.1%	19	0.4%
%	29.8%	31.7%		15.1%		32.7%		19.2%	
<b>Total Number of Protocols</b>	<b>15,320</b>	<b>12,951</b>	<b>84.5%</b>	<b>1,699</b>	<b>11.1%</b>	<b>571</b>	<b>3.7%</b>	<b>99</b>	<b>0.6%</b>
%	100.0%	100.0%		100.0%		100.0%		100.0%	

See Table 2A comments on next page.

2B. ENROLLMENT REPORTED	Total All Clinical Studies	Domestic				Foreign			
		Extramural	%	Intramural	%	Extramural	%	Intramural	%
In Protocols reporting females only	4,120,055	3,678,382	89.3%	202,024	4.9%	115,369	2.8%	124,280	3.0%
%	27.8%	36.9%		13.9%		3.8%		35.0%	
In Protocols reporting males only	336,717	274,774	81.6%	3,294	1.0%	32,552	9.7%	26,097	7.8%
%	2.3%	2.8%		0.2%		1.1%		7.3%	
In Protocols excluding female-only and male-only enrollment protocols	10,374,158	6,018,281	58.0%	1,248,946	12.0%	2,902,088	28.0%	204,843	2.0%
%	69.9%	60.4%		85.9%		95.2%		57.7%	
<b>Enrollment Totals for all studies</b>	<b>14,830,930</b>	<b>9,971,437</b>	<b>67.2%</b>	<b>1,454,264</b>	<b>9.8%</b>	<b>3,050,009</b>	<b>20.6%</b>	<b>355,220</b>	<b>2.4%</b>
%	100.0%	100.0%		100.0%		100.0%		100.0%	

See Table 2B Comments on next page.

2C. MINORITY ENROLLMENT REPORTED**	Total All Clinical Studies	Domestic				Foreign			
		Extramural	%	Intramural	%	Extramural	%	Intramural	%
<b>Minority Totals for all studies</b>	<b>6,388,316</b>	<b>3,102,731</b>	<b>48.6%</b>	<b>198,404</b>	<b>3.1%</b>	<b>2,878,826</b>	<b>45.1%</b>	<b>208,355</b>	<b>3.3%</b>
% Minority enrollment	43.1%	31.1%		13.6%		94.4%		58.7%	

See Table 2C comments on next page.

\*\*See Appendix H for the Race and Ethnicity categories included in Minority Enrollment Data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

**COMMENTS**

**Table 2: Overview of NIH Extramural and Intramural Clinical Research Reported in FY2006: Number of Sex-Specific Protocols, and Domestic versus Foreign Protocols**

**Table 2A Total Number of Protocols with Enrollment**

- 1. Female Only Protocols:** There were 1,338 protocols reporting females only, representing 12.4 % (1338/10,758) of protocols with enrollment.  
90% were Extramural projects(1,162+46); 10% were NIH intramural projects(124+6).  
96% were Domestic protocols(1162+124);4% were Foreign protocols(40+6).
- 2. Male Only Protocols:** There were 581 protocols reporting males only, representing 5% (558/10,758) of protocols with enrollment.  
83 % were Extramural projects(468+17); 17% were NIH intramural projects(93+3)  
97% were Domestic protocols(468+93); 3 % were Foreign protocols(17+3).
- 3. Protocols Reporting Both Females and Males (excluding sex-specific protocols):** There were 8,839 protocols reporting both female and male participants representing 82% (8,839/10,758) of the total number of protocols.  
85% were Extramural projects(7,221+321); 15% were NIH intramural projects(1,226+71)

**Table 2B Total Enrollment Reported**

- 1. In Female Only Protocols:** There were approximately 4.1 M females, representing 28% of total enrollment.  
92.1% were in Extramural projects; 7.9% were in NIH intramural projects.  
94.2% were in Domestic protocols; 5.8% were in Foreign protocols.
- 2. In Male Only Protocols:** There were approximately 336,717 males, representing 2.3% of total enrollment.  
91.3% were in Extramural projects; 18.8% were in NIH intramural projects.  
82.6% were Domestic in protocols 17.4 % were Foreign protocols.
- 3. In Protocols Reporting Both Females and Males (excluding sex-specific studies):** There were approximately 10,374,158 subjects, representing 70% of total enrollment.  
86% were in Extramural projects;14% were in NIH intramural projects.  
70% were in Domestic protocols; 30% were in Foreign protocols.  
96% were Domestic protocols(7,221+1,226);4% were Foreign protocols(321+71).

**Table 2C Minority Enrollment Reported**

- 1. Total Minority Enrollment: 43.1% of Total Enrollment (14.8M).**  
Total Minority Enrollment, Domestic only: 28.9% (3,301,135/11,425,701)  
Total Domestic Minority Enrollment: 51.7% (3,301,135/6,388,316)  
Total Foreign Minority Enrollment: 48.3% (3,087,181/6,388,316)  
Total Extramural projects Minority enrollment: 40.33% (5,981,557/14,830,930)  
Total Intramural Projects Minority enrollment: 2.74% (406,759/14,830,930)

**Table 3. Summary of NIH Phase III Clinical Research Reported In FY2006: Total Number of Protocols and Enrollment by Sex, and Domestic versus Foreign Protocols**

	Total of Phase III Clinical Trials*	Domestic	%	Foreign	%
<b>3A. PROTOCOLS REPORTED</b>					
Protocols with Enrollment	624	564	90.4%	60	9.6%
%	82.1%	82.0%		83.3%	
Protocols with zero enrollment. Enrollment data has not yet been submitted.	136	124	91.2%	12	8.8%
	17.9%	18.0%		16.7%	
<b>Total Number of Protocols</b>	<b>760</b>	<b>688</b>	<b>90.5%</b>	<b>72</b>	<b>9.5%</b>
%	100.0%	100.0%		100.0%	

See Table 3A comments on next page.

	Total of Phase III Clinical Trials*	Domestic	%	Foreign	%
<b>3B. ENROLLMENT REPORTED</b>					
Females Enrolled	314,066	258,467	82.3%	55,599	17.7%
%	62.9%	64.6%		56.1%	
Males Enrolled	179,975	137,621	76.5%	42,354	23.5%
%	36.0%	34.4%		42.7%	
Sex of Subjects is Unknown	5,389	4,209	78.1%	1,180	0.0%
%	1.1%	1.1%		1.2%	
<b>Total Subjects Enrolled</b>	<b>499,430</b>	<b>400,297</b>	<b>80.2%</b>	<b>99,133</b>	<b>19.8%</b>
%	100.0%	100.0%		100.0%	

See Table 3B comments on next page.

	Total of Phase III Clinical Trials*	Domestic	%	Foreign	%
<b>3C. MINORITY ENROLLMENT REPORTED**</b>					
Minority Total for all Phase III studies	167,446	83,034	49.6%	84,412	50.4%
	33.5%	20.7%		85.2%	

See Table 3C on next page.

\* An NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

\*\*See Appendix H for the Race and Ethnicity categories included in Minority Enrollment Data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

NOTE: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

**COMMENTS**

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**Table 3. Summary of NIH Phase III Clinical Research Reported In FY2006: Total Number of Protocols and Enrollment by Sex, and Domestic versus Foreign Protocols**

**Table 3A Total Number of Protocols**

1. The total number of NIH defined Phase III Clinical protocols reported in the NIH database in FY2006 was 760; of these, 624(82.1%) reported subject enrollment.
2. Subsequent Tables reporting "Enrollment Reported" are based on the 624 protocols reporting subject enrollment, or a defined subset.
3. Protocols with zero enrollment (data not yet submitted) are not included in subsequent tables reporting "Enrollment reported."

**Total Domestic Protocols**

4. Domestic protocols made up the vast majority of protocols (688; 90.5%); of these 564(82%) reported domestic subject enrollment.
5. Clinical Research involving both domestic and foreign sites are reported as separate domestic and foreign protocols in subsequent tables.

**Table 3B Total Enrollment Reported**

1. The total "Enrollment Reported" in NIH Defined Phase III Protocols in the NIH database in FY2006 was 499,430 subjects in 624 protocols.
2. Females made up 62.9% (314,068) of the total subjects enrolled, while Males made up 36.0%(179,975), with 1.1%(5,389) unknown.
3. Minorities made up 33.5% (167,446) of the total subjects enrolled.

**Total Domestic Enrollment Reported**

4. The total Domestic Enrollment reported was 400,297(80.2%).
5. Females made up 64.6%(258,467) of the domestic subjects enrolled, while Males made up 34.4%(137,621), with 1.1%(4,209) unknown.

**Table 3C Minority Enrollment Reported**

1. Minorities made up 33.5% of total subjects enrolled.
2. Minorities made up 20.7%(83,034) of the Domestic Enrollment (400,297).
3. The Total Minority Enrollment was made up of 49.6% Domestic and 50.4% Foreign enrollment.

**Table 4. Overview of NIH Phase III Extramural and Intramural Clinical Research Reported In FY2006: Number of Sex-Specific Protocols and Enrollment, and Domestic versus Foreign Protocols**

	Total of Phase III Clinical Trials*	Domestic				Foreign			
		Extra-mural	%	Intra-mural	%	Extra-mural	%	Intra-mural	%
<b>4A. PROTOCOLS REPORTED</b>									
Protocols reporting female only	118	101	85.6%	2	1.7%	14	11.9%	1	0.8%
%	15.5%	15.8%		4.2%		20.9%		20.0%	
Protocols reporting male only	47	39	83.0%	4	8.5%	4	8.5%	0	0.0%
%	6.2%	6.1%		8.3%		6.0%		0.0%	
Protocols with Both Female and Male Enrollment (excluding sex-specific protocols)	459	384	83.7%	34	7.4%	38	8.3%	3	0.7%
%	60.4%	60.0%		70.8%		56.7%		60.0%	
<b>Total Number of Protocols with Enrollment</b>	<b>624</b>	<b>524</b>	<b>84.0%</b>	<b>40</b>	<b>6.4%</b>	<b>56</b>	<b>9.0%</b>	<b>4</b>	<b>0.6%</b>
%	82.1%	82%		83.3%		83.6%		80.0%	
Phase III Protocols with zero enrollment. Enrollment data has not yet been submitted.	136	116	85.3%	8	5.9%	11	8.1%	1	0.0%
%	17.9%	18.1%		16.7%		16.4%		20.0%	
<b>Total Number of Phase III Protocols</b>	<b>760</b>	<b>640</b>	<b>84.2%</b>	<b>48</b>	<b>6.3%</b>	<b>67</b>	<b>8.8%</b>	<b>5</b>	<b>0.7%</b>
%	100.0%	100.0%		100.0%		100.0%		100.0%	

See Table 4A comments on next page.

	Total of Phase III Clinical Trials*	Domestic				Foreign			
		Extra-mural	%	Intra-mural	%	Extra-mural	%	Intra-mural	%
<b>4B. ENROLLMENT REPORTED</b>									
Protocols reporting female only	167,624	148,185	88.4%	4	0.0%	17,195	10.3%	2240	1.3%
%	33.6%	38.4%		0.0%		21.0%		13.0%	
Protocols reporting male only	27,723	23,312	84.1%	177	0.6%	4,234	15.3%	0	0.0%
%	5.6%	6.0%		1.2%		5.2%		0.0%	
Protocols excluding female-only and men-only enrollment protocols	304,083	214,619	70.6%	14,000	4.6%	60,409	19.9%	15,055	5.0%
%	60.9%	55.6%		98.7%		73.8%		87.0%	
<b>Total Subjects Enrolled</b>	<b>499,430</b>	<b>386,116</b>	<b>77.3%</b>	<b>14,181</b>	<b>2.84%</b>	<b>81,838</b>	<b>16.39%</b>	<b>17,295</b>	<b>3.5%</b>
%	100.0%	100.0%		100.0%		100.0%		100.0%	

See Table 4B comments on next page.

	Total of Phase III Clinical Trials*	Domestic				Foreign			
		Extra-mural	%	Intra-mural	%	Extra-mural	%	Intra-mural	%
<b>4C. MINORITY ENROLLMENT REPORTED**</b>									
Minority Total for all Phase III studies	167,446	80,622	48.1%	2,412	1.4%	69,820	41.7%	14,592	8.7%
%	33.5%	20.9%		17.0%		85.3%		84.4%	

See Table 4C comments on next page.

\* An NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

\*\*See Appendix H for the Race and Ethnicity categories included in Minority Enrollment Data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.



## COMMENTS

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### Table 4. Overview of NIH Phase III Extramural and Intramural Clinical Research Reported In FY2006: Number of Sex-Specific Protocols and Enrollment, and Domestic versus Foreign Protocols

#### Table 4A Total Number of Protocols with Enrollment

- 1. Female Only:** There were 118 protocols reporting females only, representing 19 % (118/624) of protocols with enrollment, and 15.5% of the Total Number of Protocols.  
97% were Extramural projects (115); 3% were NIH intramural projects (3).  
87% were Domestic protocols (103); 13% were Foreign protocols (15).
- 2. Male Only:** There were 47 protocols reporting males only, representing 8% (47/624) of protocols with enrollment, and 6.2% of the Total Number of Protocols.  
91% were Extramural projects (43); 9% were NIH intramural projects (4).  
91% were Domestic protocols (43); 9% were Foreign protocols (4).
- 3. Protocols Reporting Both Females and Males (excluding sex-specific protocols):** There were 459 protocols reporting both males and females representing 60.4 % of the total number of protocols.  
92.0% were Extramural projects (422); 8.0% were NIH intramural projects (37).  
91% were Domestic protocols (418); 9.0% were Foreign protocols (41).

#### Table 4B Total Enrollment Reported

- 1. In Female Only Protocols:** There were approximately 167,624 females, representing 33.6% of total enrollment.  
98.7% (165,380) were in Extramural projects; 1.3% (2,244) were in NIH intramural projects.  
88.4% (148,189) were in Domestic protocols; 11.67% (19,435) were in Foreign protocols.
- 2. In Male Only Protocols:** There were approximately 27,723 males, representing 5.6% of total enrollment.  
99.4% (27,546) were in Extramural projects; 0.6% (177) were in NIH intramural projects.  
84.7% (23,489) were in Domestic protocols; 15.3% (4,234) were in Foreign protocols.
- 3. Protocols Reporting Both Females and Males (excluding sex-specific protocols):** There were approximately 304,083 subjects, representing 60.9% of total enrollment.  
90.45% (275,028) were in Extramural projects; 9.55% (29,055) were in NIH intramural projects.  
75.2% (228,619) were in Domestic protocols; 24.8% (75,464) were in Foreign protocols.

#### Table 4C Minority Enrollment Reported

- 1. Total Minority Enrollment was 33.5% (167,446) of Total Enrollment (499,430).**  
Total Minority enrollment, *Extramural* protocols (150,442), was 30.12% of Total Enrollment (499,430) and 89.9% of Total Minority Enrollment (167,446).  
Total Minority enrollment, *Intramural* Projects (17,004), was 3.4% of Total Enrollment (499,430) and 10.15% of Total Minority Enrollment (167,446).
- 2. Total Minority Enrollment, Domestic only (83,034), was 20.7% of total Domestic Enrollment (400,297) and 49.6% of Total Minority Enrollment (167,446).**
- 3. Total Minority Enrollment, Foreign (84,412), was 85.15% of Total Foreign Enrollment (99,133) and 50.4% of Total Minority Enrollment (167,446).**

Table 5. NIH Twelve Year Trends for Protocol and Enrollment Data: 1995-2006\*

5A. Twelve Year Increases in Protocols and Enrollment Data				
FY Reported	1995		2006	Relative Increase, 2006 / 1995
Total Protocols with Enrollment	3,188		10,758	3.4
Total Enrollment	1,021,493		14,830,930	14.5
Total Minorities	374,433		6,388,316	17.1
% of Minority	36.7%		43.1%	1.2
FY Reported	2002		2006	Relative Increase 2006 / 2002
Total DOMESTIC Enrollment data	10,192,401		11,425,701	1.1
Total FOREIGN Enrollment	946,083		3,405,229	3.6

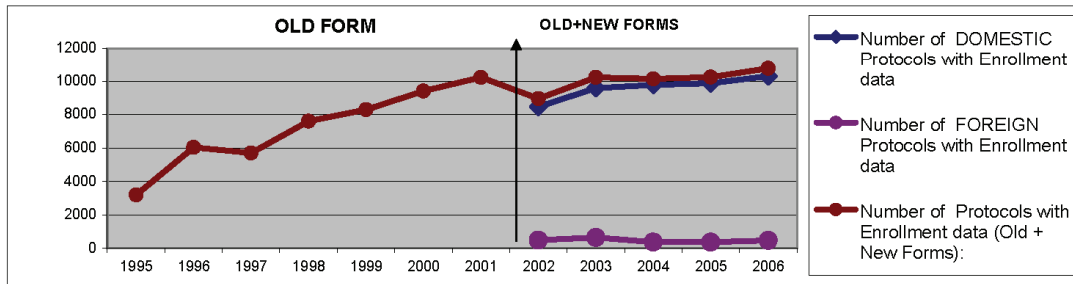
**Table 5A Comments:**

1. There was a 3.4 fold increase in protocols with enrollment reported from 1995 to 2006, from 3,188 protocols to 10,758 protocols.
2. There was a 14.5 fold increase in enrollment reported from 1995 to 2006, from approximately 1M to 15 M.
3. There was a 17.1 fold increase in minority enrollment from 1995 to 2006, from approximately 0.4 M to 6.4 M.
4. Domestic and Foreign data were reported for FY 2002-2006, and showed 1.1 fold increase in domestic enrollment (from 10.2M to 11.4M) and a 3.6 fold increase in foreign enrollment (from 0.95M to 3.4M).
5. See Table 6 for 12 year enrollment totals 1995-2006.

\*NOTE: Trend data varies over time because the data for each year represent the net total of data resulting from (1) studies continuing from the prior year; (2) the addition of new studies reported and (3) the subtraction of studies that are no longer reported.

5B. Twelve Year Summary of Total Number of Protocols Reported: FY 1995-2006						
FY Reported	FY Funded	Number of Protocols with Enrollment data (Old + New Forms):	Number of DOMESTIC Protocols with Enrollment data	Number of FOREIGN Protocols with Enrollment data	Percent Domestic Protocols	Protocol Form*
1995	1994	3,188				Old
1996	1995	6,036				
1997	1996	5,692				
1998	1997	7,602				
1999	1998	8,285				
2000	1999	9,390				
2001	2000	10,212				
2002	2001	8,945	8,463	482	94.6%	Old + New
2003	2002	10,216	9,578	638	93.8%	
2004	2003	10,125	9,760	365	96.4%	
2005	2004	10,233	9,862	371	96.4%	
2006	2005	10,758	10,294	464	95.7%	

Total Protocols by Year Reported



**Table 5B Comments:**

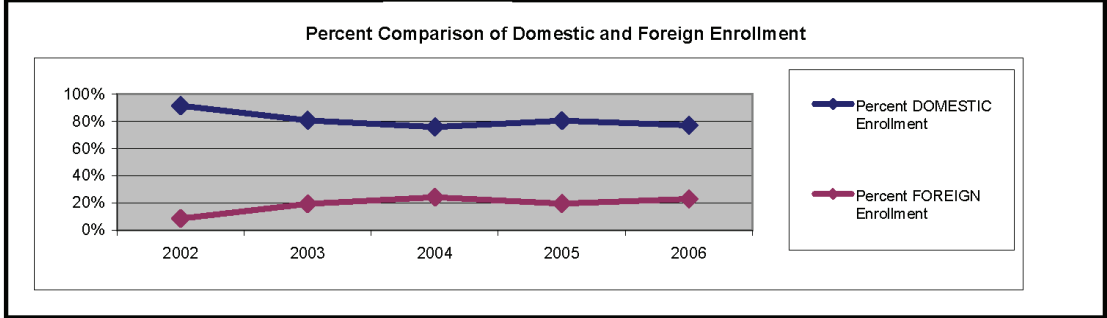
1. Table 5B and 5B Graph provide the number of OLD and NEW protocols year by year (1995-2006) and the distribution between domestic and foreign protocols for years 2002-2006.
2. The total number of protocols reported with enrollment have leveled off at about 15,000 over the last 4 years.
3. The vast majority of protocols were for domestic studies for 2002-2006, ranging from 93.8% to 96.4% of protocols.

\* Data have been reported using a combined race/ethnicity format (OLD FORM) since 1995. New protocols began reporting separate race and ethnicity data in FY2002 (NEW FORM). During 2002-2006, data have been reported using both Old and New Forms.

\*See Appendix H for the Race and Ethnicity categories included in Minority Enrollment Data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

**5C. Comparison of Domestic and Foreign Enrollment Reported in FY 2002-2006**

FY Reported	FY Funded	Total Enrollment data (Old + New Forms):	Total DOMESTIC Enrollment data	Percent DOMESTIC Enrollment	Total FOREIGN Enrollment	Percent FOREIGN Enrollment
2002	2001	11,138,484	10,192,401	91.5%	946,083	8.5%
2003	2002	14,772,254	11,911,357	80.6%	2,860,897	19.4%
2004	2003	18,923,920	14,359,793	75.9%	4,564,127	24.1%
2005	2004	15,722,752	12,669,858	80.6%	3,052,894	19.4%
2006	2005	14,830,930	11,425,701	77.0%	3,405,229	23.0%



**Table 5C Comments:**

1. Overall total enrollment has increased, as well as total domestic and foreign enrollment during the last five years. The percentage of domestic enrollment has decreased to approximately 79% as the foreign enrollment has increased to approximately 21%.

Table 6. NIH Twelve Year Minority Trend Summary of NIH Extramural and Intramural Clinical Research Reported in FY 1995-2006: Enrollment by Race and Ethnicity

6A. TWELVE YEAR SUMMARY TOTALS: ENROLLMENT BY SEX/GENDER AND MINORITY CATEGORIES IN ALL PROTOCOLS (Old + New Forms)											
FY Reported	FY Funded	Form	Females	Males	Unknown	Total All Subjects (Old + New Forms)	Subtotal: All Subjects Enrolled by US Minority Categories	Number of Protocols with Enrollment data (Old + New Forms):			
1995	1994	Old	528,421	459,921	33,151	1,021,493	374,430				3,188
		%	51.7%	45.0%	3.2%	100.0%	36.7%				
1996	1996	Old	4,130,389	2,883,865	91,054	6,805,304	2,125,988				6,036
		%	60.7%	38.0%	1.3%	100.0%	31.2%				
1997	1996	Old	3,320,610	1,930,783	68,540	5,319,933	1,709,220				5,692
		%	62.8%	36.3%	1.2%	100.0%	32.2%				
1998	1997	Old	4,246,130	2,716,890	116,566	7,079,576	2,923,662				7,602
		%	60.0%	38.4%	1.6%	100.0%	41.3%				
1999	1998	Old	5,102,306	2,712,068	169,863	7,984,237	3,105,228				8,285
		%	63.9%	34.0%	2.1%	100.0%	38.9%				
2000	1999	Old	5,585,042	3,919,055	64,990	9,569,097	3,406,297				9,390
		%	58.4%	41.0%	0.7%	100.0%	35.6%				
2001	2000	Old	6,808,822	4,740,887	44,547	11,594,256	3,619,119				10,212
		%	58.7%	40.9%	0.4%	100.0%	31.1%				
2002	2001	Old + New	7,155,549	3,904,560	78,375	11,138,484	3,655,880				8,945
		%	64.2%	35.1%	0.7%	100.0%	32.9%				
2003	2002	Old + New	8,514,481	6,121,496	136,277	14,772,254	5,387,692				10,216
		%	57.8%	41.4%	0.9%	100.0%	36.5%				
2004	2003	Old + New	10,889,087	7,741,852	292,931	18,923,920	7,811,611				10,125
		%	57.5%	40.9%	1.5%	100.0%	40.2%				
2005	2004	Old + New	9,503,922	5,941,907	276,920	15,722,752	6,245,436				10,230
		%	60.4%	37.8%	1.8%	100.0%	39.7%				
2006	2006	Old + New	9,473,273	5,172,205	185,482	14,830,930	6,388,316				10,758
		%	63.9%	34.9%	1.2%	100.0%	43.1%				

Table 6A Comments:

- Table 6A summarizes enrollment by sex/gender and minority race/ethnicity categories for the twelve year reporting period (1995-2006). The data are compiled from Tables 6B, 6C and 6D below, which provide the detailed distributions by sex/gender and race/ethnicity using the OLD Enrollment Form (Table 6B) and the NEW Enrollment Form (Tables 6C and 6D).
- The Race and Ethnicity data in the OLD FORM and the NEW FORM cannot be combined by individual race and ethnicity categories because the categories reflect the different OMB Formats used based on the 1977 OMB standards (OLD FORM) and the 1997 OMB Standards (NEW FORM).

NOTE: Trend data varies over time because the data for each year represent the net total of data resulting from:(1) studies continuing from the prior year; (2) the addition of new studies reported; (3) and the subtraction of studies that are no longer reported.

**Table 6. NIH Twelve Year Minority Trend Summary of NIH Extramural and Intramural Clinical Research Reported in FY 1995-2006: Enrollment by Race and Ethnicity**

**Notes Tables B-D**

NOTE 1: The shaded portions of the Tables B, C and D below show the race/ethnicity categories that are identified as minority categories. The Data Reported in FY 2002 and later are from the new Population Tracking System that was deployed with data reported in FY 2002 and later, and allows separate reporting using the Old Form and the New Form, and separate reporting for Foreign and Domestic Data.

NOTE 2: Data from Tables 6B, 6C and 6D are combined to provide the summary data in Table 6A.

6B. OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format												
FY Reported	FY Funded	American Indian/Alaska Native	Asian/Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM	Number of Protocols with Enrollment data (Old Form)		
1995	1994	11,221	38,952	234,976	89,284	540,313	106,747	1,021,493	374,433	3,188		
		1.1%	3.8%	23.0%	8.7%	52.9%	10.5%	100.0%	36.7%			
1996	1995	146,319	617,211	823,102	539,326	4,114,249	565,097	6,805,304	2,125,968	6,036		
		2.2%	9.1%	12.1%	7.9%	60.5%	8.3%	100.0%	31.2%			
1997	1996	36,638	321,479	864,102	487,004	3,199,778	407,932	5,316,933	1,709,223	5,692		
		0.7%	6.0%	16.3%	9.2%	60.2%	7.7%	100.0%	32.1%			
1998	1997	85,957	1,237,030	1,096,218	504,457	3,713,729	441,155	7,078,576	2,923,662	7,602		
		1.2%	17.5%	15.5%	7.1%	52.5%	6.2%	100.0%	41.3%			
1999	1998	71,436	1,429,022	1,081,210	526,563	4,470,966	405,043	7,984,237	3,108,228	8,285		
		0.9%	17.9%	13.5%	6.6%	56.0%	5.1%	100.0%	39.9%			
2000	1999	82,728	1,525,392	1,209,789	588,408	5,589,942	578,858	9,569,097	3,406,297	9,390		
		0.9%	15.5%	12.6%	6.1%	58.4%	6.0%	100.0%	35.6%			
2001	2000	105,067	1,495,279	1,199,625	819,148	7,314,449	660,688	11,694,256	3,619,119	10,212		
		0.9%	12.9%	10.3%	7.1%	63.1%	5.7%	100.0%	31.2%			
2002	2001	45,843	1,222,296	702,234	398,651	4,044,052	321,349	6,734,431	2,369,030	6,187		
		0.7%	18.1%	10.4%	5.9%	60.1%	4.8%	100.0%	35.2%			
2003	2002	36,575	730,242	472,426	288,523	3,239,284	278,901	5,045,256	1,628,070	4,903		
		0.3%	14.5%	9.4%	5.7%	64.2%	5.5%	100.0%	30.3%			
2004	2003	29,387	307,092	342,138	214,322	2,348,329	172,130	3,413,608	892,949	2,782		
		0.9%	9.0%	10.0%	6.3%	68.8%	5.0%	100.0%	26.2%			
2005	2004	22,373	254,598	229,615	134,972	1,267,089	102,405	2,011,054	641,560	1,786		
		1.1%	12.7%	11.4%	6.7%	63.0%	5.1%	100.0%	31.9%			
2006	2005	19,648	131,786	148,948	76,596	883,041	63,231	1,325,250	378,978	1,391		
		1.5%	9.9%	11.2%	5.9%	66.6%	4.8%	100.0%	28.6%			

**ORIENTATION TO TABLES 6C and 6D.**

1. The New Form consists of Parts A and B (Tables 6C and 6D) for reporting years 2002-2006. This Form is provided as part of the annual progress report.
2. Table 6C displays the New Form Part A for reporting separate race and ethnicity data.
3. Table 6D displays the New Form Part B, which is the Distribution of Hispanics reported by race, using the totals from the "Hispanic or Latino" column in Part A.

6C. New Form Part A: Total of All Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats													
Total of All Subjects by Race		Total of All Subjects by Ethnicity											
FY Reported	FY Funded	American Indian/Alaska Native	Asian	Black or African American	Hawaiian/Pacific Islander	White	More Than One Race	Unknown/Other	Total*	Not Hispanic	Hispanic or Latino**	Unknown/Not Reported	Total*
2002	2001	77,734	354,049	547,776	21,638	2,851,541	30,955	720,362	4,404,053	3,071,952	292,429	1,039,672	4,404,053
		1.8%	8.0%	12.4%	0.5%	60.2%	0.7%	16.4%	100.0%	69.8%	6.6%	23.6%	100.0%
2003	2002	63,544	2,138,002	960,050	37,563	5,415,710	99,462	1,012,622	9,726,959	8,162,259	611,641	953,099	9,726,959
		0.7%	22.0%	9.9%	0.4%	59.7%	1.0%	10.4%	100.0%	83.9%	6.3%	9.8%	100.0%
2004	2003	36,047	4,345,336	1,379,807	54,452	8,065,069	186,241	1,381,250	15,810,312	13,168,942	756,339	1,565,131	15,810,312
		0.8%	89.0%	8.9%	0.4%	52.0%	1.2%	8.9%	100.0%	84.9%	4.9%	10.2%	100.0%
2005	2004	292,219	3,048,370	1,358,262	83,288	7,872,830	182,933	1,105,722	13,711,698	11,804,164	773,939	1,133,595	13,711,698
		2.1%	22.2%	9.9%	0.4%	56.0%	1.3%	8.1%	100.0%	86.1%	5.6%	8.3%	100.0%
2006	2005	141,567	3,463,202	1,251,339	38,460	7,089,017	321,554	1,200,541	13,805,680	11,308,244	1,054,313	1,143,123	13,805,680
		1.0%	25.6%	9.3%	0.3%	52.5%	2.4%	8.9%	100.0%	83.7%	7.8%	8.2%	100.0%

6D. New Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)												
FY Reported	FY Funded	American Indian/Alaska Native	Asian	Black or African American	Hawaiian/Pacific Islander	White	More Than One Race	Unknown/Other	Total Hispanic or Latino**	Minority Categories (shaded): NEW FORM Parts A+B	Number of Protocols with Enrollment data (New Form)	
2002	2001	4,861	1,305	13,066	101	159,252	7,930	106,248	282,429	1,287,850	2,788	
		1.7%	0.4%	4.5%	0.0%	54.5%	2.5%	36.4%	100.0%	29.5%		
2003	2002	5,400	1,953	14,566	675	350,439	26,088	210,516	611,641	3,889,622	5,319	
		0.9%	0.3%	2.4%	0.1%	67.3%	4.6%	34.4%	100.0%	39.7%		
2004	2003	6,408	5,040	25,278	2,037	361,112	62,909	293,557	756,339	6,718,662	7,343	
		0.8%	0.7%	3.3%	0.3%	47.7%	8.3%	38.8%	100.0%	43.3%		
2005	2004	22,735	7,816	19,448	1,981	388,874	51,166	281,916	773,938	5,603,876	8,447	
		2.9%	1.0%	2.5%	0.3%	50.2%	6.6%	36.4%	100.0%	40.9%		
2006	2005	45,074	6,641	21,712	2,193	417,436	185,477	375,721	1,054,313	6,009,338	9,367	
		4.3%	0.6%	2.1%	0.2%	39.6%	17.6%	35.6%	100.0%	44.5%		

\* These totals must agree.

\*\* These totals must agree.

Table 6. NIH Twelve Year Minority Trend Summary of NIH Extramural and Intramural Clinical Research Reported in FY 1995-2006: Enrollment by Race and Ethnicity

6E. Comparison of Domestic and Foreign Enrollment & Protocols with Total Enrollment for the period FY2002-2006											
ENROLLMENT						PROTOCOLS					
FY Reported	FY Funded	Total Enrollment data (Old + New Forms)	Total DOMESTIC Enrollment	Percent DOMESTIC Enrollment	Total FOREIGN Enrollment	Percent FOREIGN Enrollment	Number of Protocols with Enrollment data (Old + New Forms)	Number of DOMESTIC Protocols	Percent Domestic Protocols	Number of FOREIGN Protocols	Percent Foreign Protocols
2002	2001	11,138,484	10,192,401	91.5%	946,083	8.5%	9,545	9,453	94.8%	482	5.4%
2003	2002	14,772,264	11,911,367	80.6%	2,860,897	19.4%	10,216	9,578	93.8%	638	6.2%
2004	2003	18,923,920	14,359,793	75.9%	4,564,127	24.1%	10,126	9,760	96.4%	365	3.6%
2005	2004	15,722,752	12,669,868	80.6%	3,052,884	19.4%	10,233	9,862	96.4%	371	3.6%
2006	2005	14,830,930	11,425,701	77.0%	3,405,229	23.0%	10,788	10,294	95.7%	484	4.3%

Percentage of Domestic and Foreign Enrollment

Number of Domestic and Foreign protocols

Table 6 E Comments:

1. The Total Enrollment, Total Domestic, and Total Foreign enrollment increase from FY2002-2006.
2. The Domestic enrollment decreased to approximately 80%, while the Foreign enrollment increased to approximately 20%.
3. The vast majority of protocols are domestic protocols (approximately 94-96%), while foreign protocols make up approximately 4-6% of total protocols.
4. Foreign enrollment was reported using the same race and ethnicity categories as domestic enrollment.

6F. Comparison of Domestic and Foreign Minority Participation for FY 2002-2006

FY Reported	FY Funded	FOREIGN Minority	Foreign Total	DOMESTIC Minority	Domestic Total
2002	2001	777,461	946,083	2,754,820	10,149,869
		82.2%	100.0%	27.1%	100.0%
2003	2002	2,462,329	2,860,897	2,936,363	11,911,367
		86.7%	100.0%	24.6%	100.0%
2004	2003	4,147,255	4,564,127	3,464,366	14,359,793
		90.8%	100.0%	24.1%	100.0%
2005	2004	2,776,565	3,052,884	3,468,864	12,669,868
		90.9%	100.0%	27.4%	100.0%
2006	2005	3,087,181	3,405,229	3,301,136	11,425,701
		90.7%	100.0%	28.9%	100.0%

NOTE MINORITY % WILL NOT ADD TO 100%

Percentage Comparison of Domestic Minority Enrollment to Total Domestic Enrollment for FY 2002-2006

Percentage Comparison of Foreign Minority Enrollment to Total Foreign Enrollment for FY 2002-2006

Table 6F Comments:

1. Domestic Minority Enrollment has varied from 24.1% to 28.9% of Total Domestic Enrollment.
2. research is done in countries that are within the OMB race and ethnicity origin categories that are included in the summary
3. The Total Minority Enrollment reported in FY2006 was 52% Domestic and 48 % Foreign (see Table 1). The small percentage of foreign protocols account for a significant proportion (48%) of the Total Minority Enrollment, as shown by comparing both domestic and foreign enrollment data.

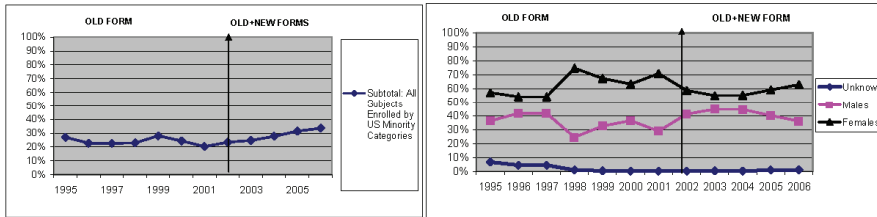


**Table 7: Twelve Year Minority Trend Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY1995-2006: Enrollment by Race and Ethnicity**

7A. Phase III TWELVE YEAR SUMMARY TOTALS: ENROLLMENT BY SEX/GENDER IN ALL PROTOCOLS (Old + New Forms)									
FY Reported	FY Funded	Females	Males	Unknown	Total All Subjects (Old + New Forms)	Subtotal: All Subjects Enrolled by US Minority Categories	Number of Protocols with Enrollment data (Old + New Forms):		
1996	1994	171,181	108,324	19,818	299,323	80,882	650		
	%	57.2%	36.2%	6.6%	100.0%	26.9%			
1996	1995	264,755	203,698	21,210	489,663	110,669	608		
	%	54.1%	41.6%	4.3%	100.0%	22.6%			
1997	1996	264,755	203,698	21,210	489,663	110,000	608		
	%	54.1%	41.6%	4.3%	100.0%	22.5%			
1998	1997	228,417	74,389	2,705	305,511	69,599	320		
	%	74.8%	24.3%	0.9%	100.0%	22.8%			
1999	1998	339,530	163,950	1,446	504,929	141,449	578		
	%	67.2%	32.5%	0.3%	100.0%	28.0%			
2000	1999	313,952	180,705	1,086	495,743	120,338	689		
	%	63.3%	36.5%	0.2%	100.0%	24.3%			
2001	2000	412,379	188,085	1,273	591,737	117,873	645		
	%	70.9%	29.9%	0.2%	100.0%	20.3%			
2002	2001	278,876	195,090	781	474,747	111,268	754		
	%	59.7%	41.1%	0.2%	100.0%	23.4%			
2003	2002	294,950	239,403	1,914	536,267	132,302	852		
	%	55.0%	44.6%	0.4%	100.0%	24.7%			
2004	2003	301,353	242,913	1,101	545,367	150,456	673		
	%	55.3%	44.8%	0.2%	100.0%	27.5%			
2006	2004	290,977	197,300	4,723	493,000	154,191	547		
	%	59.0%	40.0%	1.0%	100.0%	31.3%			
2006	2005	314,066	179,975	5,389	499,430	167,446	624		
	%	62.9%	36.0%	1.1%	100.0%	33.5%			

Total Phase III Enrollment by Year Reported

Sex/Gender Phase III Enrollment by Year Reported



**Table 7A Comments:**

1. Table 7A summarizes enrollment by sex/gender and minority race/ethnicity categories for the twelve year reporting period (1995-2006). The data are compiled from Tables 7B, 7C and 7D below, which provide the detailed distributions by sex/gender and race/ethnicity using the OLD Enrollment Form (Table 7B) and the NEW Enrollment Form (Tables 7C and 7D).
2. The Race and Ethnicity data in the OLD FORM and the NEW FORM cannot be combined by individual race and ethnicity categories because the categories reflect the different OMB Formats used based on the 1977 OMB standards (OLD FORM) and the 1997 OMB Standards (NEW FORM).

NOTE: Trend data varies over time because the data for each year represent the net total of data resulting from: (1) studies continuing from the prior year; (2) the addition of new studies reported; (3) and the subtraction of studies that are no longer reported.

**Table 7: Twelve Year Minority Trend Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY1995-2006: Enrollment by Race and Ethnicity**

Notes Tables 7B-D

NOTE 1: The shaded portions of the Tables B, C and D below show the race/ethnicity categories that are identified as minority categories. The Data Reported in FY 2002 and later are from the new Population Tracking System that was deployed with data reported in FY 2002 and later, and allows separate reporting using the Old Form and the New Form, and separate reporting for Foreign and Domestic Data.

NOTE 2: Data from Tables 7B, 7C and 7D are combined to provide the summary data in Table 7A.

7B. Phase III OLD FORM: Total of All Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format												
FY Reported	FY Funded	American Indian/Alaska Native	Asian/Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/Other	Total	Subtotal Using US Minority Categories (shaded): OLD FORM	Number of Protocols with Enrollment data (Old Form)		
1995	1994	5,358	2,740	52,433	20,031	172,773	49,988	299,323	80,562	560		
	%	1.8%	0.9%	17.5%	6.7%	57.7%	15.4%	100.0%	26.9%			
1996	1995	4,235	40,126	46,838	19,470	321,445	57,549	489,663	110,669	608		
	%	0.9%	8.2%	9.6%	4.0%	65.6%	11.8%	100.0%	22.6%			
1997	1996	4,235	40,126	46,838	19,470	321,445	57,549	489,663	110,669	608		
	%	0.9%	8.2%	9.6%	4.0%	65.6%	11.8%	100.0%	22.6%			
1998	1997	5,030	5,324	42,805	16,440	229,534	6,378	305,511	69,599	320		
	%	1.6%	1.7%	14.0%	5.4%	75.1%	2.1%	100.0%	22.8%			
1999	1998	3,685	20,276	76,921	40,567	336,703	26,777	504,929	141,443	578		
	%	0.7%	4.0%	15.2%	8.0%	66.7%	5.3%	100.0%	28.0%			
2000	1999	3,726	24,017	62,512	30,064	335,824	39,680	495,743	120,338	589		
	%	0.8%	4.9%	12.6%	6.1%	67.7%	8.0%	100.0%	24.3%			
2001	2000	4,079	11,132	70,110	32,552	422,802	41,063	581,737	117,873	649		
	%	0.7%	1.9%	12.1%	5.6%	72.7%	7.1%	100.0%	20.3%			
2002	2001	1,845	20,560	51,991	29,698	315,543	12,228	431,603	103,839	660		
	%	0.38%	4.6%	12.0%	6.9%	73.1%	2.6%	100.0%	24.1%			
2003	2002	1,689	20,038	49,255	29,066	331,650	16,615	454,317	100,048	656		
	%	0.4%	4.4%	10.8%	6.4%	74.3%	3.7%	100.0%	22.0%			
2004	2003	1,505	18,807	45,268	32,974	265,764	14,050	378,389	96,571	296		
	%	0.4%	5.0%	12.0%	8.7%	70.2%	3.7%	100.0%	26.1%			
2006	2004	1,319	17,740	39,402	21,825	231,495	4,537	316,289	80,299	210		
	%	0.4%	5.6%	12.5%	6.9%	73.2%	1.4%	100.0%	25.4%			
2006	2005	1,012	16,800	20,359	9,524	175,724	6,349	229,763	47,691	215		
	%	0.4%	7.3%	8.9%	4.1%	76.5%	2.6%	100.0%	20.8%			

**ORIENTATION TO TABLES 7C and 7D.**

1. The New Form consists of Parts A and B (Tables 7C and 7D) for reporting years 2002-2006. This Form is provided as part of the annual progress report.
2. Table 7C displays the New Form Part A for reporting separate race and ethnicity data.
3. Table 7D displays the New Form Part B, which is the Distribution of Hispanics reported by race, using the totals from the "Hispanic or Latino" column in Part A.

7C. Phase III New Form: Total of All Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity													
		Total of All Subjects by Race							Total of All Subjects by Ethnicity				
FY Reported	FY Funded	American Indian/Alaska Native	Asian	Black or African American	Hawaiian/Pacific Islander	White	More Than One Race	Unknown/Other	Total	Not Hispanic	Hispanic or Latino	Unknown/Not Reported	Total
2002	2001	59	799	4,647	52	34,854	560	2,278	43,144	36,220	1,629	5,291	43,144
	%	0.37%	1.85%	10.77%	0.12%	80.32%	1.30%	5.27%	100.00%	83.96%	3.78%	12.26%	100.00%
2003	2002	484	2,609	21,641	220	47,863	969	8,136	81,950	64,299	7,831	9,624	81,950
	%	0.6%	3.2%	26.4%	0.3%	58.4%	1.2%	9.9%	100.0%	78.5%	9.6%	12.0%	100.0%
2004	2003	1,396	4,369	43,721	611	106,793	4,419	5,627	166,932	145,742	13,435	7,805	166,932
	%	0.9%	2.5%	25.2%	0.4%	64.0%	2.6%	3.4%	100.0%	87.3%	8.0%	4.7%	100.0%
2005	2004	2,164	9,192	50,338	462	101,238	3,063	10,254	176,711	156,660	10,397	9,664	176,711
	%	1.2%	5.2%	28.5%	0.3%	57.3%	1.7%	5.8%	100.0%	88.6%	5.9%	5.6%	100.0%
2006	2005	4,630	32,360	50,780	555	126,670	4,245	50,446	269,667	202,358	31,034	36,275	269,667
	%	1.7%	12.0%	19.8%	0.2%	47.6%	1.6%	18.7%	100.0%	75.0%	11.5%	13.6%	100.0%

7D. Phase III Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)												
FY Reported	FY Funded	American Indian/Alaska Native	Asian	Black or African American	Hawaiian/Pacific Islander	White	More Than One Race	Unknown/Other	Total	Subtotal Using US Minority Categories (shaded): NEW	Number of Protocols with Enrollment data (New Form)	
2002	2001	49	22	31	4	660	304	560	1,630	7,437	94	
	%	3.0%	1.3%	1.9%	0.2%	40.5%	18.7%	34.4%	100.0%	17.2%		
2003	2002	37	70	186	23	2,115	203	5,197	7,831	32,254	196	
	%	0.5%	0.9%	2.4%	0.3%	27.0%	2.6%	66.4%	100.0%	39.4%		
2004	2003	269	69	193	26	7,264	3,052	2,572	13,435	64,406	277	
	%	2.0%	0.4%	1.4%	0.2%	54.1%	22.7%	19.1%	100.0%	32.6%		
2005	2004	799	42	446	45	3,867	423	5,019	10,397	73,901	337	
	%	7.9%	0.4%	4.3%	0.4%	35.3%	4.1%	48.2%	100.0%	41.9%		
2006	2005	2,307	50	720	40	6,872	713	20,332	31,034	119,755	409	
	%	7.4%	0.2%	2.3%	0.1%	22.1%	2.3%	65.5%	100.0%	44.4%		

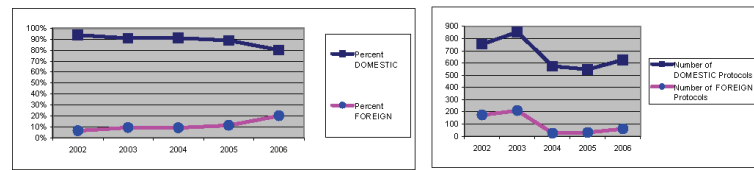
\* These totals must agree  
 \*\* These totals must agree

**Table 7: Twelve Year Minority Trend Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY1995-2006: Enrollment by Race and Ethnicity**

**7E. Comparison of Domestic and Foreign Phase III Enrollment and Protocols with Enrollment for the period FY2002-2006**

FY Reported	FY Funded	ENROLLMENT				PROTOCOLS				
		Total Enrollment data (Old + New Forms)	Total DOMESTIC	Percent DOMESTIC	Total FOREIGN	Percent FOREIGN	Number of DOMESTIC Protocols	Percent Domestic	Number of FOREIGN Protocols	Percent Foreign
2002	2001	474,747	444,436	93.6%	30,311	6.4%	754	82.2%	172	22.8%
2003	2002	538,267	496,267	92.2%	49,410	9.2%	852	84.3%	209	24.5%
2004	2003	545,367	496,241	91.0%	49,126	9.0%	673	54.9%	24	4.2%
2006	2004	469,000	437,902	93.4%	66,098	14.1%	617	94.6%	30	6.6%
2006	2005	489,430	400,297	82.0%	99,133	19.8%	624	95.4%	60	9.6%

Percentage of Phase III Domestic and Foreign Enrollment      Number of Phase III Domestic and Foreign protocols



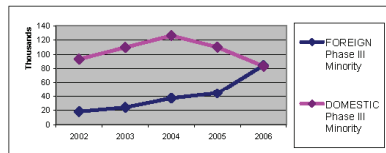
**Table 7E Comments:**

1. The Total Enrollment, Total Domestic, and Total Foreign enrollment increase from FY2002-2006.
2. The Domestic enrollment decreased to approximately 80%, while the Foreign enrollment increased to approximately 20%.
3. The vast majority of protocols in FY2004-2006 are domestic protocols (approximately 90.4-95.8%), while foreign protocols make up approximately 4.2-9.6% of total protocols.
4. Foreign enrollment was reported using the same race and ethnicity categories as domestic enrollment.

**7F. Phase III Foreign and Domestic Minority Comparison for FY 2002-2006**

FY Reported	FY Funded	FOREIGN Phase III Minority	FOREIGN Phase III Total	DOMESTIC Phase III Minority	DOMESTIC Phase III Total
2002	2001	18,308	30,311	92,961	444,436
		60.4%	100.0%	20.9%	100.0%
2003	2002	23,927	49,410	109,376	496,267
		48.4%	100.0%	22.0%	100.0%
2004	2003	37,126	49,126	125,813	496,241
		75.6%	100.0%	25.4%	100.0%
2005	2004	44,281	55,098	109,910	437,902
		80.4%	100.0%	25.1%	100.0%
2006	2005	84,412	99,133	80,034	400,297
		85.2%	100.0%	20.0%	100.0%

Number of Minority Participants in Phase III Clinical Studies for FY2002-2006



**Table 7F Comments:**

1. Domestic Minority Enrollment has varied from 24.1% to 28.9% of Total Domestic Enrollment.
2. Foreign Minority Enrollment has varied from 82.2% to 90.9% of Total Foreign Enrollment, reflecting that most of the foreign research is done in countries that are within the OMB race and ethnicity origin categories that are included in the summary minority data used in this report.
3. The Total Minority Enrollment reported in FY2006 was 52% Domestic and 48% Foreign (see Table 1). The small percentage of foreign protocols account for a significant proportion (48%) of the Total Minority Enrollment, as shown by comparing both domestic and foreign enrollment data.

**Table 8: DOMESTIC PROTOCOLS: Summary of NIH Extramural and Intramural Clinical Research Reported: FY2002-2006: Enrollment Using U.S. Race/Ethnicity Categories**

<b>8A . FIVE YEAR SUMMARY TOTALS: DOMESTIC SUBJECTS IN DOMESTIC PROTOCOLS (Old + New Forms)</b>									
FY Reported	FY Funded		Females	Males	Unknown	Total Domestic Subjects (Old + New Forms)	Subtotal: Domestic Subjects Enrolled by US Minority Categories		Domestic Protocols with Enrollment data (Old +
2002	2001		6,583,087	3,506,787	59,995	10,149,869	2,754,820		8,425
	%		64.9%	34.6%	0.6%	100.0%	27.1%		
2003	2002		7,392,404	4,393,496	125,457	11,911,357	2,935,363		9,578
	%		62.1%	36.9%	1.1%	100.0%	24.6%		
2004	2003		8,881,299	5,199,765	278,729	14,359,793	3,464,366		9,760
	%		61.8%	36.2%	1.9%	100.0%	24.1%		
2005	2004		7,887,209	4,515,242	267,407	12,669,858	3,468,864		9,862
	%		62.3%	35.6%	2.1%	100.0%	27.4%		
2006	2006		7,684,453	3,566,577	174,671	11,425,701	3,301,135		10,294
	%		67.3%	31.2%	1.5%	100.0%	28.9%		

**Table 8A Comments:**

1. There were approximately an average of 63% females, 35% males and 2% of unknown sex enrolled in domestic protocols from 2002-2006.
2. There were approximately an average of 27% domestic minority subjects enrolled in domestic protocols from 2002-2006.
3. Total domestic enrollment ranged from 10.1M to 11.5M during these 5 years.
4. The number of domestic protocols increased from 8,425 to 10,294 in 2006.

**NOTE on FY2002 Reported Data:**

One domestic study had an enrollment of 540,833 subjects (Old Form).  
 One domestic study had an enrollment of 1,571,305 subjects (Old Form).

**NOTE on FY2003 Reported Data:**

One domestic study had an enrollment of 800,000 subjects (New Form).  
 One domestic study had an enrollment of 1,389,920 subjects (New form).  
 One domestic study had an enrollment of 1,799,820 subjects (New form).

**NOTE on FY2004 Reported Data:**

One domestic study had an enrollment of 540,833 subjects (New Form).  
 One domestic study had an enrollment of 800,000 subjects (New Form).  
 One domestic study had an enrollment of 1,138,302 subjects (New form).  
 One domestic study had an enrollment of 1,419,475 subjects (New form).  
 One domestic study had an enrollment of 1,799,820 subjects (New form).

**NOTE on FY2005 Reported Data:**

One domestic study had an enrollment of 540,833 subjects (New Form).  
 One domestic study had an enrollment of 800,000 subjects (New Form).  
 One domestic study had an enrollment of 1,595,620 subjects (New form).  
 One domestic study had an enrollment of 1,799,820 subjects (New form).

**NOTE on FY2006 Reported Data:**

One domestic study had an enrollment of 875,010 subjects (New Form).  
 One domestic study had an enrollment of 1,964,668 subjects (New Form).  
 One domestic study had an enrollment of 540,833 subjects (New form).

**Table 8: DOMESTIC PROTOCOLS: Summary of NIH Extramural and Intramural Clinical Research Reported in FY2002-2006: Enrollment Using U.S. Race/Ethnicity Categories**

**NOTE 1:** The shaded portions of the Tables B, C and D below show the race/ethnicity categories that are identified as minority categories. The Data Reported in FY 2002 and later are from the new Population Tracking System that was deployed with data reported in FY 2002 and later, and allows separate reporting using the Old Form and the New Form, and separate reporting for Foreign and Domestic Data.

**NOTE 2:** Data from Tables 8B, 8C and 8D are combined to provide the summary data in Table A.

**8B. OLD FORM: Total of All Domestic Subjects Reported Using the 1977 OMB Standards in a combined race/ethnicity format**

FY Reported	FY Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown /Other	Total Domestic Enrollment (Old Form)	Domestic Subtotal Using US Minority Categories (shaded): OLD FORM	Number of Domestic Protocols with Enrollment data (Old Form):
2002	2001	45,639	752,203	673,726	378,300	3,880,431	316,053	6,046,352	1,849,868	5,783
	%	0.8%	12.4%	11.1%	6.3%	64.2%	5.2%	100.0%	30.6%	
2003	2002	36,238	249,420	455,329	264,336	3,100,815	266,339	4,372,477	1,005,323	4,478
	%	0.8%	5.7%	10.4%	6.0%	70.9%	6.1%	100.0%	23.0%	
2004	2003	28,953	196,647	322,078	194,762	2,273,619	157,464	3,173,523	742,440	2,702
	%	0.9%	6.2%	10.1%	6.1%	71.6%	5.0%	100.0%	23.4%	
2005	2004	22,375	89,119	210,465	126,351	1,245,337	93,239	1,786,886	448,310	1,736
	%	1.3%	5.0%	11.8%	7.1%	69.7%	5.2%	100.0%	25.1%	
2006	2005	19,628	51,701	148,224	74,312	868,683	61,480	1,222,028	293,865	1,361
	%	1.6%	4.2%	12.1%	6.1%	70.9%	5.0%	100.0%	24.0%	

**8C. NEW FORM PART A: Inclusion Enrollment Report (Total of All Domestic Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats)**

Part A: TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race													
		Total of All Subjects by Race							Total of All Subjects by Ethnicity				
FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White	More Than One Race	Unknown or Not Reported	*Total of All Subjects by Racial Categories (New Form)	Not Hispanic	**Hispanic or Latino	Unknown/ Not Reported	**Total of All Subjects by Ethnic Category
2002	2001	74,593	174,215	473,699	7,623	2,628,547	30,200	716,840	4,103,517	2,785,590	285,921	1,032,006	4,103,517
	%	1.8%	4.2%	11.5%	0.2%	64.0%	0.7%	17.5%	100.0%	67.9%	7.0%	25.1%	100.0%
2003	2002	61,526	295,061	897,518	23,068	5,161,965	94,138	1,005,604	7,538,880	6,003,326	802,018	933,536	7,538,880
	%	0.8%	3.9%	11.9%	0.3%	68.5%	1.2%	13.3%	100.0%	79.6%	8.0%	12.4%	100.0%
2004	2003	97,854	485,137	1,280,129	42,945	7,772,927	172,185	1,335,093	11,186,270	8,893,158	720,551	1,572,561	11,186,270
	%	0.9%	4.3%	11.4%	0.4%	69.5%	1.5%	11.9%	100.0%	79.5%	6.4%	14.1%	100.0%
2005	2004	291,044	655,959	1,232,957	42,993	7,485,193	164,096	1,010,730	10,882,972	9,120,293	721,138	1,041,541	10,882,972
	%	2.7%	6.0%	11.3%	0.4%	68.8%	1.5%	9.3%	100.0%	83.8%	6.6%	9.6%	100.0%
2006	2005	111,048	946,813	1,032,199	35,142	6,844,960	178,275	1,055,436	10,203,673	8,384,860	796,556	1,022,757	10,203,673
	%	1.1%	9.3%	10.1%	0.3%	67.1%	1.7%	10.3%	100.0%	82.2%	7.8%	10.0%	100.0%

**8D. New Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)**

FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White (Hispanic)	More Than One Race	Unknown or Not Reported	**Total of Hispanics or Latinos by Racial Categories	Domestic Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B	Number of Domestic Protocols with Enrollment data (New Form):
2002	2001	1,163	436	12,005	98	69,313	5,626	75,309	163,950	904,952	2,642
	%	0.7%	0.3%	7.3%	0.1%	42.3%	3.4%	45.9%	100.0%	22.1%	
2003	2002	3,756	1,950	13,345	678	349,844	23,560	208,885	602,018	1,930,040	5,100
	%	0.6%	0.3%	2.2%	0.1%	58.1%	3.9%	34.7%	100.0%	25.6%	
2004	2003	6,293	5,026	12,498	2,037	356,575	51,031	287,091	720,551	2,721,916	7,058
	%	0.9%	0.7%	1.7%	0.3%	49.5%	7.1%	39.8%	100.0%	24.3%	
2005	2004	22,057	7,810	19,282	1,981	362,707	36,503	270,798	721,138	3,020,654	8,126
	%	3.1%	1.1%	2.7%	0.3%	50.3%	5.1%	37.6%	100.0%	27.8%	
2006	2005	15,498	6,540	19,870	1,505	374,830	49,150	329,163	796,556	3,007,270	8,933
	%	1.9%	0.8%	2.5%	0.2%	47.1%	6.2%	41.3%	100.0%	29.5%	

\* These totals must agree  
\*\* These totals must agree

**Table 9: DOMESTIC PROTOCOLS: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY2002-2006:Enrollment Using U.S. Race/Ethnicity**

<b>9A . Phase III FIVE YEAR SUMMARY TOTALS: DOMESTIC SUBJECTS IN DOMESTIC PROTOCOLS (Old + New Forms)</b>											
<b>FY Reported</b>	<b>FY Funded</b>		<b>Females</b>		<b>Males</b>		<b>Unknown</b>		<b>Total Domestic Subjects (Old + New Forms)</b>	<b>Subtotal: Domestic Subjects Enrolled by US Minority Categories</b>	<b>Number of Domestic Protocols with Enrollment data (Old + New Forms):</b>
2002	2001		264,517		179,179		740		444,436	92,961	582
	%		59.5%		40.3%		0.2%		100.0%	20.9%	
2003	2002		266,913		218,166		1,778		486,857	109,376	643
	%		54.8%		44.8%		0.4%		100.0%	22.5%	
2004	2003		277,333		217,890		1,018		496,241	125,813	549
	%		55.9%		43.9%		0.2%		100.0%	25.4%	
2005	2004		261,589		174,137		2,176		437,902	109,910	517
	%		59.7%		39.8%		0.5%		100.0%	25.1%	
2006	2005		258,467		137,621		4,209		400,297	63,034	564
	%		64.6%		34.4%		1.1%		100.0%	20.7%	

**Table 9A Comments:**

1. There were approximately an average of 57% females, 42% males and 0.3% of unknown sex enrolled in domestic protocols from 2002-2005.
2. There were approximately an average of 23.5% domestic minority subjects enrolled in domestic Phase III protocols from 2002-2006.
3. Total domestic Phase III enrollment ranged from 400,297 to 496,241 during these 5 years.
4. The number of domestic Phase III protocols ranged from 517 to 564 in 2006.



**Table 9: DOMESTIC PROTOCOLS: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY2002-2006:Enrollment Using U.S. Race/Ethnicity Categories**

**NOTE 1:** The shaded portions of the Tables B, C and D below show the race/ethnicity categories that are identified as minority categories. The Data Reported in FY 2002 and later are from the new Population Tracking System that was deployed with data reported in FY 2002 and later, and allows separate reporting using the Old Form and the New Form, and separate reporting for Foreign and Domestic Data.

**NOTE 2:** Data from Tables 9B, 9C and 9D are combined to provide the summary data in Table A.

<b>9B. OLD FORM: Total of All Domestic Subjects Reported Using the 1977 OMB Standards in a combined race/ethnicity format</b>											
FY Reported	FY Funded	American Indian/Alaska Native	Asian/Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/Other	Total Domestic Enrollment (Old Form)	Domestic Subtotal Using US Minority Categories (shaded): OLD FORM	Number of Domestic Protocols with Enrollment data (Old Form):	
2002	2001	1,586	8,291	49,184	27,912	305,964	10,670	403,607	86,973	494	
	%	0.4%	2.1%	12.2%	6.9%	75.8%	2.6%	100.0%	21.5%		
2003	2002	1,612	7,610	48,975	25,567	322,600	8,638	414,902	83,764	468	
	%	0.4%	1.8%	11.8%	6.2%	77.8%	2.1%	100.0%	20.2%		
2004	2003	1,504	6,739	45,233	31,967	262,671	6,447	354,561	85,443	286	
	%	0.4%	1.9%	12.8%	9.0%	74.1%	1.8%	100.0%	24.1%		
2005	2004	1,319	5,488	39,401	20,646	229,235	4,493	300,562	66,854	205	
	%	0.4%	1.8%	13.1%	6.9%	76.3%	1.5%	100.0%	22.2%		
2006	2005	996	4,505	20,325	9,512	171,191	5,673	212,202	35,338	207	
	%	0.5%	2.1%	9.6%	4.5%	80.7%	2.7%	100.0%	16.7%		

<b>9C. NEW FORM Part A: Inclusion Enrollment Report (Total of All Domestic Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats)</b>													
<b>Part A: TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race</b>													
		Total of All Subjects by Race								Total of All Subjects by Ethnicity			
FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White	More Than One Race	Unknown or Not Reported	*Total of All Subjects by Racial Categories (New Form)	Not Hispanic	**Hispanic or Latino	Unknown/ Not Reported	*Total of All Subjects by Ethnic Category
2002	2001	159	798	3,199	52	34,541	560	1,520	40,829	34,662	1,629	4,538	40,829
	%	0.4%	2.0%	7.8%	0.1%	84.6%	1.4%	3.7%	100.0%	84.9%	4.0%	11.1%	100.0%
2003	2002	477	2,566	14,031	220	46,774	969	6,878	71,955	55,575	7,828	8,552	71,955
	%	0.7%	3.6%	19.5%	0.3%	65.0%	1.4%	9.6%	100.0%	77.2%	10.9%	11.9%	100.0%
2004	2003	1,396	4,373	22,307	611	106,260	1,949	4,864	141,660	123,770	10,863	7,047	141,660
	%	1.0%	3.1%	15.7%	0.4%	75.0%	1.3%	3.4%	100.0%	87.4%	7.7%	5.0%	100.0%
2005	2004	1,775	4,920	24,390	462	93,662	3,063	9,048	137,320	118,528	9,773	9,019	137,320
	%	1.3%	3.6%	17.8%	0.3%	68.2%	2.2%	6.6%	100.0%	86.3%	7.1%	6.6%	100.0%
2006	2005	2,724	5,312	23,267	530	118,577	4,077	33,608	188,095	141,638	13,550	32,857	188,095
	%	1.4%	2.8%	12.4%	0.3%	63.0%	2.2%	17.9%	100.0%	75.3%	7.2%	17.5%	100.0%

<b>9D. New Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date</b>											
FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White (Hispanic)	More Than One Race	Unknown or Not Reported	**Total of Hispanics or Latinos by Racial Categories	Domestic Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B	Number of Domestic Protocols with Enrollment data (New Form):
2002	2001	49	21	31	4	660	304	560	1,629	5,988	88
	%	3.0%	1.3%	1.9%	0.2%	40.5%	18.7%	34.4%	100.0%	14.7%	
2003	2002	37	70	186	23	2,113	203	5,196	7,828	26,612	175
	%	0.5%	0.9%	2.4%	0.3%	27.0%	2.6%	66.4%	100.0%	35.6%	
2004	2003	269	59	193	26	7,262	482	2,572	10,863	40,370	263
	%	2.5%	0.5%	1.8%	0.2%	66.9%	4.4%	23.7%	100.0%	28.5%	
2005	2004	371	42	446	45	3,683	423	4,783	9,773	43,056	312
	%	3.8%	0.4%	4.6%	0.5%	37.5%	4.3%	48.9%	100.0%	31.4%	
2006	2005	458	47	507	40	5,544	712	6,242	13,550	47,696	357
	%	3.4%	0.3%	3.7%	0.3%	40.9%	5.3%	46.1%	100.0%	25.4%	

\* These totals must agree

\*\* These totals must agree



**Table 10. FOREIGN PROTOCOLS: Summary of NIH Extramural and Intramural Clinical Research Reported in FY2002-2006: Enrollment Using U.S. Race/Ethnicity Categories**

<b>10A . FIVE YEAR SUMMARY TOTALS: FOREIGN SUBJECTS IN FOREIGN PROTOCOLS (Old + New Forms)</b>							
FY Reported	FY Funded	Females	Males	Unknown	Total Foreign Subjects (Old + New Forms)	Subtotal: Foreign Subjects Enrolled by US Minority Categories	Number of Foreign Protocols with Enrollment data (Old + New Forms):
2002	2001	553,056	379,294	13,833	946,083	777,461	482
	%	58.5%	40.1%	1.5%	100.0%	82.2%	
2003	2002	1,122,077	1,728,000	10,820	2,860,897	2,452,329	638
	%	39.2%	60.4%	0.4%	100.0%	85.7%	
2004	2003	2,007,798	2,542,127	14,202	4,564,127	4,147,255	365
	%	44.0%	55.7%	0.3%	100.0%	90.8%	
2005	2004	1,616,713	1,426,665	9,516	3,052,894	2,776,585	371
	%	53.0%	46.7%	0.3%	100.0%	90.9%	
2006	2005	1,788,820	1,605,628	10,781	3,405,229	3,087,181	464
	%	52.5%	47.2%	0.3%	100.0%	90.7%	

**Table 10A Comments:**

1. The percent females varied from 39.2% to 58.5% in foreign protocols from 2002-2005; the percent males varied from 40.1% to 60.4%.
2. The percent foreign subjects enrolled by U.S. Minority Categories in foreign protocols increased from 82.2% to 90.9% from 2002 to 2005.
3. Total foreign enrollment ranged from 777,461 to 4.15M during these 5 years.
4. The number of foreign protocols ranged from 638 in 2003 to 317 in 2005.

**NOTE on FY2002 Reported Data:**

One study in Vietnam had an enrollment of 302,381 subjects (Old Form).

**NOTE on FY2003 Reported Data:**

One study in Vietnam had an enrollment of 302,381 subjects (Old Form).  
One study in China had an enrollment of 1,910,000 subjects (New form).

**NOTE on FY2004 Reported Data:**

One study in India had an enrollment of 2,000,000 subjects (New Form).  
One study in China had an enrollment of 1,910,000 subjects (New form).

**NOTE on FY2005 Reported Data:**

One study in India had an enrollment of 2,200,000 subjects (New Form).

**NOTE on FY2006 Reported Data:**

One study in India had an enrollment of 2,200,000 subjects (New Form).

**Table 10. FOREIGN PROTOCOLS: Summary of NIH Extramural and Intramural Clinical Research Reported in FY2002-2006: Enrollment Using U.S. Race/Ethnicity Categories**

**NOTE 1:** The shaded portions of the Tables B, C and D below show the race/ethnicity categories that are identified as minority categories. The Data Reported in FY 2002 and later are from the new Population Tracking System that was deployed with data reported in FY 2002 and later, and allows separate reporting using the Old Form and the New Form, and separate reporting for Foreign and Domestic Data.

**NOTE 2:** Data from Tables 10B, 10C and 10D are combined to provide the summary data in Table A.

**10B. OLD FORM: Total of All FOREIGN Subjects Reported Using the 1977 OMB Standards in a combined race/ethnicity format**

FY Reported	FY Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/Other	Total Foreign Enrollment (Old Form)	FOREIGN Subtotal Using US Minority Categories (shaded): OLD FORM	Number of Foreign Protocols with Enrollment data (Old Form):
2002	2001	89	468,958	21,407	19,075	143,768	3,565	656,842	509,509	380
	%	0.0%	71.4%	3.3%	2.9%	21.9%	0.5%	100.0%	77.6%	
2003	2002	341	481,122	17,097	24,187	137,469	12,562	872,778	522,747	425
	%	0.1%	71.5%	2.5%	3.6%	20.4%	1.3%	100.0%	77.7%	
2004	2003	434	110,405	20,110	19,560	74,910	14,666	240,085	150,509	80
	%	0.2%	46.0%	8.4%	8.1%	31.2%	6.1%	100.0%	62.7%	
2006	2004	0	165,479	19,150	8,621	21,752	9,168	224,168	193,250	60
	%	0.0%	73.8%	8.5%	3.8%	9.7%	4.1%	100.0%	86.2%	
2006	2005	20	80,085	724	4,284	16,358	1,751	103,222	85,113	30
	%	0.0%	77.6%	0.7%	4.2%	15.8%	1.7%	100.0%	82.5%	

**10C. NEW FORM Part A: Inclusion Enrollment Report (Total of All FOREIGN Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats)**

**Part A: TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race**

FY Reported	FY Funded	Total of All Subjects by Race							Total of All Subjects by Ethnicity				
		American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White	More Than One Race	Unknown or Not Reported	*Total of All Subjects by Racial Categories (New Form)	Not Hispanic	**Hispanic or Latino	Unknown/Not Reported	*Total of All Subjects by Ethnic Category
2002	2001	3,271	180,022	88,071	14,013	19,970	741	3,153	289,241	278,618	6,084	4,559	288,241
	%	1.1%	82.2%	23.5%	4.8%	6.9%	0.3%	1.1%	100.0%	98.3%	2.1%	1.6%	100.0%
2003	2002	2,018	1,842,941	62,572	14,501	253,745	5,324	7,018	2,188,119	2,158,933	9,823	19,563	2,188,119
	%	0.1%	84.2%	2.9%	0.7%	11.6%	0.2%	0.3%	100.0%	98.7%	0.4%	0.9%	100.0%
2004	2003	193	3,880,259	89,728	11,507	282,142	14,056	46,157	4,324,042	4,275,684	35,788	12,570	4,324,042
	%	0.0%	89.3%	2.3%	0.3%	6.8%	0.3%	1.1%	100.0%	98.3%	0.6%	0.3%	100.0%
2006	2004	1,171	2,390,404	126,305	10,293	187,897	18,897	84,899	2,828,728	2,803,671	52,801	82,054	2,828,728
	%	0.0%	84.5%	4.4%	0.4%	6.8%	0.7%	3.4%	100.0%	94.9%	1.9%	3.3%	100.0%
2006	2005	30,519	2,516,889	219,140	3,318	244,057	143,279	145,105	3,302,007	2,923,885	257,798	120,388	3,302,007
	%	0.9%	76.2%	6.6%	0.1%	7.4%	4.3%	4.4%	100.0%	88.5%	7.8%	3.6%	100.0%

**10D. New Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date**

FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White (Hispanic)	More Than One Race	Unknown or Not Reported	**Total of Hispanics or Latinos by Racial Categories	FOREIGN Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B	Number of Foreign Protocols with Enrollment data (New Form):
2002	2001	1,461	0	4	0	1,659	683	175	3,982	267,962	102
	%	36.7%	0.0%	0.1%	0.0%	41.7%	17.2%	4.4%	100.0%	92.6%	
2003	2002	1,844	3	1,222	0	632	4,528	1,594	9,623	1,929,682	213
	%	17.1%	0.0%	12.7%	0.0%	6.6%	47.1%	16.6%	100.0%	38.2%	
2004	2003	116	14	12,778	0	4,537	11,879	6,486	35,789	3,996,746	285
	%	0.3%	0.0%	35.7%	0.0%	12.7%	33.2%	18.1%	100.0%	92.4%	
2006	2004	882	8	1,64	0	26,161	14,664	11,124	52,801	2,683,316	321
	%	1.3%	0.0%	0.3%	0.0%	49.5%	27.8%	21.1%	100.0%	91.3%	
2006	2005	29,576	101	1,842	689	42,865	136,326	46,558	257,756	3,002,068	434
	%	11.5%	0.0%	0.7%	0.3%	16.6%	52.9%	18.1%	100.0%	90.8%	

\* These totals must agree  
\*\* These totals must agree

**Table 11. FOREIGN PROTOCOLS: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY2002-2006: Enrollment Using U.S. Race/Ethnicity Categories**

11A. Part A. Phase III FIVE YEAR SUMMARY TOTALS: FOREIGN SUBJECTS IN FOREIGN PROTOCOLS (Old + New Forms)											
FY Reported	FY Funded		Females		Males		Unknown		Total Foreign Subjects (Old + New Forms)	Subtotal: Foreign Subjects Enrolled by US Minority Categories	Number of Foreign Protocols with Enrollment data (Old + New Forms):
2002	2001		14,359		15,911		41		30,311	18,308	172
	%		47.4%		52.5%		0.1%		100.0%	60.4%	
2003	2002		28,037		21,237		136		49,410	23,927	209
	%		56.7%		43.0%		0.3%		100.0%	48.4%	
2004	2003		24,020		25,023		83		49,126	37,126	24
	%		48.9%		50.9%		0.2%		100.0%	75.6%	
2005	2004		29,388		23,163		2,547		55,098	44,281	30
	%		53.3%		42.0%		4.6%		100.0%	80.4%	
2006	2005		55,599		42,354		1,180		99,133	84,412	60
	%		56.1%		42.7%		1.2%		100.0%	85.2%	

**Table 11A Comments:**

1. The percent females varied from 47.4% to 56.7% in Phase III foreign protocols from 2002-2006; the percent males varied from 42.0% to 52.5%.
2. The percent foreign subjects enrolled by U.S. Minority Categories in Phase III foreign protocols increased from 60.4% to 85.2% from 2002 to 2006.
3. Total Phase III foreign enrollment increased from 30,311 to 99,133 during these 5 years.
4. The number of Phase III foreign protocols dropped from 209 in 2003 to 60 in 2006.

**Table 11. FOREIGN PROTOCOLS: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY2002-2006: Enrollment Using U.S. Race/Ethnicity Categories**

**NOTE 1:** The shaded portions of the Tables B, C and D below show the race/ethnicity categories that are identified as minority categories. The Data Reported in FY 2002 and later are from the new Population Tracking System that was deployed with data reported in FY 2002 and later, and allows separate reporting using the Old Form and the New Form, and separate reporting for Foreign and Domestic Data.

**NOTE 2:** Data from Tables 11B, 11C and 11D are combined to provide the summary data in Table A.

11B. OLD FORM: Total of All FOREIGN Subjects Reported Using the 1977 OMB Standards in a combined race/ethnicity format											
FY Reported	FY Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/Other	Total Foreign Enrollment (Old Form)	FOREIGN Subtotal Using US Minority Categories (shaded): OLD FORM		Number of Foreign Protocols with Enrollment data (Old Form):
2002	2001	59	12,269	2,807	1,724	9,579	1,558	27,996	16,859		166
	%	0.2%	43.8%	10.0%	6.2%	34.2%	5.6%	100.0%	60.2%		
2003	2002	77	12,428	280	3,499	15,054	8,077	39,415	16,284		188
	%	0.2%	31.5%	0.7%	8.9%	38.2%	20.6%	100.0%	41.3%		
2004	2003	1	12,068	52	1,007	3,093	7,603	23,824	13,128		10
	%	0.0%	50.7%	0.2%	4.2%	13.0%	31.9%	100.0%	55.1%		
2005	2004	0	12,252	1	1,183	2,257	14	15,707	13,436		6
	%	0.0%	78.0%	0.0%	7.5%	14.4%	0.1%	100.0%	85.5%		
2006	2005	16	12,295	30	12	4,533	675	17,561	12,353		8
	%	0.1%	70.0%	0.2%	0.1%	25.8%	3.8%	100.0%	70.3%		

11C. NEW FORM Part A: Inclusion Enrollment Report (Total of All FOREIGN Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats)													
Part A: TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race													
Total of All Subjects by Race													
FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White	More Than One Race	Unknown or Not Reported	*Total of All Subjects by Racial Categories (New Form)	Total of All Subjects by Ethnicity			
										Not Hispanic	**Hispanic or Latino	Unknown/Not Reported	*Total of All Subjects by Ethnic Category
2002	2001	0	1	1,448	0	113	0	753	2,315	1,562	0	753	2,315
	%	0.0%	0.0%	62.5%	0.0%	4.9%	0.0%	32.5%	100.0%	67.5%	0.0%	32.5%	100.0%
2003	2002	7	23	7,610	0	1,095	0	1,260	9,995	8,720	3	1,272	9,995
	%	0.1%	0.2%	76.1%	0.0%	11.0%	0.0%	12.6%	100.0%	87.2%	0.0%	12.7%	100.0%
2004	2003	0	12	21,414	0	553	2,570	753	25,302	21,972	2,572	758	25,302
	%	0.0%	0.0%	84.6%	0.0%	2.2%	10.2%	3.0%	100.0%	86.8%	10.2%	3.0%	100.0%
2005	2004	389	4,272	25,948	0	7,576	0	1,206	39,391	38,122	624	645	39,391
	%	1.0%	10.8%	65.9%	0.0%	19.2%	0.0%	3.1%	100.0%	96.8%	1.6%	1.6%	100.0%
2006	2005	1,906	27,048	27,513	5	8,093	169	26,839	91,572	60,670	17,484	3,418	81,572
	%	2.1%	29.5%	30.0%	0.0%	8.8%	0.2%	29.3%	100.0%	74.4%	21.4%	4.2%	100.0%

11D. New Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date											
FY Reported	FY Funded	American Indian or Alaska Native	Asian	Black or African American	Native Hawaiian or Pacific Islander	White (Hispanic)	More Than One Race	Unknown or Not Reported	**Total of Hispanics or Latinos by Racial Categories	FOREIGN Subtotal Using US Minority Categories (shaded): NEW FORM Parts A+B	Number of Foreign Protocols with Enrollment data (New Form):
2002	2001	0	0	0	0	0	0	0	0	1,449	6
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	62.6%	
2003	2002	0	0	0	0	2	0	1	3	7,643	21
	%	0.0%	0.0%	0.0%	0.0%	66.7%	0.0%	33.3%	100.0%	76.5%	
2004	2003	0	0	0	0	2	2,570	0	2,572	23,999	14
	%	0.0%	0.0%	0.0%	0.0%	0.1%	99.9%	0.0%	100.0%	94.8%	
2005	2004	389	0	0	0	4	0	232	624	30,845	25
	%	62.2%	0.0%	0.0%	0.0%	0.6%	0.0%	37.2%	100.0%	78.3%	
2006	2005	1,849	3	213	0	1,328	1	14,090	17,484	72,069	52
	%	10.6%	0.0%	1.2%	0.0%	7.6%	0.0%	80.6%	100.0%	78.7%	

\* These totals must agree  
 \*\* These totals must agree

**Appendix F**

**Report of the Advisory Committee on Research on Women's  
Health**

**Office of Research on Women's Health and  
NIH Support for Research on Women's Health Issues  
Fiscal Years 2005 & 2006**

Following are excerpts of the report—the Introduction and Overview. The full report will be available at <http://orwh.od.nih.gov/>.

## Introduction

When the National Institutes of Health announced that it was establishing an Office of Research on Women's Health (ORWH) in September 1990, there were great expectations of what might result, but it is unlikely that, at that time, anyone expected the magnitude of programs and accomplishments related to women's health research and careers that would flourish across the NIH in the years that would follow.

The ORWH became the first office within the Department of Health and Human Services to have the specific purpose of addressing women's health issues, yet its initial intent was to abate the criticisms that NIH did not have a consistent or enforced policy that required the inclusion of women in the research that it funded, especially when that research was on conditions that were not female specific. Over the years that have followed, the NIH Institutes and Centers, often with ORWH's collaborative support, have funded research that addresses specific gaps in knowledge about women. But they also have independently given increasing attention to ensuring research that allows comparisons of differences, or similarities, between men and women in responses to interventions being examined through clinical research. And, these concepts are beginning to penetrate the thinking at the basic laboratory research level, although without a specific NIH policy requirement. While the ORWH has specific goals to enhance women's health research, develop programs to promote biomedical career advancement for women, and, for both men and women, to conduct women's health research or studies that provide sex/gender aspects of health by comparing men and women in their responses to the interventions studied, the ORWH has continued its initial mission by leading trans-NIH efforts for consistent monitoring of the inclusion of women and minorities in clinical research.

This report is a comprehensive summary of all of the activities and programs of the ORWH, as well as an Executive Summary followed by more detailed information of highlights of women's health research within the NIH ICs and Office of the Director Program Offices.

Many continue to attempt to evaluate progress on women's health research by referring to budgetary expenditures on women's health when compared to men's health. This is not the most reliable way to assess progress, primarily because basic laboratory studies are at the foundation of progress about women's health, and often such basic studies have the potential to increase knowledge about both men and women, or serve as the foundation for ensuing clinical research. Further, with the current concepts of women's health extending beyond that of the reproductive system, and with the NIH policy of inclusion requiring that both men and women be included in clinical research on conditions that affect them—therefore, referring to research that is not female specific, both sexes are included in the studies. The result is that NIH research dollars must be summarized as that related to women's health research, that related to men's health research, and that related to, or including, both men and women. Consequently, the figures reported as specific for women's health research must be considered to be less than the total spent to explore women's health, with consideration of the additional amount listed under both. A section included in this report, based upon figures provided by the ICs, provides specific amounts for FY 2005 and FY 2006 included in this report.

Approximately \$3.5 billion was spent each year on sex/gender-specific research related to women's health. In addition, over \$22.5 billion was spent on research that benefits both women and men as either basic or laboratory research or clinical studies that included both women and men. Another way of reporting this data is that almost 13 percent of the NIH research budget was expended on research specific to women, almost 6 percent was expended on research specific to men, while the overwhelming majority (over 81 percent) of research funds were spent on research that either included both women and men, or was laboratory investigation that was important for exploring the health of both women and men.

Report of the Advisory Committee on Research on Women's Health

In accordance with the NIH Revitalization Act of 1993<sup>2</sup>, the Office of Research on Women's Health (ORWH) collaborated with NIH staff and members of the Coordinating Committee on Research on Women's Health (CCRWH)<sup>3</sup> to provide these programmatic summaries of NIH research and other efforts related to women's health in FY 2005 and 2006. The ORWH also describes its role in catalyzing interdisciplinary career development and research centers on women's health and sex/gender research. In addition, the Office develops programs to strengthen and foster women's participation and advancement in biomedical careers and to promote careers for both men and women to conduct women's health or sex/gender based research. A complete listing of research, career development, and other projects supported by the ORWH during FY 2005 and 2006 is included in the appendices. The specific trans-NIH activities that monitor and track the inclusion of women and minorities in clinical research are also described. Highlights of women's health and sex/gender research supported by the NIH institutes, centers, and offices are also included in this report. The NIH Institutes and Centers with grant-making authority have reported progress in basic, clinical, and/or translational research that is benefiting girls and women, as well as serving to identify if and when sex/gender differences exist. The Offices within the Office of the NIH Director have also contributed to this research and this report.

A major ORWH research area relates to interdisciplinary programs. One of these programs is the Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCOR). Eleven SCOR Centers have demonstrated exciting new developments from interdisciplinary research approaches to advancing studies on how sex and gender factors affect women's health. Each SCOR promotes interdisciplinary collaborations and the development of research bridging basic and clinical sciences on sex and gender factors underlying a priority health issue. Research areas addressed by the centers include mental health, reproductive health, pain disorders, substance abuse, and urinary tract health. The SCOR program complements other federally supported programs addressing women's health issues. Another major interdisciplinary program is the Building Interdisciplinary Research Careers in Women's Health (BIRCWH). The BIRCWH program grants provide an opportunity for institutions to be involved in women's health and sex/gender oriented research and to build a national supply of investigators by providing research training in conjunction with strong scientific and career mentoring that will enhance the career development of the women and men who are selected as scholars. This program has made impressive progress, with the 35 BIRCWH centers producing 287 scholars, most of whom have gone on to academic positions and received NIH grant awards. Other career development programs supported by the ORWH include the Women's Reproductive Health Research Career Development Centers (WRHR) of the National Institute of Child Health and Human Development, and numerous other NIH RFAs and PAs.

The NIH ICs and Offices present a brief accounting of their scientific advances in the Executive Summary section of this report. More detailed discussions of these advances are included in the section on Reports of the Institutes, Centers, and Offices.

This report is prepared for, and reviewed by, the Advisory Committee on Research on Women's Health, that has the responsibility for preparing a report on the activities related to women's health at the NIH.

You are invited to read this in-depth report to become acquainted with the tremendous advancements that have taken place during this 2-year period and the promise for even greater advancements in the future, representing the broad diversity and success of the ORWH, and the trans-NIH activities to advance the health of women and men, and career opportunities in biomedical sciences.

Vivian W. Pinn, M.D.  
Associate Director for Research on Women's Health  
Director, Office of Research on Women's Health

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<sup>2</sup>Public Law 103-43, 107, stat. 22 (codified at 42 USC [sec.486 (A)]).

<sup>3</sup>See pages 17-20 for a list of the CCRWH members.



## Executive Summary

### OVERVIEW

The scope and expansion of women's health research across the NIH has been remarkable over the past two years. This report is evidence of the progress that has been achieved. In this Overview, we describe the missions of the NIH Institutes and Centers (ICs), with a special focus on how they address women's health issues. The Highlights of Institute and Center Activities section that follows provides a synopsis of their research agenda and accomplishments in women's health that have been achieved in FY 2005 and 2006. Readers are encouraged to review the detailed reports of the individual NIH ICs that follow. These present important advances in understanding diseases and conditions that disproportionately affect women.

The Fogarty International Center (FIC) supports a range of research and research training programs, many of which include activities on women's health. Research training programs working in low- and mid-income nations on topics, such as population and health, maternal and child health, AIDS, and stigma and global health, represent FIC's efforts that include significant attention to women's health issues. The ORWH supports many of these efforts, along with other NIH Institutes. In addition, the FIC and the ORWH have teamed up to explore issues facing women in science in developing countries and to consider gender and global health issues. These initiatives have informed the programmatic directions of the FIC and other NIH ICs.

Cancer continues to take a devastating toll on American women. However, important progress is being achieved in the fight against cancer overall as well as specific cancers differentially affecting women. These include cancer of the breast, cervix, ovaries, endometrium, colon and rectum, and lung as well as malignancies associated with acquired immunodeficiency syndrome (AIDS). In 2007, an estimated 678,060 women will be diagnosed with cancer, and approximately 270,100 women will die of the disease. Despite these

grim statistics, the U.S. is making important progress against cancer. Incidence rates for cancer of all sites, sexes, and populations combined were stable from 1992 through 2003 after increases that started in 1975. Incidence rates for cancer overall for women were stable from 1975 through 1979 but then increased from 1979 through 2003. However, there was a 6 percent relative decline in breast cancer incidence among women between 2002 and 2003, including a 14 percent decrease in 50- to 60-year-olds who had been diagnosed with estrogen receptor (ER) positive breast cancer. The decrease in this age group may be due to the recent decline in use of hormone therapy (HT) by postmenopausal women. Mortality rates for all cancers have declined, but the annual decline in men is twice as large as that for women. While mortality has decreased for 10 of the top 15 cancers in women, lung cancer deaths in women continue to increase, although at a slower rate in more recent years. Survival rates for cancer patients show improvement overall, although the amount of improvement is slightly less for women than men. The National Cancer Institute (NCI) supports an extensive research program through their intramural and extramural programs, with a number of programs and activities focusing on women's cancers, including the NCI Office of Women's Health, located within the NCI Office of Science Planning and Assessment; the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention; the Breast Cancer Surveillance Consortium (BCSC) and the International Breast Screening Network in the Division of Cancer Control and Population Sciences; the Gynecologic Oncology Group (GOG) and the Clinical Trials Cooperative Group in the Division of Cancer Treatment and Diagnosis; the intramural Breast and Gynecologic Malignancies Faculty and the trans-NCI Human Papillomavirus (HPV) Working Group. By working with partners from public, private, and academic settings and focusing investment in strategic areas with high potential, we hope to accelerate the pace of discovery and facil-

Report of the Advisory Committee on Research on Women's Health

tate the translation of research knowledge into clinical applications.

The mission of the National Center for Complementary and Alternative Medicine (NCCAM) is to explore complementary and alternative healing practices in the context of rigorous science, train CAM researchers, and disseminate authoritative information to the public and professionals. Complementary and alternative medicine (CAM) encompasses those health care and medical practices that are not currently an integral part of conventional medicine. The list of CAM practices and therapies changes as interventions proven to be safe and effective become accepted as mainstream health care practices. The NCCAM groups CAM practices within the following areas: (1) whole medical systems (i.e., traditional Chinese medicine, naturopathic medicine, Ayurveda); (2) mind-body medicine (i.e., meditation, yoga); (3) biologically based practices (i.e., herbal therapies, special diets); (4) manipulative and body-based practices (i.e., chiropractic, massage); and (5) energy medicine (i.e., Reiki, Qi gong). The NCCAM conducts and supports basic and applied (clinical) research and research training within these areas. CAM therapies are used to treat a broad range of health conditions by both men and women, including back and neck problems, allergies, fatigue, arthritis, headaches, diabetes, and CVD. CAM therapies for women treat a variety of conditions, such as menopausal symptoms, breast cancer, osteoporosis, pain associated with osteoarthritis and fibromyalgia, and reproductive issues. Thus, NCCAM's research portfolio includes investigations focused on a variety of diseases, using a myriad of CAM therapeutic interventions.

The National Center for Research Resources (NCRR) provides laboratory scientists and clinical researchers with the environments and tools they need to understand, detect, treat, and prevent a wide range of diseases. This support enables discoveries that begin at a molecular and cellular level to move to animal-based studies and on to patient-oriented clinical research, resulting in cures and treatments for both common and rare diseases. The NCRR develops and supports a wide range of biomedical resources. Through its support of multidisciplinary research, the NCRR is uniquely positioned to provide funds directly

for research or to act in partnership with other NIH components to address emerging clinical and basic research needs, including those addressing women's health issues.

The National Center on Minority Health and Health Disparities (NCMHD) promotes minority health and leads, coordinates, and assesses the NIH effort to reduce and eliminate health disparities. To achieve its mission, the NCMHD employs a multifaceted strategy to conduct and support research in basic, clinical, social, and behavioral sciences; disseminate information, promote research infrastructure and training; foster emerging programs; and extend its reach to minority and other health disparity communities. Congress mandated the development of three principal programs within the NCMHD aimed at addressing health disparities: the Loan Repayment Program, the Centers of Excellence Program, and the Research Endowment Program. Additionally, the NCMHD supports the Research Infrastructure in Minority Institutions Program (RIMI) and the Minority Health and Health Disparities International Research Training Program (MHIRT). These combined efforts position the NCMHD to lead and coordinate the NIH health disparities activities for the benefit all affected populations, including women of diverse populations.

The mission of the National Eye Institute (NEI) is to conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons. The major causes of blindness (i.e., glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and men. However, because women live longer on average than men, more women than men are affected by these age-related eye diseases in the U.S. Several eye conditions affect women significantly more frequently than men. These conditions are optic neuritis, a demyelinating disease of the optic nerve that may be a precursor of multiple sclerosis; dry eye, a common condition that is associated with decreased tear secretion and in most cases mild discomfort, but in more severe cases may result in corneal scarring and blindness; corneal endothelial dystrophy, a slowly progressive

disease that occurs when endothelial cells deteriorate as a result of cell loss from age or trauma; keratoconus, a visually disabling thinning disorder of the central cornea that results in irregular astigmatism, progressive corneal distortion, and corneal scarring; and age-related macular degeneration, a deterioration of the region of the retina that is responsible for high-resolution vision.

The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for research, training, and education programs to promote the prevention and treatment of heart, lung, and blood diseases. The NHLBI stimulates basic discoveries about the causes of disease, speeds the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public. The NHLBI creates and supports a collaborative research infrastructure in partnership with private and public organizations. The Institute also collaborates with patients, families, health care professionals, scientists, professional societies, patient-advocacy groups, community organizations, and the media to maximize the use of research results and resources to address the public health needs of the nation. The NHLBI places high priority on improving the cardiovascular health of women through its research programs, which have generated new knowledge about the influences of lifestyle, menopause, chest pain, hypertension, diabetes, and drug treatment (including hormone therapy) in women and also have led to improved diagnostic tests and treatment guidelines for women. The NHLBI has had responsibility for the NIH Women's Health Initiative since 1998 and provides support for the Women's Ischemia Syndrome Evaluation as well as other important studies.

The National Human Genome Research Institute (NHGRI) led the NIH's contribution to the International Human Genome Project (HGP). The finished sequence of the human genome was completed in April 2003, and has already begun to change the way we address research on women's health. In October 2005, a different international consortium of scientists from six countries, led by the NHGRI, announced the production of a different map of the human genome, one that may prove

even more powerful because of its medical applications. The result is the "HapMap." Like the earlier sequence, all of the data from the HapMap has been placed in the public domain. The HPG spelled out the letters of the DNA code that all human beings share. The HapMap provides detailed information about the variation in the genome. The HapMap investigates those spelling differences in the human instruction book that predispose some people to different types of cancer as well as other diseases. In December 2006, the NHGRI awarded a contract to continue the HapMap Project to make it an even more powerful tool to reveal the way in which genetic variation is organized into chromosomal neighborhoods. As this information unfolds, the NHGRI will continue to investigate diseases specific to women. In 1994, NHGRI investigators were among the first to report that women carrying the gene mutations called Breast Cancer 1 (BRCA1) or Breast Cancer 2 (BRCA2) have a higher risk of developing both breast and ovarian cancer than women without such mutations. The NHGRI continues to investigate the role of these genes in breast and ovarian cancer, and this research has led to better screening and treatment of those with a family history of breast cancer. In hopes of expanding the usefulness of this research, the NHGRI also supports research that explores the effect of educating women of different ages and ethnic group about benefits of genetic screening in evaluating their risk of inherited diseases.

The National Institute of Allergy and Infectious Diseases (NIAID) funds basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses that affect the health of women and girls. The NIAID involves women in many of its clinical studies on the treatment and prevention of autoimmune diseases, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and sexually transmitted infections (STIs). The NIAID also collaborates with other organizations on research initiatives aimed at improving women's health.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, clinical, and epidemiologic research, research training, and information

Report of the Advisory Committee on Research on Women's Health

programs on many of the more debilitating diseases affecting Americans. The NIAMS supports research on a number of diseases that disproportionately affect women including osteoarthritis, osteoporosis, rheumatoid arthritis, temporomandibular joint and muscle disorders (TMJD), fibromyalgia, scleroderma, and systemic lupus erythematosus (lupus). Scleroderma and lupus are diseases in which health disparities have been clearly identified. The NIAMS is committed to uncovering the bases of these gender, racial, and ethnic disparities and to devising effective strategies to treat or prevent them.

The National Institute of Biomedical Imaging and Bioengineering (NIBIB), which was established by law in December 2000, is the newest research institute within the NIH. This Institute serves as the hub within the NIH for the coordination of biomedical imaging and bioengineering efforts. The NIBIB: (1) fosters, conducts, supports, and administers research and research training programs in biomedical imaging and bioengineering by means of grants, contracts, and cooperative agreements; (2) provides coordination, integration, and review of progress and planning of biomedical imaging and bioengineering research; (3) formulates research goals and long-range plans with the guidance of the National Advisory Council for Biomedical Imaging and Bioengineering; and (4) sponsors scientific meetings and symposia, collaborates with industry and academia, and fosters international cooperation regarding biomedical imaging and bioengineering. The NIBIB recognizes the significant potential of improved imaging technologies in early disease detection. During FY 2005 and 2006, the NIBIB funded grants that were focused on women's health research or technologies aimed at improving devices for female populations. These projects range from advanced imaging methodologies to new drug delivery systems designed specifically for women's diseases, such as breast cancer, and disorders and conditions that predominate in women, such as osteoporosis. Researchers supported by the NIBIB plan to develop high resolution x-ray grids in mammography to detect breast cancer at its earliest stage, thereby greatly increasing patient survival rates. In addition, NIBIB-funded investigators are working on novel drug delivery treatments that will

promote bone resorption for women suffering from osteoporosis. During the past two years, the NIBIB supported research on women's health in the following disease areas: aging, autoimmune disease, breast cancer, cervical cancer, reproduction, diabetes-related research, obesity, epilepsy, HIV/AIDS, heart disease, osteoporosis, and TMJD.

The National Institute of Child Health and Human Development (NICHD) sponsors research that spans human growth and development, starting from before conception and continuing through infancy, childhood, and adolescence. This research covers all critical stages of development that provide the foundation for adult health. The Institute's research aims to overcome many of the complex challenges that face women in addition to those faced by their children and families. The NICHD's portfolio includes research on infertility, preterm birth, complications of childbirth, HIV infection in women, parenting, and many other scientific areas that are critical to improving the quality of life for women.

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to promote the general health of the American people by improving craniofacial, oral, and dental health through research. As a central part of this mission, the NIDCR funds scientific research to prevent diseases and improve the quality of life for the millions of Americans who suffer from chronic and infectious diseases affecting the mouth and face. NIDCR-supported research spans areas as diverse as understanding the oral infections that lead to dental decay, periodontal diseases, and recurrent herpes lesions; oral manifestations of osteoporosis and other bone diseases; salivary gland dysfunction and disease; craniofacial birth defects and developmental disorders; and connective tissue diseases and disorders. The NIDCR has a long tradition of support and leadership in the field of pain research, including conditions where gender-based differences have been reported, such as temporomandibular joint and muscle disorders (TMJD). The NIDCR's commitment to the fundamental study of the body's hard tissues, such as teeth, cartilage, and bone, has led to advances in biomaterials research and to the emerging field of tissue engineering and biomimetics, fields that use the body's own cellular and molecu-

lar processes to repair and regenerate tissues and organs. Among the NIDCR's efforts in this area are studies that are characterizing the TMJ disk at tissue and cellular levels, thus providing vital information that will one day allow for biological approaches to reconstruct or regenerate the temporomandibular joint. Recognizing the importance of gene-to-gene, gene-environment, and behavioral interactions, the Institute has long emphasized the importance of genetic, behavioral, social science, and epidemiological research. The research advances that affect women in particular are to be found within many of the Institute's broad research categories.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Within NIDDK's research mission, diseases and health risks that disproportionately, predominantly, or solely affect women include gestational diabetes; obesity (especially in racial and ethnic minority populations); coronary artery disease; cardiovascular and end-stage renal disease associated with diabetes; eating disorders; irritable bowel syndrome (IBS) and other functional gastrointestinal disorders; osteoporosis; thyroid diseases (including Graves disease, goiter, and hypothyroidism); hyperparathyroidism; gallstones; primary biliary cirrhosis; painful bladder syndrome/interstitial cystitis (PBS/IC); urinary tract infections (UTIs); urinary NIDDK mission also may have an important impact on diseases that are primarily within the mission of other ICs, such as hormonal factors in breast cancer and the relationship of obesity to cardiovascular disease (CVD). The NIDDK supports research that directly addresses important women's health issues, both through basic research directed to understanding underlying disease processes and through clinical research that translates this understanding into therapies and preventive interventions.

Because environmental agents are likely to play a role in a numbers of diseases that differentially affect females, the National Institute of Environmental Health Sciences (NIEHS) supports research on diseases such as breast

cancer, osteoporosis, ovarian dysfunction, uterine fibroids, and autoimmune diseases. The Institute's approach is to define the underlying susceptibilities to these diseases, to investigate the role of estrogenic and other endocrine-active compounds in their etiology, to identify important environmental triggers for their development and important nutritional factors that can reduce risk, and to determine the importance of the timing of exposure on disease risk. As results of these studies become available, women can better determine how to alter lifestyle factors leading to these diseases, and environmental health regulators can better define standards that protect women from environmental triggers of these diseases. The Institute has several groups that focus on women's health, including the Laboratory of Reproductive and Developmental Toxicology, the Hormones and Cancer Group, the Chromatin and Gene Expression Group, and the Comparative Pathology Group. These research groups and others are conducting basic research on issues such as toxicology and reproductive and developmental health, hormone regulation of tumor development and growth in target organs, including the uterus and mammary gland, genetic regulation of cancer susceptibility, as well as epidemiologic research on women's health issues, such as fertility, early pregnancy, and uterine fibroids. By understanding the basic mechanisms of disease, new therapeutic interventions can be developed to prevent and treat these diseases.

The mission of the National Institute of General Medical Sciences (NIGMS) is to support research and research training for the basic biomedical sciences. For example, the NIGMS supports research on cell structure and function, from the outer plasma membrane to the activation of genes in the nucleus. This knowledge is necessary to understand the disease process. Most studies supported by the NIGMS do not target any particular disease or condition but rather encompass basic research in cellular and molecular biology, chemistry, biochemistry, molecular biophysics, and genetics. Often basic research supported by the Institute will result in findings pertinent to women's health.

The National Institute of Mental Health (NIMH) supports research on a range of mental disorders, including those that affect



Report of the Advisory Committee on Research on Women's Health

women exclusively, such as perinatal depression, or are more prevalent in women, such as eating disorders. Through programs, such as the Women's Mental Health Team, the NIMH has fostered interdisciplinary collaboration and research to improve diagnosis, treatment, services, and the prevention of mental disorders in women. Data on the epidemiology of mental disorders and associated disability highlight differences in both the prevalence and clinical course of mental disorders between men and women. Starting in childhood, girls have higher rates of anxiety disorders and eating disorders than boys, while boys are more likely to suffer from autism and attention deficit disorder. After puberty, women have higher rates than men of depression, eating disorders, and anxiety disorders, including posttraumatic stress disorder. The course and severity of mental disorders also differ between men and women. For example, men have an earlier average age of onset of schizophrenia, while women are more likely to suffer from the rapid cycling form of bipolar disorder. Within the female populations, some women are at increased risk of depression during certain times of reproductive change, such as the perinatal period. Through its research programs and related programmatic activities, the NIMH seeks to improve scientific understanding of the effects of sex and gender differences in mental health and mental illness.

The National Institute of Neurological Disorders and Stroke (NINDS) mission is to reduce the burden of neurological disease, a burden borne by every age group, every segment of society, and people all over the world. Most nervous system disorders affect men and women equally, but certain disorders are more prevalent in or are of special interest to women. Examples of such diseases include multiple sclerosis (MS), pain, stroke, epilepsy, and Rett syndrome. MS is a chronic autoimmune disease of the central nervous system that causes inflammation and the loss of myelin, a protective covering around nerve fibers. MS is one of the most common neurological disorders leading to disability in young adults. Hormonal factors may influence some forms of MS, making them more common in women. Strokes are caused by a rapid disruption in the blood supply to part

of the brain as a result of blood vessel blockage (ischemic stroke) or blood vessel rupture (hemorrhagic stroke). A stroke can result in sudden numbness or weakness, confusion, trouble with vision, speech, or coordination, or a sudden severe headache. Stroke is the third leading cause of death in the U.S. and a major cause of disability in both women and men. In general, women have a lower risk of stroke than men, but because of their longer life expectancy, they account for 60 percent of stroke fatalities. Epilepsy is characterized by chronic, recurring seizures caused by abnormal electrical activity in the brain. Although anti-epileptic drugs (AEDs), brain stimulation, or surgery can help many patients control the disorder, for others, the seizures are resistant to therapy or the treatments cause unacceptable side effects. Women with epilepsy can face special problems, such as increased seizure frequency during phases of the menstrual cycle (called catamenial epilepsy). Female patients taking selected AEDs must consider changing medications if they wish to become pregnant since certain AEDs can cause higher-than-normal rates of birth defects. Rett syndrome is a childhood neurological impairment seen almost exclusively in females, causing severe cognitive impairment, autistic behavior, stereotypic movements, and frequently seizures. The NINDS supports basic, translational, and clinical research on these and other neurological disorders.

The mission of the National Institute of Nursing Research (NINR) is to support clinical and basic research that establishes a scientific basis for the care of individuals across the life span. NINR-supported research encompasses the health of individuals, their families, and their caregivers. It also focuses on the special needs of at-risk and underserved populations, with an emphasis on health disparities. The Institute's research focus transcends many disciplines to promote health and improve patient and caregiver quality of life across a broad range of diseases and conditions. The NINR unites the disciplines of biological and behavioral sciences to elucidate the complex interactions between the physiological factors of health and disease and the behavior, decisions, and perceptions of the individual. In 2006, the NINR released its new five-year strategic plan, titled *Changing Practice, Changing*

*Lives*. Developed in close consultation with representatives of the extramural community, this new plan details the NINR's scientific priorities. The Institute will focus its research on health promotion and disease prevention; improving quality of life through self-management, symptom management, and caregiving; eliminating health disparities; and leading critical research on the end of life. The plan also highlights four cross-cutting strategies for advancing nursing science, including advancing the integration of biological and behavioral sciences, promoting the design and use of new patient care technologies, improving nursing science methods, and developing the next generation of investigators. The NINR's mission and research goals are inherently suited to addressing the current challenges in women's health research.

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies of Alzheimer's disease and other dementias, menopause and hormone therapy, osteoporosis, physical disability, and other diseases and conditions. NIA-supported investigators continue to explore the reasons behind gender differences in disability, morbidity, and mortality at older ages. In addition, the NIA supports an extensive program of research pertaining to health disparities among special populations. The NIA has several ongoing research initiatives dealing specifically with women's health, including the Study of Women's Health Across the Nation (SWAN), the Women's Health Initiative Study of Cognitive Aging (WHISCA), and Women's Health and Aging Study (WHAS). These studies and others are providing valuable information about the menopausal transition in women of diverse racial and ethnic backgrounds; the effects of hormone therapy on memory and cognitive functions; disability among older women; and other health issues of importance to older women, who are more likely than men to live alone and in poverty and to be institutionalized at an earlier age.

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports research on the behavioral and medical causes and consequences of alcohol use, abuse, and alcoholism, and on new ways to prevent and treat these significant public health problems. It is

estimated that there are 18 million alcohol-abusing or alcohol-dependent individuals in the U.S., of which more than four million are women. Women drink less alcohol and have fewer alcohol-related problems and dependence symptoms than men, but among the heaviest drinkers, women equal or surpass men in the problems that occur because of their drinking. In contrast to young people who begin drinking at age 21, equal numbers of young men and women who begin drinking at age 13 are four times more likely to develop alcohol dependence sometime during their lifetime. The NIAAA continues to expand its research portfolio on the impact of alcohol and alcohol misuse on women's health. Research related to women's health is found in each programmatic division of the institute. Because of the multidimensional and multidisciplinary nature of alcohol use disorders and their prevalence worldwide, collaborative research endeavors on a national and international scale are required for progress toward the goals of reducing alcohol abuse disorders and alcoholism among women. Significant scientific advances in understanding the causes, consequences, prevention, and treatment of alcohol use, abuse, and dependence among women have occurred in the past two fiscal years.

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on normal mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. The Institute also conducts and supports research and research training that is related to disease prevention and health promotion. The research portfolio addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute also supports efforts to create devices that substitute for lost and impaired sensory and communication functions. A number of diseases, disorders, or conditions within the mission of the NIDCD affect women disproportionately.

The National Institute on Drug Abuse (NIDA) addresses critical questions concerning drug abuse and addiction by monitoring emerging trends, identifying and studying underlying physiological and social factors,



Report of the Advisory Committee on Research on Women's Health

and determining how best to use this knowledge to develop, test, and implement prevention and treatment programs. An important focus in NIDA's portfolio is research to investigate issues specific to women and to sex/gender differences in drug abuse and addiction. There is a complex relationship between drug use and biological vulnerability that may vary by sex or gender. Growing evidence suggests that drug abuse may begin and progress differently for men and women. These patterns of progression are characterized by different risk and protective factors and motivations and carry different consequences. In recognition of the important role that sex/gender plays in drug abuse, sex/gender research findings are being taken into account in the design, testing, and implementation of interventions to prevent and treat drug abuse and to provide services for both males and females. NIDA has established a Women and Gender Research Group to promote research on issues specific to women and substance abuse. This group has representation from all of NIDA's divisions and offices, covering topics from genetics and basic biology to risk factors, prevention, consequences, and treatment of substance abuse. The major goal of this effort is to infuse the study of sex/gender differences and female-specific issues in all areas of drug abuse research and to disseminate research findings.

In addition to the involvement of the NIH ICs mentioned before, several of the Offices within the Office of the Director of NIH participate in activities related to women's health and sex/gender issues. The Office of Dietary Supplements (ODS) supports research to expand the evaluation of the role of dietary supplements in disease prevention and risk reduction associated with diseases of interest to women, including breast cancer. In addition, ODS supports research to further scientific understanding of the biochemical and cellular effects of dietary supplements on biological systems and their physiological impact across the life cycle. The Office of Behavioral and Social Sciences Research (OBSSR) opened on July 1, 1995. Congress established OBSSR in recognition of the key role that behavioral and social factors play in illness and health. The OBSSR mission is to stimulate behavioral and social sciences research throughout the

NIH and to integrate these areas of research more fully into other NIH health research enterprises, thereby improving the understanding, treatment, and prevention of diseases. Many of these diseases are related to women's health, such as type two diabetes, coronary heart disease, obesity, addictive behaviors, and disorders of mood and affect. The Office of Rare Diseases (ORD) seeks to stimulate and coordinate research on rare diseases and to support research to respond to the needs of patients who have one of the approximately 7,000 rare diseases recognized today. Several of these rare diseases differentially affect women, including lymphangioleiomyomatosis, Rett syndrome, congenital adrenal hyperplasia, and preeclampsia. The ORD collaborates with the NIH ICs and Offices to stimulate research on rare diseases, to foster collaborations with other national and international entities, and to support a range of outreach activities related to rare diseases. The Office of AIDS Research (OAR) was established in 1988. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every NIH IC. The NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection, its associated co-infections, opportunistic infections, malignancies, and other complications. This diverse basic, clinical, and behavioral research portfolio demands an unprecedented level of scientific coordination and management of research funds. The OAR coordinates the scientific, budgetary, and policy elements of NIH AIDS research. Through its unique, trans-NIH planning, budgeting, and portfolio assessment processes, the OAR ensures that research dollars are invested in the highest priority areas of scientific opportunity. As such, the OAR represents the roadmap for NIH AIDS research, allowing NIH to pursue a united research front against the pandemic. The trans-NIH strategic plan for AIDS research establishes an agenda in the following areas of emphasis: vaccines; therapeutics; etiology and pathogenesis; natural history and epidemiology; behavioral and social science; training, infrastructure, and capacity building; and information dissemination. Research relevant to the needs of women is addressed in all of these areas.

## Index

- ¡Cuidate! ... 2-240  
 \$1,000 Genome Initiative ... 3-40, 3-176  
 \$100,000 Genome Initiative ... 3-40, 3-176  
 Abdomen ... 2-135, 2-230  
 Abdominal Fat ... 2-135, 2-230  
 Abstinence ... 2-47, 2-159, 2-163, 2-240, 3-127  
 Academic Health Centers ... 3-99, 3-130, 3-142, 3-207  
 Access to Care ... 1-10, 2-78, 2-153, 2-229, 3-14, 4-30  
 Acculturation ... 2-153, 2-229, 3-14  
 ACE (see Autism Centers of Excellence)  
 ACEs (see Autoimmunity Centers of Excellence)  
 Acetaminophen ... 2-125, 2-165:2-166, 2-194  
 Achievement ... 2-202  
 Acoustic Nerve (see Vestibulocochlear Nerve)  
 Acquired Immunodeficiency Syndrome ... 1-11, 1-15, 1-20, 2-2, 2-17:2-18, 2-28, 2-33, 2-47, 2-61, 2-68, 2-72:2-79, 2-82, 2-84:2-90, 2-94:2-95, 2-97:2-101, 2-114:2-115, 2-120, 2-130, 2-135, 2-153:2-154, 2-159, 2-163, 2-167, 2-172:2-173, 2-184:2-185, 2-191, 2-193, 2-204, 2-211, 2-213, 2-215, 2-219, 2-225:2-226, 2-233:2-234, 2-240, 2-249, 2-255, 2-259, 2-262, 3-2, 3-7:3-8, 3-21, 3-23:3-24, 3-28, 3-32, 3-45, 3-85, 3-96:3-98, 3-106, 3-110, 3-116:3-117, 3-123:3-124, 3-126, 3-131, 3-134:3-136, 3-153, 3-162, 3-170, 3-175, 3-181, 3-189, 3-200, 3-205, 3-208, 3-211:3-212, 3-216, 3-228, 3-236, 4-20, 4-25, 4-30, B-1:B-2, B-6:B-7, C-2, F-4, F-6:F-7, F-11  
 Action for Health in Diabetes ... 2-128, 2-144:2-145, 2-221, 2-235, 3-96, 3-116  
 ACTIVE (see Advanced Cognitive Training for Independent and Vital Elderly)  
 Activities of Daily Living ... 2-63, 2-205:2-206, 3-86  
 Acupuncture ... 2-46, 2-69, 2-131, 2-155, 2-170, 3-85, 3-114, 3-120:3-121, 3-131  
 Acupuncture Therapy ... 2-46, 2-69, 2-131, 2-155, 2-170, 3-85, 3-114, 3-120:3-121, 3-131  
 Acute Liver Failure Study Group ... 2-125, 2-165, 2-193  
 Acute Respiratory Distress Syndrome ... 2-250  
 AD (see Alzheimer Disease)  
 Ad Hoc Working Group on Minority Research ... 2-225  
 Adamantanes ... 2-83, 3-39  
 Adaptive Immune Response ... 2-92, 3-77  
 ADD (see Attention Deficit Disorder)  
 Addiction ... 1-24, 2-3, 2-7, 2-23, 2-25, 2-27, 2-32:2-37, 2-39:2-40, 2-42:2-45, 2-47:2-48, 2-66, 2-71, 2-79, 2-84, 2-88, 2-95, 2-98, 2-101, 2-123:2-124, 2-130, 2-147, 2-153:2-154, 2-159:2-160, 2-172, 2-180, 2-190:2-191, 2-226, 2-242, 3-11, 3-43:3-44, 3-62, 3-84, 3-97, 3-106, 3-123:3-124, 3-126:3-127, 3-132, 3-179, 3-183, 3-199, 3-226, 3-228:3-229, 3-232, 3-243, 3-245, B-3, F-10:F-11  
 Addictive Behavior (see Behavior, Addictive)  
 ADEAR (see Alzheimer's Disease Education and Referral)  
 ADHD (see Attention Deficit Disorder with Hyperactivity)  
 Adhesion ... 2-108, 2-114, 2-208, 3-111, 3-189  
 Adhesives ... 2-208, 3-111, 3-189  
 Adjustment ... 1-19  
 Adjuvants ... 2-80, 2-92:2-93, 3-76:3-77, 4-28  
 Administrator ... E-7  
 Adolescent ... 2-12, 2-18, 2-25, 2-33, 2-35, 2-42:2-44, 2-77, 2-84:2-85, 2-94, 2-97, 2-101, 2-106, 2-128, 2-130, 2-141:2-142, 2-145, 2-149:2-150, 2-162:2-163, 2-174, 2-179:2-180, 2-182:2-183, 2-188, 2-190:2-193, 2-199:2-204, 2-211, 2-226, 2-228, 2-240, 2-261, 3-1, 3-4:3-5, 3-10:3-11, 3-16, 3-22, 3-24, 3-116:3-117, 3-119, 3-124, 3-149, 3-157, 3-225, 3-228, 3-235, 3-240:3-241, 4-17, F-7  
 Adolescent Development ... 2-43, 2-150, 2-203, 3-241  
 Adolescent Health ... 2-188, 3-5, 3-16  
 Adolescent Medicine ... 2-85, 2-204  
 Adolescent Medicine Trials Network for HIV/AIDS Interventions ... 2-85, 2-204  
 Adult Stem Cells ... 3-60  
 Advanced Cognitive Training for Independent and Vital Elderly ... 2-205  
 Advancing Novel Science in Women's Health Research ... 2-166  
 Adverse Event ... 1-30:1-31, 2-149, 2-204, 3-15, 3-100, 3-244, 4-32  
 Advisory Council to the Director, NIH ... C-4  
 African Americans ... 2-14, 2-20:2-21, 2-65:2-66, 2-68, 2-84, 2-87, 2-112, 2-125, 2-127, 2-134, 2-141, 2-145, 2-148, 2-175, 2-198, 2-213, 2-215:2-220, 2-222, 2-224:2-227, 2-229:2-236, 2-238, 2-242:2-243, 3-7, 3-11, 3-13, 3-17, 3-19:3-20, 3-25, 3-32, 3-124:3-125, 3-172, 3-183, 3-199, 3-222, 3-225, 3-227, 3-231, 3-235:3-236, 3-238, 3-240, 3-242, 4-7:4-8, 4-12:4-13, 4-15, 4-24:4-26, 4-28, D-7, E-10, E-34, E-37, E-44, E-46  
 Age-Related Eye Disease Study ... 2-53, 2-126, 2-129, 2-139, 2-160, 3-6, 3-35, 3-117, 3-155  
 Age-Related Macular Degeneration ... 1-9, 2-38, 2-53, 2-129, 2-139:2-140, 2-160, 3-35:3-36, 3-117, 3-155  
 Agency for Healthcare Research and Quality ... 2-7, 2-221, 2-236, 3-51, 3-137, 3-191  
 Agent Orange & Dioxin ... 2-249:2-250  
 Aggression ... 2-47, 2-159, 3-126  
 Aging ... 1-10, 1-14:1-15, 2-2:2-3, 2-6, 2-28, 2-33:2-34, 2-38, 2-54, 2-71, 2-97, 2-133, 2-172, 2-174:2-177, 2-179:2-183, 2-185:2-186, 2-189, 2-191, 2-195, 2-206, 2-209, 2-211, 2-218, 2-227, 2-247, 2-250, 3-9, 3-15, 3-20, 3-23:3-24, 3-30, 3-47, 3-53, 3-61, 3-110, 3-116, 3-141, 3-185, 3-213, 3-217, 3-222, 3-224:3-225, 3-227, 3-236, 3-241, 4-1, 4-3:4-5, 4-9:4-14, B-3, F-7, F-10  
 AHRQ (see Agency for Healthcare Research and Quality)  
 AIDS (see Acquired Immunodeficiency Syndrome)  
 AIDS Clinical Trials Group ... 2-94  
 AIDS International Training and Research Program ... 2-99, 3-134:3-135, 3-208, 3-211:3-212  
 AIDS Malignancy Consortium ... 2-78  
 AIDS Vaccines ... 2-18, 2-61, 2-74:2-75, 2-78, 2-84:2-88, 2-90, 2-94:2-95, 2-97:2-100, 2-172, 2-191, 2-204, 3-2, 3-23:3-24, 3-97, 3-106, 3-116:3-117, 3-236  
 AIDSinfo ... 2-89, 2-219  
 Alcohol Biosensors Program ... 2-126, 2-139, 3-184  
 Alcohol Consumption ... 2-42:2-43, 2-50, 2-54, 2-119, 2-122, 2-126:2-128, 2-134, 2-139, 2-141, 2-149:2-150, 2-177, 2-203:2-204, 2-227, 2-247, 3-14:3-15, 3-19, 3-76, 3-80, 3-184, 3-228:3-229, 3-241, 3-243:3-244, B-4, F-10  
 Alcohol-Related Disorders ... 2-43, 2-126, 2-139, 2-150, 2-177, 2-203, 3-241, 3-243, F-10  
 Alcoholic Liver Disease ... 2-122, 2-175  
 Alcoholism ... 1-15, 2-7, 2-50, 2-54, 2-59:2-60, 2-71, 2-95, 2-101, 2-123:2-124, 2-126, 2-134, 2-139, 2-144, 2-153, 2-158, 2-172, 2-211, 2-250, 3-43, 3-74, 3-76, 3-80, 3-106, 3-133, 3-229, 3-232, 3-243, B-3, F-10  
 Allergens ... 2-128, 2-143, 2-161, 2-220, 3-21:3-22, 3-61, 3-118  
 Allergic (see Hypersensitivity)  
 Allergic Rhinitis (Hay Fever) ... 2-250  
 Allergies ... 2-116, 2-143, 2-220, 3-71, 3-132, B-2, F-5  
 Allergy ... 2-161, 2-248, 3-21, 3-118, D-8  
 Allergy and Immunology ... 2-161, 3-21, 3-118  
 Alliance of Glycobiologists for detection of Cancer and Cancer Risk ... 3-64, 3-105, 3-188  
 Alopecia Areata ... 2-106:2-107, 2-113, 3-149, 3-156, 3-159

- Alopecia Areata Registry ... 2-113, 3-149, 3-159  
 ALS (see Amyotrophic Lateral Sclerosis)  
 Alternative Medicine (see Complementary and Alternative Medicine)  
 Alzheimer Disease ... 1-6:1-7, 2-31, 2-33:2-34, 2-38, 2-40, 2-44, 2-51:2-52, 2-54, 2-56, 2-60, 2-63, 2-120, 2-132, 2-169, 2-180, 2-182, 2-188, 2-193, 2-204:2-205, 2-250, 3-2, 3-16, 3-32, 3-60, 3-62, 3-70, 3-87, 3-93, 3-109, 3-131, 3-148, 3-156, 3-162, 3-165, 3-170, 3-189, 3-217, 3-227, 3-236, 4-1:4-9, 4-13, 4-42, B-3, F-10  
 Alzheimer's Clinical Research and Training Awards Act ... 4-7  
 Alzheimer's Disease Centers ... **4-2:4-7**, 1-7, 2-38, 2-54, 4-9, 4-42  
 Alzheimer's Disease Cooperative Study ... 2-38, 2-52, 3-131, 4-5:4-6  
 Alzheimer's Disease Education and Referral ... 3-227, 3-236, 4-7  
 Alzheimer's Disease Genetics Initiative ... 2-54, 4-4  
 Alzheimer's Disease Neuroimaging Initiative ... 2-38, 2-51, 2-204:2-205, 4-5:4-7  
 Alzheimer's Disease Research Centers ... 4-4  
 American Cancer Society ... 2-3  
 American Indian ... 2-43, 2-195, 2-233:2-234, 3-22, 3-240, 4-25, E-10, E-15:E-18, E-34, E-40, E-44, E-46  
 American Indian/Alaska Native ... 3-231, 4-25:4-26, E-10, E-15:E-18  
 American Medical Association ... 3-89  
 Amino Acid Motifs ... 3-50  
 Amino Acids ... 2-196, 3-82, B-6  
 Amnesia ... 2-31, 2-47, 2-159, 3-126  
 Amyloid ... 2-38, 4-8:4-9  
 Amyloid Beta-Protein ... 4-8  
 Amyloid Beta-Protein Precursor ... 2-38, 4-8:4-9  
 Amyloid Plaques ... 4-3  
 Amyotrophic Lateral Sclerosis ... 2-32, 2-58, 2-68:2-69, 2-250, 3-109, 3-155, 3-166, 4-8:4-9  
 Analgesia ... 2-45, 2-59, 2-65, 2-131, 2-155, 2-168:2-169, 3-63, 3-113  
 Analgesic Drugs ... 2-45, 2-70, 2-168, 3-59, 3-63, 3-68  
 Analgesics, Non-Narcotic ... 2-45, 2-168, 3-63  
 Analgesics, Opioid ... 2-45, 2-131, 2-155, 2-168, 3-63, 3-113  
 Andersen Syndrome ... 4-33  
 Anemia ... 2-122  
 Anesthetics ... 2-64, 2-138, 3-102  
 Angel Flight NIH ... 4-34  
 Angina Pectoris ... 2-121  
 Angiogenesis ... 2-6, 2-17:2-18, 3-60, 3-62, 3-64, 3-79  
 Angiogenesis Inhibitors ... 2-6, 2-18  
 Angiotensin-Converting Enzyme Inhibitors ... 4-14  
 Animal Husbandry ... 1-32  
 Animal Welfare ... 1-18, 1-31  
 Ankylosing Spondylitis ... 2-106  
 Anorexia ... 2-250  
 Anoxia ... 2-158, 3-115:3-116  
 ANSWHR (see Advancing Novel Science in Women's Health Research)  
 Antalarmin (see Pyrimidines)  
 Anthrax ... 1-11, 2-73, 2-77, 2-80:2-81, 2-83, 2-90, 2-100, 2-250, 3-39, 3-216  
 Anthrax Vaccines ... 1-11, 2-73, 2-77, 2-80:2-81, 2-83, 2-90, 2-100, 2-250, 3-39, 3-216  
 Anti-Infective Agents ... 2-89, 2-148, 3-133  
 Anti-influenza drugs ... 2-80  
 Antibiotic ... 1-11, 2-88, 2-91, 2-137, 3-68, 3-133  
 Antibodies, Monoclonal ... 2-14, 3-21, 3-135  
 Anticonvulsant Screening Program ... 2-37  
 Antidepressive Agents ... 2-63:2-64, 2-150, 2-204, 3-47  
 Antigens ... 2-10, 3-172, 3-183  
 Antimicrobial Agents ... 2-85, 2-91  
 Antimicrobial Resistance ... 2-76, 2-91:2-92, 2-250, 3-133  
 Antioxidants ... 2-53, 2-56, 2-160, 3-85, 3-87, 3-117, 3-131  
 Antiphospholipid Syndrome ... 2-106, 4-33  
 Antiretroviral Medications ... 2-78  
 Antiretroviral Therapy, Highly Active ... 1-10  
 Antiviral Agents ... 2-18, 2-86, 2-166, 3-122  
 Anxiety ... 2-60, 2-141, 2-144, 2-164, 2-184, 2-199, 2-206, 2-227, 3-19, 3-43, 3-74, 3-128  
 Anxiety Disorders ... 2-32, 2-36, 2-204, 3-233, F-9  
 Aortic Aneurysms ... 2-165, 3-62, 3-79:3-80, 3-121  
 Apert Syndrome ... 2-197, 3-72  
 Aphasia ... 2-250  
 Apnea, Sleep ... 2-121  
 ApoE ... 2-54, 3-156  
 ApoE4 ... 2-40  
 Apoptosis ... 3-45  
 APP Protein, Human (see Amyloid Beta-Protein Precursor)  
 Appetite ... 2-33, 2-46:2-47, 2-50, 2-133, 3-80  
 Appetite Regulation ... 2-46, 2-133  
 Appointments ... 3-218  
 Appropriations ... 1-19, 3-191, 4-17, C-2  
 Arctic ... 2-250, 3-228  
 AREDS (see Age-Related Eye Disease Study)  
 AREDS2 (see Age-Related Eye Disease Study)  
 Arm ... 2-70, 2-208, 3-46, 3-166, 3-221, 4-14  
 Arteriosclerosis ... 3-59, 3-64, 3-105, 3-188  
 Arteriovenous ... 2-132, 2-161, 3-71, 3-140, 3-186  
 Arteriovenous Fistula ... 2-161, 3-140  
 Arteriovenous Graft ... 2-161  
 Arthritis ... 1-15, 2-69, 2-103:2-108, 2-110:2-111, 2-113:2-114, 2-117:2-118, 2-122, 2-136, 2-167, 2-170, 2-172, 2-236, 2-250, 3-32, 3-62, 3-85, 3-87, 3-96, 3-121, 3-128, 3-131, 3-147, 3-156, 3-241, 4-17, B-2:B-3, F-5:F-7  
 Artificial Intelligence ... 1-28  
 Artificial Limb ... 2-186, 2-208  
 Asian ... 2-196, 2-216:2-217, 2-225:2-226, 2-228, 2-230, 3-10, 3-17, 3-25, 3-82, 3-158, 3-199, 4-7, 4-25, D-7, E-9:E-10, E-34, E-37, E-44, E-46  
 Asian Americans ... 2-14, 2-213, 2-220, 2-223, 2-229, 2-233:2-234, 2-236, 3-13, 3-199, 3-227, 3-240, D-7, E-9:E-10, E-15:E-18  
 Asperger's Disorder ... 4-37:4-38  
 Aspergillosis ... 2-83, 3-39  
 Aspirin ... 2-161, 3-140  
 Assistive Technology ... 2-194, 2-250  
 Asthma ... 2-116, 2-121, 2-123, 2-127:2-128, 2-130, 2-132, 2-143:2-144, 2-153, 2-157, 2-161, 2-169, 2-174, 2-189, 2-216, 2-218, 2-220, 2-229, 2-234, 2-251, 3-14, 3-21, 3-24, 3-28, 3-61, 3-71, 3-73, 3-85, 3-92, 3-98, 3-118, 3-125, 3-131:3-132, 3-162, 3-189, 4-27, B-2  
 Asthma Exacerbations: Biology and Disease Progression ... 2-130, 3-92  
 Ataxia Telangiectasia ... 2-72, 2-251  
 Atherosclerosis ... 2-18, 2-148, 2-226, 2-230, 2-251, 3-17, 3-25, 3-192, 4-3, 4-5  
 Atherosclerosis Risk in Communities ... 2-148, 2-230, 3-25  
 Atrial Fibrillation ... 2-121, 2-174, 3-32, 3-166  
 Atrial Septal Defects (see Heart Septal Defects, Atrial)  
 Attention Deficit Disorder ... 2-251, F-9  
 Attention Deficit Disorder with Hyperactivity ... 2-32, 2-34, 2-151, 3-33, 3-36:3-37, 3-177, 3-230  
 Attitudes ... 2-87, 2-228, 3-4, 3-10, 3-149, 3-157, 3-236  
 Audiology ... D-2  
 Auditory Hair Cell (see Hair Cells, Auditory)  
 Auditory Nerve ... 2-46, 2-210, 3-174  
 Autism ... 1-6:1-7, 2-32:2-34, 2-36, 2-41:2-42, 2-72, 2-180, 2-183, 2-185, 2-189, 2-202, 2-251, 3-24, 3-48, 3-148, 3-162, 3-189, 3-225, 4-2, 4-36:4-41, 4-46, F-9  
 Autism Centers of Excellence ... **4-36:4-41**, 1-6:1-7, 2-41, 2-110, 4-2, 4-46

- Autism Spectrum Disorders ... 2-36, 4-36:4-41
- Auto-Antibodies ... 2-103
- Autoantibodies ... 2-108
- Autoantigens ... 2-110
- Autoimmune Disease ... **2-103:2-118**, 1-3, 1-7, 1-20, 2-39, 2-53, 2-120, 2-122, 2-135, 2-138, 2-154, 2-157, 2-217, 2-226, 2-251, 3-11:3-12, 3-18, 3-45, 3-61, 3-69, 3-71, 3-77:3-78, 3-103, 3-107, 3-110, 3-112, 3-132, 3-149, 3-156, 3-159, A-5, B-2, F-6:F-9
- Autoimmune Disease Coordinating Committee ... 2-104, 4-9
- Autoimmunity ... 2-103, 2-107:2-108, 2-110, 2-115, 3-110
- Autoimmunity Centers of Excellence ... 2-110, 4-36
- Avian Flu ... 2-80, 2-93, 3-34, 3-228
- AZT ... 2-73
- B-Cells ... 3-77
- Back Pain ... 2-131, 2-170, 3-128
- Bacteria ... 1-12, 1-23, 2-45, 2-73, 2-76, 2-83, 2-87, 2-91, 2-96, 2-115, 2-122, 2-124, 2-135, 2-137:2-138, 2-225, 3-29, 3-39, 3-57, 3-62, 3-69, 3-84, 3-133, 3-169:3-171, 3-179, 3-189, C-7
- Bacterial Endocarditis ... 2-83, 3-40
- Bacterial Infection ... 3-169
- Bacterial Toxins ... 2-91
- Bacteriological Techniques ... 2-87
- Bacteriology ... D-1
- Baltimore Longitudinal Study of Aging ... 2-189, 3-9, 4-13
- Bariatric Surgery ... 2-130, 2-162, 2-201, 3-119, 4-14
- Base Pairs ... 3-27:3-29, 3-35, 3-41, 3-169, 3-176
- Base Sequence ... 2-83, 2-96, 2-151, 3-27:3-30, 3-39:3-41, 3-44:3-45, 3-47, 3-50, 3-52, 3-61, 3-65:3-66, 3-78, 3-148, 3-154, 3-165, 3-169, 3-172, 3-176:3-177, 3-183
- Basic Behavioral and Social Science ... 2-79, 2-251
- Basic Research ... **3-55:3-87**, 1-7, 1-10, 2-8, 2-17, 2-56, 2-74:2-77, 2-82, 2-86, 2-91, 2-120, 2-124:2-126, 2-132, 2-139, 2-142, 2-161, 2-164, 2-199, 2-217, 2-224, 2-239, 3-32, 3-91, 3-93, 3-103, 3-105, 3-109, 3-133, 3-136, 3-139, 3-144, 3-151, 3-162, 3-166, 3-168, 3-174, 3-184, 3-186:3-188, 3-199, 4-9:4-10, 4-19, 4-22:4-23, B-1, F-5, F-8:F-9
- Batten Disease ... 2-69, 2-251, 3-109
- Becker Muscular Dystrophy (see Duchenne/Becker Muscular Dystrophy)
- Behavior Therapy ... 2-47, 2-130, 2-159, 2-164, 3-126, 3-128, 3-163
- Behavior, Addictive ... 2-23, 2-25, 2-27, 2-34, 2-42:2-43, 2-45, 2-47, 2-66, 2-88, 2-98, 2-123, 2-130, 2-147, 2-153:2-154, 2-159, 2-190:2-191, 3-11, 3-43:3-44, 3-84, 3-123, 3-126:3-127, 3-132, 3-179, 3-183, 3-228, 3-243, 3-245, B-3
- Behavioral and Social Science ... 1-4, 1-15, 2-18, 2-74, 2-78:2-79, 2-145, 2-239, 2-251, 3-62, 3-86, 3-193, 3-206, 4-30, B-6, F-11
- Behavioral Interventions ... 2-79, 2-90, 2-127:2-128, 3-96, 4-38:4-39, E-11
- Behavioral Research ... 1-3, 1-5, 1-9, 1-14, 1-22, 1-28, 1-31:1-32, 2-89, 2-214, 2-222, 2-225, 2-234, 2-240:2-241, 2-246, 3-199, 3-209, 3-214, 3-221, 3-223, 3-232, 4-24, A-4, B-5, B-7, C-4, E-8, F-11
- Behavioral Science ... 1-24, 2-210:2-211, 2-221, 2-245, 3-1, 3-55, 3-84, 3-141, 3-192:3-193, 3-198, 3-207, 3-210, B-4, F-5, F-9:F-10
- Behaviors, Health ... 3-4
- Behaviors, Risk ... 2-240
- Benign Prostatic Hyperplasia ... 2-122, 2-175
- Best Pharmaceuticals for Children Act ... 3-123
- Beta Carotene ... 2-53, 2-160, 3-117
- Beta Cell Biology Consortium ... 2-109, 2-114, 2-125, 2-135, 3-60, 3-78
- Beta Interferon ... 2-53
- Beta-Thalassemia ... 2-63, 3-109
- Bioassays ... 3-154
- Biocompatible Materials ... 2-197, 3-72
- Biodefense ... **2-73:2-102**, 1-3, 1-7, 1-29, 2-17:2-18, 2-61:2-62, 2-120, 2-135, 2-154, 2-204, 2-227, 2-251, 3-19, 3-21, 3-24, 3-39:3-40, 3-45, 3-52, 3-76:3-78, 3-106, 3-116:3-117, 3-124, 3-134:3-136, 3-154, 3-160, 3-185, 3-192, 3-208, 3-212, 3-216, 3-236
- Biodefense Research ... 2-74, 2-76, 2-81:2-82, 2-90, 2-93, 2-100:2-101
- Biodefense Research Infrastructure ... 2-93
- Biodefense Strategy ... 2-73
- Biodefense Therapeutics ... 2-92
- Biodefense Vaccines ... 2-90
- Biodosimetry ... 2-81
- Bioengineering Consortium ... 3-167
- Bioengineering Research Partnership ... 2-91, 3-167, 3-192
- Bioethical Issues ... 1-31
- Bioethics ... 1-31, 3-205
- Bioinformatics (see Computational Biology)
- Bioinformatics Resource Centers ... 2-83, 3-39
- Biological Countermeasures Research ... 2-80
- Biological Marker ... 2-127, 2-133, 2-188, 3-5, 3-9, 3-16, 3-42, 3-79, 3-214
- Biological Specimen Repositories ... 2-106
- Biological Toxins ... 2-73
- Biological, Chemical, or Nuclear/Radiological Terrorism ... 2-80
- Biomarkers ... 2-7:2-8, 2-20, 2-25, 2-27, 2-36, 2-38, 2-41, 2-51, 2-53:2-54, 2-57, 2-105, 2-109:2-110, 2-112, 2-124:2-125, 2-134, 2-145, 2-147:2-148, 2-164, 2-191, 2-204, 2-225, 3-42, 3-63, 3-76, 3-87, 3-92, 3-102, 3-112, 3-144, 3-180, 3-208, 4-6, 4-8, 4-12, B-3
- Biomarkers Consortium ... 2-109, 2-114, 2-195, 3-47, 3-79, 3-110
- Biomaterials ... 2-38, 2-60, 2-144, 3-43, 3-74, F-7
- Biomedical Informatics Research Network ... 3-151, 3-161, 3-173, 3-187
- Biomedical Information Systems ... **3-145:3-163**
- Biomedical Research Training Programs for Individuals from Underrepresented Groups ... 2-244
- Biomedical Technology ... 1-4, 3-64, 3-74, 3-104:3-105, 3-167:3-168, 3-173, 3-187:3-188, B-4
- Biomedical Technology Research Resources ... 3-64, 3-74:3-75, 3-104:3-105, 3-168, 3-173, 3-187:3-188
- Biometry ... D-6
- BioMS ... 2-53, 2-112, 3-112
- Biophysics ... 3-181, B-2, D-1, D-6, F-8
- Biopsies ... 2-9, 2-21, 2-56, 3-37, 3-125, 3-159, 3-183, 4-22
- Biopsy ... 2-24, 2-116, 2-157, 3-12, 3-103, 3-129, 3-171, 3-182
- Biosecurity ... 1-29, 2-74, 2-94
- Biosensors ... 2-126, 2-139, 3-184
- Biostatistics ... 2-188, 3-5, 3-16, 3-198:3-199, 3-214, D-1
- Biotechnology ... 1-14, 1-27, 1-29, 2-251, 3-79, 3-165, 4-20, D-1
- Bioterrorism ... 1-11, 2-80, 2-83, 2-90, 2-92, 2-148, 3-39, 3-76, A-5, B-2
- Bipolar Disorder ... 2-39, 2-58, 2-64, 2-130, 2-154, 3-31, 3-33, 3-36:3-37, 3-95, 3-97, 3-113, 3-162, 3-189, F-9
- Bird Flu (see Avian Flu)
- Birth ... 2-73, 2-107, 2-119, 2-179:2-180, 2-183:2-184, 2-187, 2-189, 2-195, 2-198, 2-259, 3-20, 3-24, 3-66
- Birth Defects ... 2-33, 2-180, 2-184, 2-196:2-197, 3-71:3-72, 3-81, 4-33, F-7, F-9
- Birth Rate ... 4-38
- Birth Weight, Low ... 2-181, 2-259
- Bisexual ... 2-97, 2-191, 3-24, 3-116
- Bismuth Subsalicylate ... 2-206
- Blacks ... E-15:E-18
- Bladder ... 2-5, 2-14, 2-96, 2-135, 3-6, 3-14, 3-38
- Bladder Disease ... 2-171
- Bleeding ... 2-122:2-123, 2-156, 3-174

- Blind Persons ... F-5  
 Blindness ... 2-38, 2-49, 2-53, 2-121, 2-123, 2-129, 2-155:2-156, 2-160, 2-176, 2-197, 2-207, 3-31, 3-57, 3-79, 3-82, 3-114, 3-117, 3-138, 3-190, 4-12, B-2, F-5  
 Blister-Causing Agents ... 2-81  
 Blood ... 1-15, 2-2, 2-51, 2-73, 2-84, 2-87, 2-93, 2-120:2-121, 2-131, 2-133, 2-146, 2-152, 2-171, 2-175, 2-179, 2-188, 2-196, 2-205, 2-220, 2-237, 3-9, 3-11, 3-21, 3-42, 3-49, 3-58, 3-62, 3-83, 3-106, 3-156, 3-185, 4-4, 4-6, 4-32, B-1, E-2, F-6  
 Blood Banks ... 2-87, 3-21, D-8  
 Blood Circulation ... 2-133, 2-156, 3-157  
 Blood Clot ... 2-122, 2-156, 3-58, 3-108, 3-174  
 Blood Coagulation Disorders ... 2-122  
 Blood Diseases ... 2-63, 2-122, 3-109, F-6  
 Blood Donors ... 2-86:2-87, 3-21  
 Blood Glucose ... 2-146, 2-220, 2-237, 3-11  
 Blood Pressure ... 2-146, 2-153, 2-164, 2-219:2-220, 2-229, 2-237, 3-11, 3-14, 3-79, 3-128, 3-148  
 Blood Transfusion ... 2-86:2-87, 3-21  
 Blood Vessel ... 1-9, 2-6, 2-18, 2-121, 2-132, 2-160, 2-226, 3-17, 3-60, 3-62, 3-71, 3-79, 3-138, 3-186, B-1, F-9  
 Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research ... 2-90  
 Blue Ribbon Panel on Influenza Research ... 2-80, 2-101  
 Blueprint for Neuroscience Research ... 2-39, 2-57, 2-63, 2-72, 3-86, 3-198, 3-208  
 BMI (see Body Mass Index)  
 Body Mass Index ... 2-121, 2-188:2-189  
 Body Weight ... 2-7, 2-25, 2-121, 2-128, 2-140:2-141, 2-191, 2-198, 3-36, 3-155, 3-235  
 Bone Diseases ... 2-124, 2-141, 3-9, 3-236, F-7  
 Bone Diseases, Metabolic ... 2-124  
 Bone Growth ... 2-201, 3-240  
 Bone Mineral Content ... 2-149, 2-201  
 Bone Mineral Density ... 2-127, 2-141, 2-188, 2-227, 3-9  
 Bone Resorption ... F-7  
 Bones ... 1-9, 2-115, 2-122, 2-126, 2-137, 2-149, 2-176, 2-186, 2-201, 2-208, 2-224, 3-69, 3-106, 3-192, 3-201, 3-232, 3-236:3-237, F-7  
 Border Epidemiology Work Group ... 2-228, 3-10, 3-157  
 Boston Area Community Health Study ... 3-19  
 Botulinum Toxins ... 2-101  
 Botulism ... 2-92  
 Brain ... 1-24, 2-2, 2-19, 2-23, 2-31:2-32, 2-35:2-40, 2-43:2-51, 2-54, 2-56, 2-59, 2-61, 2-63:2-65, 2-67, 2-70:2-71, 2-124:2-125, 2-133:2-134, 2-136, 2-138, 2-150, 2-155:2-156, 2-167:2-169, 2-172, 2-179, 2-183, 2-185:2-188, 2-190, 2-197, 2-203, 2-205:2-206, 3-5, 3-11, 3-16, 3-23, 3-33, 3-37, 3-43, 3-47, 3-62:3-63, 3-68, 3-70, 3-72, 3-76, 3-80, 3-82:3-85, 3-87, 3-101, 3-113:3-114, 3-131:3-132, 3-157, 3-165:3-166, 3-170, 3-179, 3-195, 3-241, 4-3:4-6, 4-8, 4-13, 4-39:4-40, B-3, F-9  
 Brain Cancer ... 2-251  
 Brain Development ... 2-35, 2-43:2-44, 2-47, 2-61, 2-150, 2-159, 2-183, 2-187:2-188, 2-190, 2-193, 2-203, 3-5, 3-11, 3-16, 3-126, 3-241  
 Brain Disorders ... 2-32, 2-40, 2-42, 2-49, 2-60, 2-193, 2-207, 2-251, 3-44, 3-125, 3-183, 3-190, 3-228:3-229, B-3  
 Brain Disorders in the Developing World ... 2-40, 2-60, 2-193  
 Brain Imaging ... 2-31, 2-35:2-36, 2-39, 2-43:2-45, 2-143, 2-188, 2-190, 3-11, 3-84:3-85, 3-131, 3-179, 4-5  
 Brain Injuries ... 2-49  
 Brain Pathology ... 4-7  
 Brain stimulation ... 2-49, 2-207, 3-170, 3-190, F-9  
 Brain Tumor ... 2-19, 2-29, 2-63, 2-67:2-68, 2-72, 3-109  
 BRCA1 ... 3-33, F-6  
 BRCA2 ... 3-33, F-6  
 BRCA2 Protein ... 3-33  
 Breast ... 2-2:2-3, 2-5, 2-14, 2-20, 2-24, 2-133, 2-231, 3-3, 3-6, 3-9, 3-12:3-14, 3-32:3-33, 3-38, 3-42, 3-63, 3-129, 3-170:3-171, 4-25:4-26, F-4, F-6  
 Breast Cancer ... 2-2:2-3, 2-5:2-6, 2-8, 2-13, 2-15:2-16, 2-18:2-19, 2-23:2-24, 2-84, 2-167, 2-184, 2-192, 2-227, 2-235, 2-251, 3-3:3-4, 3-12, 3-23, 3-32:3-33, 3-64, 3-124, 3-129, 3-135, 3-147, 3-149, 3-158, 3-171, 4-26, 4-28, F-4:F-8, F-11  
 Breast Cancer 1 (see BRCA1)  
 Breast Cancer 2 (see BRCA2)  
 Breast Cancer and Environment Research Centers ... 2-2, 2-5, 2-23, 2-192  
 Breast Cancer Surveillance Consortium ... 2-24, 3-12, 3-129, F-4  
 BreastCancerTrials.org ... 3-151  
 Bridges to the Future Program ... 2-235  
 Brittle Bone Disease ... 2-149, 2-201  
 Building Interdisciplinary Research Careers in Women's Health ... 3-203, 3-215, F-3  
 Buildings and Facilities, NIH ... 1-25  
 Burch Surgical Technique ... 2-162, 3-119  
 Burden of Illness ... 1-4, 2-3, 2-12, 2-17, 2-32:2-34, 2-40, 2-53, 2-75, 2-104:2-106, 2-111, 2-119:2-120, 2-123, 2-128, 2-160, 2-174, 2-180, 2-182, 2-192, 2-196, 2-214, 2-216, 2-239, 3-3, 3-7, 3-17, 3-19, 3-117, 3-141, 3-185, 3-223, 3-245, 4-4, 4-11, 4-18:4-19, 4-25, 4-33, 4-37, B-2:B-3, F-9  
 C. elegans (see Caenorhabditis elegans)  
 caBIG (see cancer Biomedical Informatics Grid)  
 Cadherins ... 2-114  
 Caenorhabditis elegans ... 3-29, 3-34, 3-57  
 Calcinosin ... 2-135, 2-230  
 Calcium ... 2-201, 3-240  
 CALERIE (see Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy)  
 caMatch ... 3-151  
 Cancer ... **2-1:2-29**, 1-3, 1-7, 1-9:1-10, 1-14:1-15, 1-23:1-24, 2-32:2-33, 2-47, 2-68, 2-76, 2-78, 2-84, 2-86, 2-109, 2-114, 2-120:2-121, 2-123, 2-133:2-135, 2-145, 2-147:2-148, 2-167, 2-171, 2-180, 2-182, 2-184, 2-191:2-192, 2-194:2-195, 2-208, 2-211, 2-213, 2-215:2-216, 2-219:2-220, 2-227, 2-231:2-237, 2-245, 2-251:2-252, 2-255, 2-257:2-259, 2-262, 3-1:3-4, 3-6, 3-9, 3-12:3-14, 3-23, 3-25, 3-28, 3-32:3-34, 3-37:3-39, 3-42:3-47, 3-51, 3-56:3-61, 3-63:3-64, 3-69:3-70, 3-73:3-75, 3-79, 3-89, 3-92:3-96, 3-102:3-105, 3-110:3-111, 3-115, 3-124:3-126, 3-129:3-130, 3-132, 3-135:3-136, 3-140, 3-143, 3-145:3-147, 3-149:3-152, 3-154, 3-158, 3-161:3-162, 3-166:3-167, 3-170:3-172, 3-175, 3-178, 3-180:3-183, 3-186:3-190, 3-192, 3-199, 3-225:3-227, 3-231:3-234, 3-238, 3-240, 4-10:4-11, 4-25:4-26, 4-28:4-30, A-5, B-1, F-4:F-8, F-11  
 cancer Biomedical Informatics Grid ... 2-11, 3-6, 3-151, 3-190  
 Cancer Care and Outcomes Research Surveillance Consortium ... 2-24, 3-12, 3-129  
 Cancer Centers ... 2-2, 2-6, 2-11, 2-13:2-14, 2-27:2-28, 2-245, 3-95, 3-135  
 Cancer Control ... 2-11, 2-24, 2-27, 3-12, 3-129, 3-149, 3-161, F-4  
 Cancer Control P.L.A.N.E.T. ... 2-11, 2-27, 3-149  
 Cancer Detection ... 2-5, 2-9:2-10, 2-20, 2-24, 3-12, 3-125, 3-129, 3-172, 3-183  
 Cancer Genes ... 2-10, 3-33  
 Cancer Genetic Markers of Susceptibility ... 2-2, 2-5, 2-14, 3-6, 3-13, 3-33, 3-38  
 Cancer Genome Anatomy Project ... 2-8, 2-16, 3-34, 3-37:3-38  
 Cancer Genome Atlas ... 2-5, 2-20, 3-28, 3-33:3-34, 3-38, 3-175  
 Cancer Imaging Program ... 2-9, 2-13, 2-16, 3-180  
 Cancer Information ... 2-26, 3-238

- Cancer Prevention ... 2-1, 2-3:2-4, 2-6:2-8, 2-11, 2-13, 2-23:2-24, 2-234, 3-12, 3-129, 3-135, 3-233, F-4
- Cancer Research Network ... 2-24, 3-12, 3-129
- Cancer Risk ... 2-4:2-5, 2-11, 2-14, 2-16, 2-18, 2-24, 2-27, 2-180, 2-235, 3-6, 3-12:3-13, 3-23, 3-32, 3-38, 3-64, 3-105, 3-129, 3-161, 3-188
- Cancer Survivors Study ... 2-25, 2-192
- Cancer Treatment ... 2-9:2-11, 2-13:2-14, 2-17, 2-21, 2-86, 2-194, 2-236, 3-96, 3-135:3-136, F-4
- Cancer Vaccines ... 2-10, 2-255
- Candidate Gene Association Resource ... 2-126, 2-152, 3-49, 3-156
- Cannabinoids ... 2-45, 2-158, 2-168, 3-59, 3-63, 3-133
- Carbohydrates ... 3-59, 3-64, 3-105, 3-187:3-188
- Carcinogenesis (see Cell Transformation, Neoplastic)
- Carcinogens ... 3-98, 3-125:3-126
- Carcinoma ... 2-2, 2-7, 2-17, 2-24, 2-28, 2-86, 3-6, 3-12, 3-25, 3-89, 3-129, 3-136, 3-154, 4-28
- Carcinoma, Non-Small-Cell Lung ... 2-10, 2-14, 2-16, 3-135:3-136
- Cardiac Arrest and Trauma Registry ... 3-131, 3-157
- Cardiac Arrhythmias ... 2-124
- Cardiac Function ... 2-134, 2-230
- Cardiopulmonary Arrest ... 3-131, 3-157
- Cardiopulmonary Resuscitation ... 3-131, 3-157
- Cardiovascular Disease ... 2-78, 2-97, 2-112, 2-117, 2-121, 2-123, 2-125, 2-127, 2-134, 2-145, 2-148, 2-152, 2-156, 2-182, 2-189, 2-191, 2-195, 2-213, 2-217:2-219, 2-224, 2-230, 2-233, 2-235, 3-2, 3-7:3-8, 3-11, 3-17, 3-20, 3-24:3-25, 3-47, 3-49, 3-110, 3-116, 3-156, 3-174, 4-10:4-12, 4-25, 4-30, F-5, F-8
- Career Development ... **3-195:3-219**, 1-4, 1-7, 1-27, 2-57, 2-82, 2-99:2-100, 2-194, 2-210, 2-222, 2-243, 2-245, 3-20, 3-90, 3-99:3-100, 3-134:3-136, 3-143, 3-163, 4-10:4-11, 4-23, B-1, F-3
- Career Development Awards ... 2-194, 3-136, 3-196, 3-203:3-204, 3-209, 3-215, 3-217
- Career Enhancement Award for Stem Cell Research ... 3-204
- Career Planning ... 1-25
- Caregivers ... 2-26, 2-52, 2-89, 2-132, 2-169, 2-180, 2-220, 3-222, 3-236, 3-238, 4-7, F-9
- Carrier Proteins ... 2-125
- Cartilage ... 2-108, 2-114, 2-122, 2-148, 2-225, F-7
- Cartilage Diseases ... 2-35, 2-44, 3-16
- Cataracts ... 2-38, 2-53, 2-139, 2-160, 3-6, 3-35, 3-117, 3-155, 3-227, F-5
- Cattle ... 2-142, 2-199, 3-29
- CDC (see Centers for Disease Control and Prevention (U.S.))
- Celiac Disease ... 2-107, 2-122, 2-231, 3-31:3-32, 3-235
- Cell arrays ... 2-91
- Cell Culture Techniques ... 3-77
- Cell Cultures ... 2-58, 3-48, 3-155, 4-39, 4-41
- Cell Cycle ... 2-70, 3-45, 3-68
- Cell Death ... 2-1, 2-32, 2-38, 2-71, 2-115, 2-137, 2-172, 3-45, 3-69:3-70, 4-8
- Cell Differentiation ... 2-37, 2-54, 2-134, 3-60, 3-76
- Cell Division ... 3-27, 3-33, 3-45
- Cell Lines ... 2-58, 2-60, 2-144, 3-43, 3-74, 3-77:3-78, 3-155, 3-188, 4-4, 4-9
- Cell Membranes ... 2-22, 2-69, 3-67, 3-115, 3-181
- Cell Transformation, Neoplastic ... 2-5, 2-14, 3-38, 3-63
- Census ... E-8, E-14
- Center for HIV/AIDS Vaccine Immunology ... 2-79, 2-98
- Center for Information Technology ... 1-15, 1-26, B-5
- Center for Inherited Disease Research ... 4-7
- Center for Multicultural Mental Health Research ... 2-218
- Center for Scientific Review (see NIH Center for Scientific Review)
- Centers for Disease Control and Prevention (U.S.) ... 2-7, 2-68, 2-84, 2-88, 2-101, 2-131, 2-147:2-148, 2-190, 2-194, 2-210, 2-219, 2-227, 2-235:2-236, 2-238, 3-17, 3-24, 3-51, 3-96, 3-124, 3-137, 3-213, 3-242, 3-246, 4-19, 4-38
- Centers for Medicare and Medicaid Services (see United States Centers for Medicare and Medicaid Services)
- Centers of Excellence for ELSI Research ... 3-52
- Centers of Excellence in Medical Chemical Research ... 2-81
- Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training ... 4-24
- Centers of Research Translation ... 2-217, 2-224, 3-92, 3-106
- Central Nervous System ... 2-37, 2-45, 2-103, 2-143, 3-170, 3-184, 4-8, F-9
- Central Nervous System Stimulants ... 2-47, 2-159, 3-126
- Cerebral Palsy ... 2-33, 2-60, 2-64, 2-93, 2-138, 2-181, 2-193, 2-252, 3-40, 3-51, 3-102, 3-127, 3-162, 3-180, 3-189, 3-219, 3-243, C-8
- Cerebrovascular Disorders ... 2-218, 4-7
- Cervical Cancer ... 1-10, 2-2, 2-7, 2-17, 2-24, 2-28, 2-86, 2-252, 2-255, 3-12, 3-25, 3-89, 3-129, 3-136, 3-154, 4-28:4-29, F-7
- Cervix ... F-4
- Cervix Uteri ... 2-28, 2-255, 3-25, 3-154
- Cesarean Delivery ... 2-198
- Charcot-Marie-Tooth Disease ... 2-68, 2-70, 2-252, 3-46
- Chemical Countermeasures ... 2-81
- Chemical Exposure ... 2-184, 2-213
- Chemical Warfare Agents ... 2-62, 2-96
- Chemical Weapons ... 2-73
- Chemistry, Organic ... D-5
- Chemistry, Physical ... D-5
- Chemotherapy ... 2-10, 2-14, 2-16, 2-19, 2-21, 2-68, 3-33, 3-56, 3-75, 3-104, 3-135:3-136, 3-187
- Cherubism ... 3-124
- Chest ... 2-46, 2-155:2-156, 2-208, 3-114, 3-235
- Chest Pain ... 2-121, 2-131, 3-114, F-6
- Cheyne-Stokes Respiration ... 1-16, 2-118, 2-173
- Chicken Pox ... 2-76
- Child Abuse ... 2-252, 3-91, 3-141
- Child Abuse and Neglect Research ... 2-252
- Child Development ... 2-193, 3-4:3-5, 3-10, D-3
- Child Development Disorders, Pervasive ... 2-41, 4-36
- Child Guidance ... 2-189, 3-24
- Child Health ... 2-72, 2-180, 2-189, 3-24, F-4
- Child, Preschool ... 4-37
- Childbirth ... F-7
- Childhood Asthma ... 2-220
- Childhood Autism Risk from Genes and Environment ... 2-41
- Childhood Deaths ... 2-75
- Childhood Leukemia ... 2-252
- Children with HIV Early Antiretroviral Therapy ... 2-78, 2-87, 3-117
- Children's Oncology Group ... 2-25, 2-192
- Chinese Medicine, Traditional ... 2-164, 3-85, 3-131
- Chiropractic ... 2-131, F-5
- Chlamydia ... 2-83, 3-39
- Chloroquine ... 2-76
- Chloroquine Resistance ... 2-76
- Cholangitis, Sclerosing ... 2-122
- Cholecystolithiasis ... 2-122, 3-32, F-8
- Cholelithiasis ... 2-122
- Cholera ... 2-83, 3-1, 3-39
- Cholera Vaccines ... 3-1
- Cholesterol ... 2-131, 2-219, 3-79, 3-98
- Cholesterol, HDL ... 3-121
- Chondrodysplasia Punctata ... 3-124
- Chondroitin Sulfate ... 2-131, 2-165, 3-121
- Chromatin ... F-8
- Chromosome Mapping ... 2-83, 2-108, 2-151, 3-6, 3-13, 3-28, 3-30, 3-33:3-34, 3-36:3-37, 3-39:3-41, 3-154, 3-177

- Chromosomes ... 2-57, 2-113, 3-27, 3-46, 3-51:3-52, 3-81, 3-159, 3-237
- Chronic Diseases ... **2-119:2-174**, 1-3, 1-7, 1-10, 1-23, 2-18, 2-26:2-27, 2-33, 2-43, 2-45:2-48, 2-53:2-54, 2-56, 2-58:2-61, 2-64:2-66, 2-69, 2-96, 2-98, 2-114:2-117, 2-177, 2-180, 2-182:2-183, 2-186, 2-188, 2-194, 2-196:2-197, 2-199:2-201, 2-206:2-207, 2-209, 2-223:2-225, 2-228:2-230, 2-235, 2-237, 3-2, 3-8:3-9, 3-11, 3-14:3-16, 3-18:3-23, 3-25, 3-32, 3-36:3-37, 3-42:3-43, 3-45, 3-49:3-51, 3-53, 3-63, 3-68:3-69, 3-71, 3-73:3-74, 3-76, 3-78, 3-80, 3-87, 3-103, 3-107, 3-111, 3-113:3-114, 3-116:3-122, 3-124:3-128, 3-133:3-134, 3-138:3-140, 3-144, 3-155:3-157, 3-161, 3-168, 3-174, 3-177, 3-184, 3-186, 3-235, 3-239, 3-241, 3-243:3-245, A-5, B-1, F-9
- Chronic Fatigue Syndrome ... 2-61, 2-167, 2-252
- Chronic Insomnia ... 3-98
- Chronic Kidney Disease ... 2-122, 3-17:3-18
- Chronic Kidney Insufficiency (see Renal Insufficiency, Chronic)
- Chronic Liver Disease ... 2-175, 2-252
- Chronic Liver Disease and Cirrhosis ... 2-252
- Chronic Obstructive Pulmonary Disease ... 2-121, 2-124, 2-127, 2-129, 2-131, 2-153, 2-156, 2-158, 2-174, 2-229, 2-252, 3-14, 3-95, 3-115:3-116, 3-234:3-235, 4-14
- Chronic Pain ... 2-33, 2-36, 2-45, 2-119, 2-127, 2-131:2-132, 2-150, 2-168, 2-170, 3-22, 3-63, 3-118
- Cigarette Smoking ... 2-177, 3-149
- Ciliary Dyskinesia, Primary ... 3-125
- Ciliary Motility Disorders ... 3-125
- Circumcision ... 2-79, 2-90
- Cirrhosis ... 2-63, 2-129, 2-166, 2-175, 2-252, 3-109, 3-122, F-8
- Claude D. Pepper Older Americans Independence Centers ... **4-10:4-16**, 1-6:1-7, 2-209, 4-2, 4-43
- Cleft Lip ... 2-196:2-197, 3-71:3-72, 3-81:3-82
- Cleft Palates ... 2-183, 2-187, 2-196:2-197, 3-57, 3-67, 3-71:3-72, 3-81
- Climate ... 2-252, 2-254:2-255
- Climate Change ... 2-252, 2-254:2-255
- Clinical and Translational Science Award ... 1-12, 3-90, 3-99, 3-130, 3-142:3-143, 3-198, 3-203, 3-207:3-208, A-7, C-6:C-7
- Clinical Islet Transplantation Consortium ... 2-110, 2-130, 2-163
- Clinical Medicine ... 2-89, 2-225, 3-136, 3-142, 3-152, 3-166, 3-211, F-11
- Clinical Oncology Program ... 2-8, 2-13, 3-95, 3-135
- Clinical Proteomic Technologies Initiative for Cancer ... 2-9, 2-12, 3-44, 3-178
- Clinical Protocols ... 1-17, 2-9, 2-20, 2-64, 2-130, 2-138, 3-94, 3-102, 3-125, 3-142, 3-183, 4-32, 4-34, E-27
- Clinical Research ... **3-89:3-144**, 1-6:1-8, 1-12:1-13, 1-18, 1-20, 1-25, 1-29:1-30, 1-33, 2-9, 2-13, 2-16, 2-26, 2-52, 2-62, 2-65:2-66, 2-73:2-74, 2-76, 2-79, 2-85, 2-91, 2-94:2-96, 2-105, 2-120, 2-124:2-125, 2-128:2-130, 2-143, 2-145:2-146, 2-155, 2-157, 2-159:2-160, 2-163, 2-171, 2-186, 2-193, 2-204, 2-217, 2-221:2-222, 2-224, 2-235, 2-237, 2-240:2-242, 2-244:2-245, 2-249, 2-252, 3-3, 3-8, 3-10, 3-59, 3-62, 3-64:3-65, 3-73, 3-145, 3-147, 3-151, 3-153, 3-163, 3-168, 3-180, 3-188, 3-190, 3-195:3-196, 3-198, 3-204:3-207, 3-209, 3-211, 3-214:3-215, 3-217, 3-224, 3-226, 3-242, 3-245, 4-2, 4-7, 4-19, 4-23, 4-32, 4-35, 4-45, A-5, A-7, B-1:B-2, B-5:B-6, C-3, C-6:C-8, E-1:E-9, E-11:E-12, E-14:E-29, E-33:E-46, F-2:F-3, F-5, F-8:F-9
- Clinical Research Education and Career Development ... 3-100
- Clinical Research Information System ... 1-29
- Clinical Research Policy Analysis and Coordination ... 1-30:1-31, 3-100, C-7
- Clinical Research Protocols ... 2-242, 2-245, 3-196, E-8, E-14, E-16, E-18, E-20
- Clinical Research Subjects ... 2-240
- Clinical Research Training ... 2-221, 3-142:3-143, 3-198, 3-205, 3-207, 3-209
- Clinical Research Training Program ... 3-142, 3-205, 3-207, 3-209
- Clinical Trials ... 1-9, 1-13, 1-17, 1-22, 1-26, 2-5:2-6, 2-8:2-10, 2-13:2-18, 2-22:2-23, 2-26, 2-32, 2-35, 2-37:2-40, 2-46, 2-48, 2-51:2-53, 2-55:2-56, 2-58, 2-60, 2-62:2-63, 2-65:2-66, 2-69, 2-73, 2-77:2-83, 2-85:2-87, 2-90, 2-92:2-94, 2-96:2-99, 2-105:2-106, 2-110:2-112, 2-117, 2-126, 2-128:2-131, 2-133, 2-140, 2-142:2-143, 2-145, 2-147, 2-154:2-162, 2-165:2-167, 2-169:2-170, 2-180, 2-187, 2-191, 2-193, 2-195, 2-198:2-200, 2-204:2-206, 2-208, 2-217, 2-220:2-221, 2-223, 2-228, 2-232, 2-235, 2-240, 2-249, 2-252, 2-254, 3-1, 3-3, 3-9:3-10, 3-13, 3-15, 3-18, 3-21:3-22, 3-24, 3-29:3-31, 3-42, 3-45, 3-47, 3-49, 3-57, 3-67, 3-80, 3-86:3-87, 3-89:3-90, 3-93:3-97, 3-100, 3-104, 3-107:3-122, 3-126:3-131, 3-133:3-136, 3-138, 3-140, 3-142:3-143, 3-147, 3-150:3-151, 3-153:3-154, 3-157, 3-163, 3-170, 3-180, 3-191, 3-198:3-201, 3-206, 3-209, 3-212, 3-221:3-222, 3-225:3-226, 3-233:3-234, 3-236, 3-240, 3-244:3-245, 4-6:4-7, 4-11, 4-13, 4-18:4-19, 4-21:4-22, 4-24:4-25, 4-29:4-30, 4-32, 4-34, 4-39:4-40, A-5, B-1, B-3, C-3, C-5, C-7, E-5:E-9, E-11:E-12, E-14, E-18, E-22, E-26, F-3:F-4, F-9
- Clinical Trials in Organ Transplantation ... 2-130, 2-158, 3-134
- Clinical Trials Infrastructure ... 2-106
- Clinical Trials, Phase III as Topic ... E-19
- Clinical, Operational and Health Services Research Training Program for HIV/AIDS and TB ... 2-99, 3-134, 3-208
- ClinicalTrials.gov ... 3-120, 3-147, 3-150, 3-153, 3-160, 3-239
- Cloning ... 3-55, 4-5
- CMV and Hearing Multicenter Screening ... 3-20
- Co-infections ... 2-74, 2-78, 2-89, 2-225, F-11
- Coalition of Patient Advocacy Groups ... 4-33:4-34
- Cocaine ... 2-47, 2-159, 3-127
- Cochlear Implants ... 1-9, 2-46, 2-49, 2-207, 2-210, 3-166, 3-168, 3-174:3-175, 3-190
- Code of Federal Regulations ... 1-16, 1-30
- Cognition ... 2-32, 2-35, 2-43, 2-51, 2-63, 2-67, 2-179, 2-202, 2-205, 3-11, 3-83:3-84, 3-86, 3-179, 4-6
- Cognition Disorders ... 2-38, 2-52, 2-64, 2-138, 2-189, 3-15, 3-101, 3-131
- Cognitive and Emotional Health Project ... 2-54, 3-23
- Cohort Studies ... 2-63, 2-97, 2-152, 2-190:2-191, 3-17:3-18, 3-23:3-25, 3-49, 3-86, 3-116, 3-156
- Collaboration ... 1-20:1-21, 1-28:1-29, 2-7, 2-14, 2-18, 2-25, 2-27, 2-31, 2-39, 2-57, 2-59, 2-78, 2-81, 2-84, 2-88, 2-98, 2-104, 2-108:2-109, 2-119, 2-130, 2-132, 2-141, 2-145, 2-148, 2-163, 2-169, 2-188, 2-190:2-191, 2-225, 2-228, 2-245, 2-247, 3-1, 3-7, 3-10, 3-14, 3-16, 3-19, 3-24, 3-32, 3-38, 3-85, 3-94, 3-123, 3-134, 3-157, 3-161, 3-167, 3-171, 3-201, 3-213, 3-216, 3-235, 3-246, 4-1, 4-10, 4-19, 4-32:4-34, A-3, B-6, C-7, E-5
- Collaboration, Education and Test Translation ... 3-124
- Collaborative Community-Based Research ... 2-236, 2-246, 3-136:3-137
- Collaborative Programs of Excellence in Autism ... 1-6, 4-2, 4-36, 4-38
- Collaborative Psychiatric Epidemiology Surveys ... 2-218, 2-229, 3-13
- Collaborative Study on the Genetics of Alcoholism ... 2-60, 2-126, 2-144, 3-43, 3-74
- Collagen ... 2-137, 2-149, 2-201
- Colon ... 2-14, 2-143, 2-215, 3-6, 3-14, 3-38, 3-150, 3-170, F-4
- Colon Cancer ... 2-3, 3-32
- Colonic Neoplasm ... 3-150
- Colorectal Cancer ... 2-215, 2-252, 3-3, 3-227
- Combating Autism Act of 2006 ... 4-36, 4-40



- Combined Modality Therapy ... 2-19, 2-68  
 CombiRX Trial ... 2-53, 2-112, 3-112  
 Commercialization Assistance Program ... 3-133  
 Common Fund, NIH ... 1-6, 1-8, 1-12, 1-21:1-23, 3-58, B-6, C-1:C-5, C-7:C-8  
 Communication Disorders ... 1-15, 2-32, 2-57, 2-70:2-71, 2-211, 3-81, 4-36, B-3, F-10  
 Communication Impairment (see Communication Disorders)  
 Communications Media ... 3-141, 3-192, 3-233:3-234  
 Community Cancer Centers ... 2-11, 2-14, 3-95, 3-135  
 Community Drug Treatment Programs ... 2-84, 2-227, 3-124  
 Community Epidemiology Work Group ... 2-228, 3-10, 3-157  
 Community for Advanced Graduate Training ... 3-199, 3-211  
 Community Health Care ... 2-236, 3-137  
 Community Health Center ... 2-236, 3-100, 3-241  
 Community Health Education ... 2-145, 2-224, 3-20  
 Community Health Networks ... 2-132, 2-169  
 Community Hospital ... 2-66, 2-232  
 Community Networks ... 2-14, 2-220, 2-235  
 Community Networks Program ... 2-14, 2-220, 2-235  
 Community Outreach ... 2-24, 2-214, 2-232, 2-235, 3-129, 3-233, 3-240, 4-24  
 Community Participation in Research ... 3-141, 4-30  
 Community Treatment Programs ... 2-66, 2-159, 3-126, 3-245  
 Community-Acquired Infection ... 2-91, 3-133  
 Community-Based Organizations ... 2-231, 2-235, 3-244  
 Community-Based Participatory Research Program ... 2-233  
 Comorbidities ... 2-42, 2-78, 2-111, 2-117, 2-128, 2-153, 3-44, 3-183, 4-27, 4-30:4-31  
 Comorbidity ... 2-28, 2-141, 2-218, 2-227, 2-229, 3-13, 3-19, 4-28  
 Comparative Oncology Program ... 2-10  
 Complementary and Alternative Medicine ... 1-15, 2-28, 2-71, 2-101, 2-118, 2-120, 2-131, 2-139, 2-166, 2-173, 2-252, 3-62, 3-84:3-86, 3-99, 3-103, 3-199:3-200, 3-203, 3-216, 3-218, 3-226, B-4, F-5  
 Complementary Therapies ... 1-15, 2-28, 2-118, 2-120, 2-131, 2-139, 2-164, 2-166, 2-173, 2-252, 3-85:3-86, 3-99, 3-103, 3-131, 3-203, 3-216, 3-218, B-4, F-5  
 Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy ... 2-194  
 Comprehensive Sickle Cell Centers ... 2-161, 2-217, 2-224, 3-139  
 Compulsive Behavior ... 2-46, 3-84, 3-179  
 Computational Biology ... 2-2:2-4, 2-11, 2-15, 2-83, 2-105, 2-109, 2-246, 3-6, 3-39, 3-74, 3-78, 3-137, 3-151, 3-161:3-162, 3-167, 3-188, 3-192, 3-200, 3-214, 4-20, 4-41, B-2, C-5  
 Computational Sciences ... 2-125, 3-167  
 Computational Tools ... 1-12, 2-132, 3-71, 3-162, 3-165, 3-186, 3-188, C-5  
 Computer Model ... 2-65, 2-196, 3-61, 3-78, 3-81, 3-112  
 Computer Science ... 2-6, 2-15, 2-31, 2-109, 2-114, 2-135, 3-45, 3-56, 3-74, 3-171, 3-192, D-5  
 Conditioning, Operant ... 2-43  
 Conferences ... 1-20, 1-30, 2-89, 3-67, 3-98, 3-141, 3-192, 3-237, 4-20:4-21, 4-30, B-6  
 Confidentiality ... 1-33, 2-240, 3-124  
 Congenital Abnormalities ... 2-8, 2-187, 3-67, 3-225, 3-239, 4-21  
 Congenital Adrenal Hyperplasia ... F-11  
 Congenital Heart Defects ... 2-121, 2-174  
 Congenital Hypothyroidism ... 2-179  
 Congenital Iodine Deficiency Syndrome (see Congenital Hypothyroidism)  
 Congestive Heart Failure ... 4-14  
 Connective Tissue Diseases ... 2-121, F-7  
 Connective Tissues ... 3-232  
 Conserved Domain Database ... 3-50  
 Consortium for Functional Glycomics ... 3-64, 3-105, 3-188  
 Consortium for Radiologic Imaging Studies of PKD ... 2-162, 3-15, 3-119  
 Consumer Health Information ... 3-230  
 Contraception ... 2-194, 2-252, 3-205, 3-209  
 Contraception/Reproduction ... 2-252  
 Cooley's Anemia ... 2-122, 2-175, 2-252  
 Cooperative agreement ... 2-108:2-109, 2-149, 2-189, 2-203, 2-229, 2-247, 3-13:3-15, 3-51, 3-122, 3-180, 3-244, 4-17, 4-32, 4-37, E-5, F-7  
 Cooperative Research and Development Agreement ... 3-173, 3-186  
 Cooperative Study Group for Autoimmune Disease Prevention ... 2-108, 2-113, 3-61, 3-77  
 COPD (see Chronic Obstructive Pulmonary Disease)  
 COPD: Learn More, Breathe Better ... 2-131, 2-156, 3-234  
 Corneal Diseases ... 3-79  
 Corneal Endothelial Dystrophy ... F-5  
 Cornelia De Lange Syndrome ... 3-124  
 Coronary Artery ... 2-132, 3-71, 3-186  
 Coronary Artery Disease ... 2-46, 2-131, 2-155, 2-164, 3-32, 3-114, 3-128, F-8  
 Coronary Disease ... 2-121, 2-123, 2-152, 2-174, 2-234, 2-255, 3-3, 3-53, 3-89, 3-139, 3-233, F-11  
 Coronary Heart Disease (see Coronary Disease)  
 Coronary Vessels ... 2-135, 2-230  
 Corticosteroids ... 2-129, 2-156, 3-114  
 Cost Effectiveness Research ... 2-10, 2-253, 3-65, 3-91, 3-138, 3-190  
 Costs ... 1-10, 2-17, 2-23, 2-25, 2-34, 2-46:2-47, 2-51, 2-65, 2-174:2-177, 2-180:2-181, 2-192, 2-205, 2-210, 3-13, 3-28, 3-30, 3-35, 3-40:3-41, 3-43, 3-65, 3-90, 3-112, 3-130, 3-132, 3-168, 3-175:3-177, 3-185:3-186, 4-6, 4-33, 4-37  
 Council of Councils ... 1-21:1-22, C-4  
 Counseling ... 2-84, 2-217, 2-226:2-227, 3-72, 3-124, D-3  
 Couples ... 2-85, 2-185, 2-194  
 Creating Opportunities for Parental Empowerment ... 2-198  
 Crick, Francis ... 3-27  
 Crime ... 2-47, 2-159, 2-177, 3-126  
 Critical Issues in eHealth Research Conference ... 3-141, 3-192  
 Critical Period (Psychology) ... 2-36  
 Crohn's Disease ... 2-122, 2-253, 3-32  
 Cultural Adaptation ... 2-218  
 Cultural Competency ... 3-221, 3-231, 4-28  
 Cultural Diversity ... E-6  
 Cultural Relevancy ... 2-219  
 Custom Drug Synthesis ... 2-92  
 CVD (see Cardiovascular Disease)  
 Cyanide ... 2-81  
 Cyclin-Dependent Kinase 5 ... 2-70, 3-59, 3-68  
 Cystic Fibrosis ... 2-119, 2-121, 2-124, 2-147, 2-174, 2-253, 3-27, 3-31, 3-51, 3-57, 3-169  
 Cytokines ... 2-10  
 Cytomegalovirus Infections ... 3-19:3-20  
 Daily Med ... 3-160  
 Data Analysis ... 2-28, 3-25, 3-40, 3-147, 3-151, 3-154, 4-40, C-8, E-8  
 Data and Technology Coordinating Center ... 3-100, 4-32:4-35  
 Data Collection ... 1-17:1-18, 1-20, 2-134, 2-209, 2-228, 2-230, 2-247, 3-10, 3-157, 3-201:3-202, 3-212, 4-35, 4-39, B-5, E-5, E-8, E-20, E-31, E-35, E-38  
 Data Safety Monitoring Board ... 2-99  
 Data Storage ... 2-54, 3-148, 3-156, 4-39  
 Data Systems ... 2-24, 3-12, 3-18, 3-129, 3-160, 3-173, A-5, E-6  
 Database of Genotype and Phenotype ... 2-139, 3-6, 3-13, 3-35, 3-49, 3-146, 3-148, 3-154:3-155

- Databases ... 3-145:3-163, 3-239, also see Information Systems
- Deafness ... 1-15, 2-32, 2-37, 2-71, 2-123, 2-211, 4-36, B-3, F-10
- Death ... 1-11, 2-3, 2-34, 2-38, 2-71, 2-73, 2-75, 2-78, 2-84, 2-104, 2-119:2-122, 2-125, 2-128, 2-157, 2-172, 2-174:2-175, 2-181, 2-206, 2-215, 2-223, 3-30, 3-60, 3-70, 3-114, 3-228, 4-3, 4-25:4-26, B-2, F-9  
... 2-171, 3-128
- Decompression, Surgical ... 2-171, 3-128
- Deep Brain Stimulation ... 2-49, 2-207, 3-190
- Deep Vein Thrombosis ... 2-122
- Dehydroacetic Acid ... 2-38
- Delirium ... 2-51, 2-204:2-205, 4-5:4-6, 4-9, 4-12
- Delivery of Health Care ... 2-4, 2-10, 2-14, 2-25, 2-27:2-28, 2-74, 2-92, 2-144:2-145, 2-192, 2-204, 2-214, 2-217, 2-222:2-223, 2-229, 2-234:2-236, 2-239, 2-242:2-243, 2-245:2-247, 3-11, 3-15, 3-51, 3-79, 3-86, 3-95, 3-106, 3-117, 3-129, 3-134, 3-136:3-137, 3-140, 3-142, 3-158, 3-231, 3-236, 3-241, 4-24, 4-28:4-30, 4-34, A-5, B-4, B-6, C-8
- Delivery, Obstetric ... 2-198
- Dementia, Lewy Body ... 4-5
- Dementias ... 2-33, 2-38, 2-52, 2-56, 2-169, 2-189, 3-15, 3-62, 3-87, 4-3:4-5, 4-7:4-8, F-10
- Demographics ... 2-53, 2-160, 2-192, 3-9, 3-117, 3-197
- Demography ... 3-1, D-4
- Demyelinating Disease ... F-5
- Dental Care ... 2-197, 3-72
- Dental Caries ... 2-83, 2-233:2-234, 2-237, 3-40, 3-140
- Dental Caries Prevention ... 2-234
- Dental Decay ... F-7
- Dental Disease ... 2-153, 2-216, 2-229, 3-14
- Dental/Oral and Craniofacial Disease ... 2-253
- Dentists ... 1-25, 2-9, 2-20, 3-99, 3-125, 3-139, 3-183
- Depression ... 2-36, 2-55, 2-58, 2-60, 2-63:2-64, 2-67, 2-119, 2-121, 2-123, 2-130, 2-138, 2-144, 2-150, 2-154, 2-168, 2-176, 2-184:2-185, 2-193, 2-199, 2-204, 2-206, 2-216, 2-233, 2-253, 2-261, 3-33, 3-36, 3-43, 3-47, 3-74, 3-83, 3-95, 3-98, 3-102, 3-113, 3-120, 3-127, 3-225, 4-31, F-9
- Depressive Disorder ... 2-55, 2-58, 2-60, 2-64, 2-123, 2-138, 2-154, 2-168, 2-176, 2-204, 2-206, 3-36, 3-113, F-9
- Depressive Disorder, Major ... 3-36
- Dermatitis, Atopic ... 2-122, 2-148
- Developing Countries ... 2-17, 2-75, 2-82, 2-99, 2-145, 2-210, 3-20, 3-162, 3-195, 3-200, 3-212:3-213, B-5, F-4
- Developmental Biology ... 2-72, 2-210:2-211, 3-123, B-2, D-1
- Developmental Disabilities ... 2-33, 2-44, 2-72, 2-185, 2-187, 2-189, 2-202, 2-211, 3-6, 3-16, 3-24, 4-37, B-2
- Developmental Disability ... 2-179
- Device ... 1-9, 2-9, 2-20, 2-46, 2-208, 2-210, 3-125, 3-148, 3-168, 3-174, 3-183
- DHHS (see Department of Health and Human Services)
- Diabetes ... 1-10, 1-14:1-15, 1-20, 2-2, 2-70, 2-72, 2-103, 2-105:2-108, 2-110:2-111, 2-113:2-119, 2-121:2-132, 2-135, 2-137:2-138, 2-140, 2-142, 2-144:2-148, 2-151:2-154, 2-160, 2-162:2-163, 2-167, 2-169, 2-171, 2-173:2-174, 2-182, 2-184:2-185, 2-193, 2-199:2-201, 2-212:2-213, 2-215:2-216, 2-218:2-221, 2-224:2-225, 2-228:2-230, 2-232:2-235, 2-237, 2-253, 3-2, 3-7, 3-10:3-11, 3-14, 3-18, 3-22:3-23, 3-25, 3-32, 3-45, 3-51:3-53, 3-59:3-61, 3-68:3-69, 3-71, 3-77:3-78, 3-83, 3-91:3-93, 3-96, 3-98, 3-107, 3-111, 3-116, 3-119:3-120, 3-127:3-128, 3-132, 3-138:3-139, 3-146, 3-152, 3-162, 3-171, 3-182, 3-189, 3-225, 3-227, 3-234:3-235, 3-240, 4-11, 4-13, 4-25, 4-29:4-32, B-2, C-2, D-8, F-5:F-8, F-11
- Diabetes Complication ... 2-110:2-111, 2-219
- Diabetes Control and Complications Trial ... 2-111, 2-117, 2-129, 2-154, 3-18
- Diabetes Mellitus, Type 1 ... 2-72, 2-103, 2-105:2-108, 2-110:2-111, 2-113, 2-116:2-118, 2-125, 2-127:2-128, 2-130, 2-142, 2-146:2-147, 2-154, 2-163, 2-173:2-174, 2-199:2-201, 2-212, 3-18, 3-22:3-23, 3-32, 3-45, 3-61, 3-71, 3-77, 3-91:3-93, 3-107, 3-120, 3-132, 3-182, C-2
- Diabetes Mellitus, Type 2 ... 2-114, 2-119, 2-121, 2-125, 2-127:2-130, 2-135, 2-140, 2-142, 2-145:2-146, 2-152, 2-160, 2-162:2-163, 2-185, 2-193, 2-200, 2-215, 2-221, 2-224:2-225, 2-228, 2-230, 2-235, 2-237, 3-7, 3-10, 3-18, 3-22, 3-32, 3-52:3-53, 3-60, 3-78, 3-96, 3-98, 3-111, 3-116, 3-119:3-120, 3-127:3-128, 3-139, 3-235, 4-29
- Diabetes Prevention ... 2-127, 2-140, 2-234, 3-7, 3-18, 3-91, 3-96, 3-111
- Diabetes Prevention Program ... 2-127, 2-140, 3-7, 3-18, 3-91, 3-96, 3-111
- Diabetes Prevention Program Outcomes Study ... 2-127, 2-140, 3-7, 3-18, 3-111
- Diabetes Research in Children Network ... 2-199:2-200, 3-182
- Diabetes, Autoimmune ... 2-117
- Diabetes, Gestational ... 2-142, 2-182, 2-198:2-199, 3-115
- Diabetic Complications ... 2-129
- Diabetic Eye Disease ... 2-226, 3-17, 3-235
- Diabetic Kidney Disease ... 2-126, 2-146, 3-45, 3-91, 3-107
- Diabetic Mouse, Non-Obese ... 2-114
- Diabetic Nephropathy ... 3-33, 3-92
- Diabetic Retinopathy ... 2-18, 2-160, 2-176, 3-79, 3-96, 3-138, F-5
- Diabetic Retinopathy Clinical Research Network ... 2-160, 3-96, 3-138
- Diagnostic and Statistical Manual of Mental Disorders ... 2-141, 2-227, 3-19
- Diagnostic Imaging ... 2-9, 2-13, 2-16, 2-35, 2-51, 2-57, 2-204:2-205, 2-230, 3-16, 3-104, 3-151, 3-159, 3-166, 3-170:3-171, 3-173, 3-180:3-182, 3-187, 4-6, F-7
- Diagnostic Radiology ... 2-253
- Diagnostic Services ... 4-19, 4-21
- Diagnostic Tests ... 2-57, 2-89, 3-81, 3-124, 4-21, B-3, F-6
- Dialysis ... 2-122, 2-161, 3-140
- Dialysis Access Consortium ... 2-161, 3-140
- Diarrhea ... 2-75
- Diarrheal Diseases ... 2-75
- Diet ... 1-9, 2-7, 2-25, 2-70, 2-107, 2-126:2-128, 2-130:2-131, 2-142, 2-146, 2-153, 2-163, 2-179, 2-183, 2-191, 2-199:2-201, 2-213, 2-229, 2-237, 2-240, 3-14, 3-23, 3-58:3-59, 3-63, 3-68, 3-79, 3-140, 3-172, 3-182, 3-191, 3-240, 4-3, F-5
- Dietary Supplements ... 1-15, 2-52:2-53, 2-131, 2-153, 2-160, 2-165, 2-173, 2-211, 2-229, 2-242, 3-14, 3-117, 3-121, 3-191, B-6, F-11
- Diethylenetriaminepentaacetic acid ... 2-92, 3-106
- Diethylstilbestrol ... 2-253
- Digestive Diseases ... 2-142, 2-171, 2-199, 2-253, 3-21, 3-61, 3-118, B-2, F-8
- Digestive System ... 2-122
- Dipalmitoylphosphatidylserine ... 3-18, 3-111
- DiracNet (see Diabetes Research in Children Network)
- Disability ... 1-10, 1-16, 2-32:2-34, 2-40, 2-48, 2-60, 2-69, 2-119:2-123, 2-133, 2-170, 2-175:2-177, 2-179:2-186, 2-193, 2-197, 2-205:2-206, 2-209, 2-213, 2-249, 2-257, 3-3, 3-107, 3-121, 3-227, 4-11:4-15, B-2:B-3, F-9:F-10
- Disability Adjusted Life Years ... 2-176:2-177
- Disabled Persons ... 2-32:2-33, 2-49, 2-120, 2-123, 2-170, 2-175:2-176, 2-181:2-182, 2-186, 2-193, 2-205:2-206, 2-209, 3-190, 4-12:4-13, F-9
- Disadvantaged ... 2-221:2-222, 2-237, 2-241:2-245, 3-140, 3-196, 3-198:3-199, 3-209
- Disaster Planning ... 2-231, 3-244
- Disasters ... 2-62, 2-96, 2-231, 3-34, 3-148, 3-172, 3-233, 3-244, 4-31
- Discovery Initiative ... 2-92, 3-76, 3-150, 3-162
- Discs, Herniated ... 2-170, 3-128

- Disease Registry ... 1-4, 1-7, 1-26, 2-25, 2-27:2-28, 2-41, 2-52:2-54, 2-56, 2-58:2-59, 2-62, 2-93, 2-96:2-97, 2-106, 2-113, 2-133, 2-140, 2-152, 2-164, 2-202, 2-228, 3-10, 3-13, 3-25, 3-36:3-37, 3-48:3-49, 3-52, 3-78, 3-92, 3-120, 3-130:3-131, 3-145:3-163, 3-173, 3-187, 3-189, 3-212, 3-216, 3-234, A-5
- Disease Risk (see Disease Susceptibility)
- Disease Susceptibility ... 2-2, 2-5, 2-14, 2-23, 2-35:2-36, 2-41, 2-61, 2-77, 2-97, 2-103, 2-107, 2-117, 2-145, 2-148, 2-151, 2-186, 2-191:2-192, 2-210, 2-226, 3-6:3-8, 3-13:3-14, 3-24, 3-32:3-33, 3-37:3-38, 3-46, 3-49, 3-52, 3-63, 3-116, 3-149, 3-169, 3-177, 4-14, F-8
- Disease Transmission ... 2-73, 2-77, 2-91:2-92, 3-216
- Disease, Retinal ... 2-155, 2-226, 3-17, 3-96, 3-114
- Disease, Skin ... 2-117, 2-226
- Dissectomy ... 2-170, 3-128
- Dissemination Grant ... 2-233
- Distal Muscular Dystrophies ... 4-18
- Diversity ... 1-14, 2-129, 2-132, 2-192, 2-218, 2-221, 2-227, 2-241:2-243, 2-245, 2-247, 3-9, 3-30, 3-58, 3-82, 3-196, 3-198:3-199, 3-214, F-3
- Diversity Inventory ... 2-245
- Diversity Recruitment ... 2-245, 3-214
- Diversity Workgroup ... 2-245
- Division of Extramural Activities Support ... 1-29
- Division of Intramural Research ... 2-19, 2-68, 3-215
- Division of Program Coordination, Planning, and Strategic Initiatives ... 1-15, 1-21, A-3:A-4, B-6
- Division of Specialized Information Services ... 3-225
- Dizziness ... 2-176, 3-221, 4-10
- DNA ... 1-12, 1-23, 1-29:1-30, 2-1, 2-20, 2-42, 2-58, 2-60, 2-62, 2-70:2-71, 2-80, 2-83, 2-93, 2-116, 2-133, 2-144, 2-146, 2-151:2-152, 2-183, 2-188, 2-196, 3-2, 3-8:3-9, 3-27:3-29, 3-31:3-32, 3-34:3-35, 3-37:3-38, 3-40:3-51, 3-55:3-56, 3-58, 3-60, 3-63, 3-65, 3-69:3-71, 3-74:3-75, 3-82, 3-107:3-108, 3-132, 3-146, 3-148, 3-155, 3-165, 3-169, 3-172, 3-175:3-177, 3-183, 3-189, 3-238, 4-4, 4-9, 4-39, 4-41, C-8, F-6
- DNA biosynthesis (see DNA Replication)
- DNA Breaks, Double-Stranded ... 3-70
- DNA Damage ... 3-70
- DNA Microarray Chip (see Oligonucleotide Array Sequence Analysis)
- DNA Repair ... 3-32, 3-45, 3-56, 3-63
- DNA Replication ... 2-229
- DNA Sequence ... 1-12, 1-23, 2-20, 3-34:3-35, 3-38, 3-55, 3-58, 3-63, 3-65, 3-146, 3-148, 3-165, 3-172, 3-175, 3-183, C-8
- DNA, Mitochondrial ... 3-51, 3-238
- Documentation ... E-6, E-14
- Domestic Violence ... 3-4
- Donor Screening ... 2-87, 3-21
- Dopamine ... 2-49, 3-83
- Down Syndrome ... 2-33, 2-72, 2-202, 2-212, 2-253
- Drive ... 2-151, 3-44
- Drug Abuse ... 1-15, 2-3, 2-34:2-35, 2-39, 2-42:2-47, 2-66, 2-71, 2-78, 2-85, 2-88, 2-98, 2-101, 2-130, 2-153, 2-159, 2-172, 2-187, 2-190, 2-211, 2-219, 2-228, 2-242, 2-248, 2-253, 3-4:3-6, 3-10:3-11, 3-16, 3-44, 3-84, 3-97, 3-123, 3-126:3-127, 3-149, 3-157:3-158, 3-179, 3-184, 3-199, 3-225:3-226, 3-245, B-3, F-10:F-11
- Drug Abuse Trends ... 2-228, 3-10, 3-149, 3-157
- Drug Addiction ... 2-42, 2-48, 2-79, 2-95, 2-98, 2-153:2-154, 2-160, 3-44, 3-106, 3-123, 3-127, 3-183, 3-232
- Drug Dependence ... 2-45, 2-60, 2-131, 2-144, 2-168, 3-43, 3-63, 3-74
- Drug Hypersensitivity ... 3-71, 3-132
- Drug Resistance ... 2-18, 2-76, 2-86
- Drug Therapies ... 3-169, 4-38
- Drug Therapy ... 2-54, 2-56, 2-136, 3-42, 3-156
- Drug Tolerance ... 2-50, 3-80
- Drug Toxicity ... 2-139
- Drug-Induced Liver Injury Network ... 2-125, 2-139
- Drugs, Non-Prescription ... 2-165
- Dry Eye ... 3-79, F-5
- DTPA (see Diethylenetriaminepentaacetic acid)
- Duchenne/Becker Muscular Dystrophy ... 2-253, 4-17:4-18
- Dust Mite ... 2-128, 2-143
- Dysgeusia ... 2-69, 3-59, 3-68
- Dyslexia ... 3-229
- Dyspnea ... 2-121
- Dystonia ... 2-253
- Dystonic Disorders ... 2-253
- Ear ... 2-46, 2-59, 2-66, 2-123, 2-210, 3-73, 3-175, 3-237
- Ear Infection ... 2-123, 2-176, 3-133
- Ear, Inner ... 2-50, 2-51
- Early Detection ... 2-1, 2-4, 2-8, 2-11, 2-13:2-14, 2-20:2-21, 2-24, 2-54, 2-124:2-125, 2-134, 2-232, 3-12, 3-14, 3-38, 3-76, 3-79, 3-92, 3-102, 3-129, 3-135, 3-166, 3-172, 3-231, 3-235, 3-238, 4-6, 4-39
- Early Detection Research Network ... 2-8, 2-20, 3-92, 3-102
- Early Diagnosis ... 2-8, 2-20, 2-24, 2-38, 3-102, 3-183, 4-6
- Early Interventions ... 4-39
- Eating Disorders ... 2-32, 2-46, F-8:F-9
- Eating Habits ... 2-119
- Ebola Hemorrhagic Fever ... 2-74, 2-80
- Ebola Virus ... 2-76
- Economics ... 2-77, 2-145, 2-193, 2-206, 3-1, 3-9, 3-193, D-3:D-4
- Ectodermal Dysplasias ... 2-197, 3-72
- Eczema ... 2-122, 2-148
- Eczema Vaccinatum ... 2-148
- Egg Allergy ... 3-21, 3-61, 3-118
- Electrode ... 3-170
- Electronic Health Record ... 3-147, 3-150:3-151, 3-160
- Elementary Particle ... D-6
- ELSI (see Ethical, Legal and Social Implications)
- Embryo ... 2-183, 2-187, 3-67
- Embryology ... 3-165, D-1
- Embryonic Development ... 2-37, 2-183
- Embryonic Stem ... 2-37, 3-60, 3-77:3-78, 3-83, 3-200
- Embryonic Stem Cells ... 2-37, 3-60, 3-77:3-78, 3-83, 3-200
- Emergency Medicine ... 3-131, 3-157
- Emergency Preparedness ... 1-32, 2-93, 3-160
- Emergency Response Guidebook ... 2-97, 3-185
- Emerging and Reemerging Infectious Diseases ... 2-73:2-75, 2-80
- Emerging Infectious Diseases ... 2-76:2-77, 2-80, 2-82, 2-90:2-92, 2-94, 2-101, 2-232, 2-253, 3-76, 3-240
- Emigration and Immigration ... 2-219, 2-233, 3-231
- Emotional development ... 2-43, 2-190, 3-11
- Emotions ... 2-31, 2-36:2-37, 2-43, 2-50, 2-63, 2-70, 2-190, 2-206, 3-11, 3-81, 3-84, 3-86, 4-39
- Emphysema ... 2-254
- ENCODE (see Encyclopedia of DNA Elements)
- Encyclopedia of DNA Elements ... 3-28:3-29, 3-50, 3-65, 3-176
- End of Life ... 2-132, 2-207, 3-90, F-10
- End-of-Life Care ... 2-132, 2-168, 2-186, 2-206:2-207, B-4
- End-Stage Renal Disease ... 2-174, 3-17:3-18
- Endemic Diseases ... 2-99, 3-212
- Endometriosis ... 2-194, 2-254
- Endoscopy ... 2-229
- Energy Medicine ... 2-166, F-5
- Enhancing Development of Genome-Wide Association Methods ... 2-126, 2-152, 3-35:3-36
- Entomology ... D-2
- Entrez ... 3-150
- Environment ... 1-3:1-5, 1-9, 1-11:1-12, 1-15:1-22, 1-24:1-28, 1-32, 2-1:2-2, 2-5:2-7, 2-9:2-12, 2-14:2-15, 2-18, 2-21:2-23, 2-25:2-27, 2-31:2-33, 2-35:2-39, 2-41:2-42, 2-44, 2-46:2-48, 2-52:2-54, 2-58:2-59, 2-63, 2-66, 2-68, 2-73, 2-77, 2-79,

- 2-82, 2-87:2-88, 2-98, 2-103:2-104, 2-106:2-107, 2-110:2-112, 2-115:2-116, 2-119:2-122, 2-126:2-129, 2-131:2-132, 2-136:2-137, 2-140, 2-143:2-149, 2-151, 2-153:2-155, 2-158:2-160, 2-168, 2-179:2-181, 2-183:2-193, 2-197:2-198, 2-200:2-203, 2-205, 2-207:2-208, 2-210, 2-213:2-215, 2-220, 2-222:2-224, 2-226:2-227, 2-229, 2-231:2-236, 2-238, 2-241:2-246, 3-1:3-2, 3-4:3-5, 3-7:3-8, 3-10:3-11, 3-13:3-14, 3-16:3-17, 3-20:3-21, 3-23:3-24, 3-28, 3-31:3-33, 3-35, 3-37:3-38, 3-44:3-47, 3-51, 3-53:3-58, 3-60:3-61, 3-63:3-64, 3-66, 3-69, 3-71:3-72, 3-77, 3-82:3-83, 3-85, 3-90:3-91, 3-93:3-95, 3-97, 3-99, 3-101, 3-103:3-104, 3-107, 3-113:3-115, 3-117:3-118, 3-123, 3-125:3-127, 3-130:3-133, 3-137, 3-143, 3-145, 3-147:3-149, 3-151:3-153, 3-155:3-158, 3-160:3-161, 3-168, 3-170:3-175, 3-177, 3-180:3-181, 3-183:3-188, 3-193, 3-195:3-197, 3-199:3-200, 3-203:3-207, 3-209, 3-213:3-215, 3-218, 3-221, 3-225:3-227, 3-230:3-234, 3-236:3-243, 3-245, 4-1, 4-3:4-5, 4-9, 4-13:4-14, 4-20:4-21, 4-24, 4-27, 4-30, 4-36, 4-38, 4-41, 4-44:4-46, A-4:A-5, B-3:B-6, C-1, C-3:C-4, C-7, D-2:D-3, E-9, E-11:E-12, F-3, F-5:F-6, F-8, F-11
- Environmental Determinants of Diabetes in the Young ... 2-106, 2-127, 2-146, 2-200, 3-23
- Environmental Exposure ... 2-103, 3-64, 3-184
- Environmental Health Sciences ... 1-4, 1-15, 2-2, 3-63, 3-200, 3-213, 4-36, B-3
- Environmental Protection Agency ... 2-36, 2-41, 2-190, 3-24
- Environmental Science ... D-3
- Environmental Toxicology ... D-2
- Epidemic ... 1-12, 2-7, 2-17, 2-87:2-88, 2-92, 2-94, 2-98, 2-121, 2-127, 2-142, 2-145, 2-153, 2-199, 2-225, 3-21, 3-123, 3-231
- Epidemiologic Studies ... 3-17, 3-23, 3-149, E-14, E-22, F-6, F-8
- Epidemiological Studies ... 2-40, 2-104, 2-218, 3-1, 3-86, 3-93, A-5
- Epidemiology ... 3-1:3-25, 2-2, 2-18, 2-25:2-26, 2-54, 2-71, 2-86, 2-88, 2-98, 2-111, 2-117, 2-129, 2-142, 2-144:2-146, 2-154, 2-161, 2-172, 2-188, 2-190, 2-210, 2-224, 2-228:2-230, 2-235, 2-237, 3-55, 3-119, 3-125, 3-130, 3-134, 3-139, 3-147, 3-149, 3-157:3-158, 3-198:3-199, 3-201, 3-212, B-4, D-2, F-9, F-11
- Epidemiology of Diabetes Interventions and Complications ... 2-111, 2-117, 2-129, 2-154, 3-18
- Epidemiology, Molecular ... 2-4
- Epidermodysplasia Verruciformis ... 2-78, 2-87, 3-97, 3-117
- Epidermolysis Bullosa Acquisita ... 2-106
- Epigallocatechin Gallate ... 2-136, 3-87
- Epigenesis, Genetic ... 2-20, 2-42, 2-187, 3-38, 3-44, 3-58, 3-63, 3-66, 3-175, C-8
- Epigenetic ... 1-12, 1-22:1-23, 2-20, 2-41:2-42, 2-54, 2-134, 2-183, 2-187, 3-38, 3-44, 3-46, 3-58, 3-63:3-64, 3-66, 3-76, 3-175, 3-183, C-2, C-8
- Epigenomics ... 1-12, 1-23, 2-183, 3-58, C-2, C-5:C-8
- Epilepsy ... 2-31:2-32, 2-37, 2-49, 2-58, 2-60, 2-62, 2-69, 2-71, 2-96, 2-193, 2-254, 3-109, 3-155, 3-166, F-7, F-9
- Estrogen ... 2-225, 2-254, 3-3, 3-149, F-4
- Ethical, Legal and Social Implications ... 3-52
- Ethics ... 1-14, 1-27, 1-32, 2-94, 2-232, 2-237, 3-198, 3-240, 3-242
- Ethics, Research ... 1-31, 2-221, 3-77, 3-94, 3-201, E-27, E-43
- Ethnic Groups ... 2-3, 2-26, 2-54, 2-84, 2-127, 2-134, 2-141:2-142, 2-199, 2-213, 2-215:2-216, 2-218, 2-220:2-221, 2-223, 2-225, 2-227, 2-229:2-230, 2-237, 2-239, 2-241:2-243, 2-247, 3-13, 3-17, 3-19, 3-76, 3-122, 3-124, 3-140, 3-149, 3-158, 3-198, 3-230, 4-25:4-26, D-7, E-3:E-4, E-6:E-11, E-14:E-19, E-22, E-24, E-26, E-28, E-31, E-33:E-46, F-4
- Evolution ... 2-15, 2-17, 3-29, 3-41:3-42, 3-56, 3-64, 3-190, C-3
- Exercise ... 2-130, 2-157, 2-164, 2-183, 2-186, 2-200, 2-205, 2-209, 2-223, 2-240, 3-31, 3-87, 3-96, 3-114, 3-144, 3-182, 3-227, 3-236, 4-13:4-14, D-3
- Exercise Therapy ... 4-13:4-14
- Exercise Tolerance ... 4-14
- Exhibits ... 1-25, 2-232, 3-236:3-237, 3-240
- Experimental Therapeutics Program ... 2-9, 2-15, 3-93, 3-104
- EXPORT Center for the Study of Asian American Health ... 4-28
- Extensively Drug-Resistant Tuberculosis ... 2-88, 2-101, B-2
- Extramural Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds ... 2-244
- Extremities ... 2-70, 3-68
- Eye ... 1-14, 2-56, 2-59, 2-71, 2-123, 2-125, 2-136, 2-156, 2-160, 2-172, 2-176, 2-226, 3-17, 3-61, 3-73, 3-79, 3-96, 3-114, 3-138, 3-225, 3-235:3-236, B-2, F-5
- Eye Disease and Disorders of Vision ... 2-53, 2-111, 2-123, 2-126, 2-129, 2-139, 2-160, 2-254, 3-6, 3-31, 3-35, 3-75, 3-79, 3-117, 3-148, 3-155, B-2, F-5
- Eye Disease Genotyping Network ... 3-75
- Eye Movement ... 2-49, 3-83
- Fabry Disease ... 2-68
- Face ... 1-30, 2-104, 2-169, 2-180, 2-187, 2-197, 2-209, 3-67, 3-72, 3-82, 3-122, 3-221, 3-224, 3-229, 3-237, 4-12, 4-18, 4-39, F-7, F-9
- Facioscapulohumeral Muscular Dystrophy ... 2-56, 2-254, 3-37, 3-159, 4-18:4-19, 4-22
- Faculty Development ... 2-246, 3-137, 3-217, 4-24, 4-27
- Faith-Based Organizations ... 2-234, 4-24
- Families ... 1-31, 2-1, 2-4, 2-11, 2-17, 2-20, 2-54, 2-70, 2-104, 2-111, 2-113, 2-117, 2-128, 2-132, 2-141, 2-149, 2-168, 2-184:2-186, 2-188, 2-192, 2-201, 2-207, 2-216, 2-220, 2-226, 2-231, 3-5, 3-16, 3-31, 3-70, 3-81, 3-124, 3-156, 3-159, 3-225:3-227, 3-235, 3-239, 4-6:4-7, 4-34, 4-37:4-38, B-1:B-2, B-4, F-6:F-7, F-9
- Family ... 2-22, 2-78, 2-103, 2-108, 2-119, 2-137, 2-140, 2-147, 2-181, 2-183, 2-192:2-194, 2-230, 2-234, 3-4, 3-9:3-10, 3-25, 3-35, 3-51, 3-68:3-69, 3-73, 3-115, 3-155, 3-171, 3-195, 3-210, 3-221, 3-233, 3-235, 4-4, 4-8, 4-12, 4-29, D-3, F-10
- Family Member ... 2-206
- Family studies ... D-3
- Fathers ... 2-185, 2-190, 2-193, 2-199, 3-4, 3-9, 3-25
- Fatigue ... 2-61, 2-122, 2-129, 2-164, 2-167, 3-161, F-5
- Fatty Acids, Omega-3 ... 2-52:2-53, 2-137, 2-160, 3-68, 3-79, 3-117, 3-131
- Fatty Liver ... 2-122, 2-130, 2-160, 2-193
- FDA (see United States Food and Drug Administration)
- Feasibility Study ... 2-43, 2-52, 2-195, 3-22
- Federal Adverse Event Task Force ... 1-30
- Federal Technology Transfer Act ... 1-23:1-24
- Fellowship ... 3-131, 3-157, 3-195
- Fertility ... 2-192, 2-194, 3-9, 3-20, 3-213, B-2, F-8
- Fetal Alcohol Syndrome ... 2-36, 2-43, 2-184, 2-195, 2-254, 3-22
- Fetal Development ... 2-187, 3-67
- Fetal Diseases ... 2-43, 2-172, 2-184, 2-195, 3-22
- Fetus ... 2-43, 2-183:2-184, 2-190, 2-196, 3-11, 3-77, 3-82
- Fibrillin ... 2-165, 3-79:3-80, 3-121
- Fibroblast Growth Factor ... 2-196, 3-81
- Fibroblasts ... 2-115, 2-137, 3-69
- Fibroid Tumors ... 2-137, 2-254
- Fibromyalgia ... 2-167, 2-254, F-5, F-7
- Film ... 2-153, 3-243
- Financial aid ... 2-243
- Fingerprints ... 3-186
- Finland-United States Investigation of Non-Insulin-Dependent Diabetes Mellitus Genetics ... 3-52
- Fluorescence ... 2-9, 2-20:2-21, 3-75, 3-104, 3-125, 3-172, 3-183, 3-187

- FNIH (see Foundation for NIH)  
 Fogarty International Center (see John E. Fogarty International Center)  
 Food Allergy ... 2-116, 2-118, 3-21, 3-61, 3-71, 3-118, 3-132  
 Food and Drug Administration (see United States Food and Drug Administration)  
 Foot ... 2-230  
 Foreign Protocols ... E-3:E-4, E-14:E-29, E-31, E-35, E-38, E-43:E-46  
 Foreign Subjects ... E-43, E-45  
 Foundation for NIH ... 1-27, 2-151  
 Foundations ... 1-27, 2-13, 2-16, 2-82, 2-163, 3-54, 3-104, 3-186, 3-200:3-201, 3-217, 4-27, C-4  
 Fractures, Bone ... 2-124, 2-127, 2-141, 3-9  
 Fractures, Spontaneous ... 2-127, 2-141, 3-9  
 Fragile X Syndrome ... 2-64, 2-138, 2-202, 2-249, 3-93, 3-101  
 Frail Older Adults ... 2-205  
 Framingham Genetic Research Study ... 3-28  
 Framingham Heart Study ... 2-152:2-153, 3-2, 3-4, 3-8, 3-13, 3-32, 3-49, 3-148, 3-154  
 Framingham SNP-Health Association Resource ... 2-126, 2-152:2-153, 3-8, 3-49  
 Friedreich Ataxia ... 2-68  
 Frontotemporal Dementia ... 2-32, 2-254, 4-5, 4-7:4-9  
 Functional Genomics ... 2-57, 2-83, 3-39, 3-42, 3-81  
 Functional impairment ... 2-180  
 Funding ... 1-4, 1-6:1-7, 1-9, 1-12, 1-14, 1-16:1-17, 1-19, 1-27:1-29, 1-32:1-33, 2-4, 2-17, 2-25, 2-27, 2-34, 2-39, 2-48, 2-57, 2-59, 2-61, 2-65, 2-69, 2-76, 2-78, 2-83, 2-100, 2-106, 2-123, 2-134, 2-145, 2-147, 2-149:2-150, 2-167, 2-169, 2-182, 2-194, 2-203, 2-216, 2-222, 2-239, 2-243, 2-246, 2-249, 3-14, 3-33, 3-36, 3-75, 3-77:3-79, 3-95, 3-104, 3-107, 3-109, 3-112, 3-123, 3-130, 3-137, 3-143, 3-150, 3-167, 3-174, 3-187:3-188, 3-191, 3-197, 3-199, 3-201:3-203, 3-207:3-209, 3-215:3-217, 3-244:3-245, 4-1, 4-3, 4-5, 4-12, 4-15:4-16, 4-20, 4-23:4-25, 4-27, 4-29, 4-32:4-34, 4-36, 4-39, 4-41, A-5:A-7, B-5, C-1:C-5, C-7:C-8, E-6:E-7, E-12  
 Funding mechanism ... 2-149, 2-203, 3-14, 3-167, 3-244, 4-1, 4-24:4-25, C-3:C-4  
 Funding Opportunity Announcement ... 1-29, 2-59, 2-169, 2-239, 3-130  
 Gallbladder ... 2-121:2-122, 2-175, 2-253  
 Gallstones ... 2-122, 3-32, F-8  
 Gardasil ... 1-10, 2-2, 2-17, 2-86, 3-136  
 Gastroesophageal Reflux Disease ... 2-122  
 Gastrointestinal Tract ... 3-40, 3-82, 4-18  
 Gaucher Disease ... 2-68  
 Gender ... 2-95, 2-127, 2-135, 2-150, 2-167, 2-215, 3-122:3-123, 3-149, 3-210, 3-225, 3-238, 4-30, E-4, E-6:E-8, E-11:E-12, E-20, E-33, E-36, F-2:F-4, F-7, F-11  
 Gender Issues ... F-11  
 Gene Array ... 2-109  
 Gene Chips ... 2-42, 3-44, 3-183  
 Gene Expression ... 1-12, 1-23, 2-4, 2-35, 2-39, 2-41, 2-50, 2-56, 2-59, 2-114, 2-183, 2-187, 2-197, 3-27, 3-37, 3-45:3-46, 3-61, 3-63, 3-66:3-67, 3-72, 3-80, 3-82, 3-159, 3-170, 4-22, F-8  
 Gene Expression Nervous System Atlas ... 2-59, 3-61, 3-72  
 Gene Expression Profiles ... 2-8, 2-16, 3-37  
 Gene Expression Regulation ... 3-83  
 Gene Interactions ... 2-144, 2-229, 3-125  
 Gene Regulation ... 3-83  
 Gene Therapy ... 1-30, 2-37, 2-53, 2-55, 2-68:2-69, 2-95, 2-116, 2-155, 2-254, 3-71, 3-75, 3-97, 3-106, 3-109, 3-114, 3-132, 3-138, 4-18:4-19, 4-21:4-22  
 Gene Therapy Clinical Trials ... 2-254  
 General Clinical Research Centers ... 3-130  
 Genes, Environment and Health Initiative ... 3-32, 3-58, 3-213  
 Genes, Environment, and Development Initiative ... 2-42, 3-44, 3-184  
 Genes, Environment, and Health Initiative ... 2-151, 3-2, 3-7, 3-32, 3-37, 3-177, 3-184:3-185  
 Genetic Ascertainment of Large African American Family for Osteoarthritis and Early Onset Cardiovascular Disease ... 4-12  
 Genetic Association Information Network ... 2-108, 2-127, 2-146, 2-151, 3-13, 3-33, 3-36:3-37, 3-45, 3-49, 3-107, 3-154, 3-177  
 Genetic Diseases, Inborn ... 2-165, 2-195:2-196, 3-31, 3-47, 3-51, 3-79, 3-110, 3-121, 3-124, 3-185, 3-237, 4-17, F-6  
 Genetic Engineering ... 3-48, 3-61:3-62, 3-89, 3-101, 3-165  
 Genetic Factors ... 2-38, 2-42, 2-96, 2-103, 2-112, 2-127, 2-133, 2-143, 2-149, 2-203, 3-9, 3-11, 3-21, 3-28, 3-32, 3-36, 3-42, 3-51:3-52, 3-54, 3-61, 3-78, 3-118, 3-154, 3-200, 3-241, 4-15, 4-27  
 Genetic Markers ... 2-2, 2-5, 2-14, 3-6, 3-13, 3-33, 3-38  
 Genetic Modification Clinical Research Information System ... 1-29  
 Genetic Predispositions ... 2-36, 2-42, 2-107, 3-44, 3-183  
 Genetic Research ... 2-15, 3-28, 3-31, 3-33, 3-52, 3-61, 3-74, 3-192  
 Genetic Risk ... 2-5, 2-15, 2-18, 2-39, 2-107, 2-119, 2-140, 2-142, 2-146, 2-199, 3-18, 3-23, 3-111, 4-5  
 Genetic Screening ... 2-152, 2-254, 3-53, 3-75, 3-124, 3-139, F-6  
 Genetic Susceptibility ... 2-5, 2-108, 2-113, 2-127, 2-144, 2-151, 2-229, 3-53, 3-125, 3-139, 3-159  
 Genetic Testing ... 1-30, 2-152, 2-254, 3-53, 3-75, 3-124, 3-139, 3-223  
 Genetic Variation ... 2-42, 2-126:2-127, 2-152, 3-2, 3-30:3-31, 3-36, 3-44, 3-165, 3-176, 3-183, F-6  
 Genetics of Alzheimer's Disease Data Storage Site ... 3-148  
 Genetics of Kidneys in Diabetes ... 2-126, 2-146, 3-45, 3-91:3-92, 3-107  
 Genetics, Behavioral ... 2-188, 3-16  
 Genetics, Molecular ... 3-215  
 Genetics, Population ... 3-213  
 Genets (see Viverridae)  
 Genome ... 1-4:1-5, 1-12:1-15, 1-23, 1-30, 2-1:2-2, 2-5, 2-8:2-9, 2-12, 2-14, 2-16, 2-20:2-21, 2-23, 2-39, 2-42, 2-47, 2-51, 2-53, 2-56, 2-59, 2-64, 2-70, 2-76:2-77, 2-82:2-83, 2-87, 2-96, 2-104, 2-106:2-108, 2-112:2-113, 2-126, 2-139, 2-143, 2-146, 2-151:2-152, 2-195, 2-255, 3-6, 3-13:3-14, 3-27:3-46, 3-48:3-50, 3-52:3-54, 3-61, 3-65:3-66, 3-73, 3-78, 3-85, 3-103, 3-107, 3-112, 3-132, 3-139, 3-145:3-146, 3-148, 3-154:3-156, 3-159, 3-165, 3-167, 3-169, 3-175:3-178, 3-195, 3-199, 3-232, 4-7, 4-22, B-4, C-3, C-8, F-6  
 Genome Analysis ... 2-20, 3-38, 3-175  
 Genome Technology Program ... 3-35, 3-41, 3-176  
 Genome-Wide Association ... 2-5, 2-14, 2-77, 2-107:2-108, 2-126, 2-139, 2-152, 3-13, 3-31:3-33, 3-35:3-36, 3-38, 3-148, 3-155, 3-232  
 Genome-Wide Association Studies ... 2-5, 2-14, 2-77, 2-107:2-108, 2-152, 3-13, 3-31:3-33, 3-35:3-36, 3-38, 3-49, 3-148, 3-154:3-155, 3-232  
 Genomic Sequencing ... 2-76, 3-40:3-41, 3-66, 3-177  
 Genomics ... **3-27:3-54**, 1-4, 1-7, 1-23, 2-2, 2-13:2-16, 2-20, 2-22:2-23, 2-39, 2-42, 2-47, 2-52, 2-56, 2-58, 2-60, 2-64, 2-71, 2-77, 2-81:2-83, 2-96, 2-98, 2-105, 2-107, 2-109, 2-114, 2-127, 2-133, 2-135, 2-140, 2-143:2-144, 2-146:2-147, 2-150:2-153, 2-183, 2-195, 3-7:3-9, 3-13:3-14, 3-19, 3-58, 3-65:3-66, 3-73:3-74, 3-78, 3-101, 3-107, 3-110, 3-132, 3-139, 3-152, 3-154:3-156, 3-159:3-160, 3-175:3-178, 3-180, 3-184, 3-200, 3-213, 3-226, 3-238, A-5  
 Geography ... D-4  
 Geriatrics ... 4-10, 4-13, 4-15  
 Gerontology ... 2-209  
 Gestation ... 2-179:2-180, 2-182, 2-184, 2-198

- Gestational Diabetes ... F-8  
 Gila River Indian Community Longitudinal Study ... 2-127, 2-146, 2-220, 2-237, 3-10  
 Gingival Diseases ... 2-198, 3-59, 3-115  
 Gingko biloba ... 2-38, 2-56, 3-62, 3-87  
 Ginseng ... 2-52  
 Glaucoma ... 2-56, 2-123, 2-125, 2-136, 2-176, 3-32, 3-235, F-5  
 Glia ... 2-45, 2-168, 3-63  
 Gliomas, Malignant ... 2-19, 2-68  
 Global Health ... 2-28, 2-72, 2-100:2-101, 2-172:2-173, 3-162, 3-172, 3-195, 3-200, 3-212, 3-216, 3-228, B-5, F-4  
 Glucosamine ... 2-131, 2-165, 3-121  
 Glucose ... 2-51, 2-121, 2-136, 2-199, 2-205, 3-87, 3-171, 3-182, 4-6  
 Glycomics ... 3-64, 3-105, 3-173, 3-187:3-188  
 Goiter ... F-8  
 Gonorrhea ... 2-83, 3-39  
 Government Performance Results Act of 1993 ... 2-12, 2-23, 2-41, 2-44, 2-47, 2-55, 2-60, 2-62, 2-82, 2-91, 2-94, 2-96, 2-111, 2-132, 2-144:2-145, 2-157:2-160, 2-190, 2-193, 2-223, 2-235, 2-246, 3-8, 3-11, 3-20, 3-35, 3-43, 3-50, 3-52, 3-101, 3-108, 3-112, 3-116:3-117, 3-126, 3-132:3-134, 3-137, 3-175, 3-182, 3-184, 3-201:3-202, 3-218, 3-233  
 GPRA (see Government Performance Results Act of 1993)  
 Graduate Partnerships Program ... 3-204:3-205  
 Graft Rejection ... 2-116, 2-158, 3-61, 3-71, 3-132, 3-134  
 Grafts ... 2-132, 2-161, 3-71, 3-140, 3-186  
 Grant ... 1-18, 1-20:1-21, 1-25, 1-27, 2-27, 2-58, 2-68, 2-89, 2-222, 2-246, 3-28, 3-147, 3-159, 3-190, 3-198:3-199, 3-201, 3-211, 3-214, 4-7, 4-10, E-11  
 Grant Applications ... 1-16, 1-28, 1-33, 2-237, E-6  
 Graves Disease ... F-8  
 Green Tea ... 2-136, 3-62, 3-87  
 Guidelines as Topic ... 1-24, 1-32:1-33, 2-15, 2-25, 2-94, 2-192, 2-227, 3-104, 3-122, 3-135, E-4:E-8  
 GWAS (see Genome-Wide Association Studies)  
 Gynecologic Oncology Group ... F-4  
 H5N1 vaccine ... 2-80  
 H5N1 Virus ... 2-80, 2-93, 3-60  
 Haemophilia ... 2-122, 2-175  
 Hair Cells, Auditory ... 2-50:2-51  
 HALT-C (see Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial)  
 HALT-PKD ... 2-129, 2-162, 3-15, 3-119  
 Hands ... 1-25, 2-49, 2-145, 2-170, 2-207, 2-224, 2-232, 3-20, 3-128, 3-147, 3-165, 3-180, 3-184, 3-186, 3-190, 3-196:3-197, 3-200, 3-234, 3-240  
 Haplotype ... 3-29:3-30, 3-32  
 HapMap ... 1-13, 2-151, 3-6, 3-29:3-31, 3-37, 3-52, 3-177, F-6  
 Hawaiian/Pacific Islander ... D-7, E-10, E-15:E-18  
 HDL (see Lipoproteins, HDL)  
 Head and Neck Cancer ... 2-2  
 Head Off Environmental Asthma in Louisiana ... 2-144, 2-220, 2-229, 3-125  
 Headaches ... 2-33, F-5  
 Health and Retirement Study ... 2-189, 3-15  
 Health Care Costs ... 2-3, 2-104, 2-174, 2-176, 2-181  
 Health Care Delivery ... 2-11, 2-24, 2-239, 3-12, 3-129, 4-4  
 Health Care Providers ... 1-11, 2-9:2-11, 2-21, 2-26, 2-59, 2-65, 2-81, 2-93, 2-126, 2-155:2-156, 2-166, 2-169, 2-201, 2-219, 2-239, 3-21, 3-97:3-98, 3-113, 3-118, 3-122, 3-125, 3-141, 3-146, 3-160, 3-183, 3-221, 3-225, 3-227, 3-229:3-230, 3-235:3-236, 3-238, 3-240, 3-244:3-245, 4-21, B-4  
 Health Care Team ... 4-29  
 Health Communications ... **3-221:3-246**  
 Health Disparities ... **2-213:2-248**, 1-3, 1-6:1-7, 1-15, 1-19:1-20, 2-1, 2-3, 2-10, 2-14, 2-20:2-22, 2-27, 2-66, 2-68, 2-74, 2-84, 2-117, 2-135, 2-141:2-142, 2-144:2-146, 2-148, 2-153, 2-157, 2-161, 2-163, 2-167, 2-200, 2-255, 3-10:3-11, 3-13:3-14, 3-17, 3-19:3-20, 3-25, 3-52, 3-106, 3-114, 3-117, 3-124:3-125, 3-128, 3-136:3-142, 3-158, 3-185, 3-195:3-196, 3-198, 3-205, 3-209, 3-230:3-231, 3-235, 3-238, 3-240:3-242, 3-244:3-246, 4-1:4-2, 4-15, 4-24:4-25, 4-27:4-31, A-5, B-4:B-5, F-5, F-7, F-9:F-10  
 Health Disparities Bench-to-Bedside Program ... 2-235  
 Health Education ... 2-26:2-27, 2-126, 2-145, 2-205, 2-214, 2-217, 2-219:2-220, 2-224, 2-230, 2-233, 2-235, 2-245, 2-247, 3-20, 3-91, 3-142, 3-229, 3-231:3-232, 3-235:3-236, 3-238, 3-246, 4-7, 4-27, B-4  
 Health Educators ... 2-11, 2-27, 2-219, 3-161  
 Health Effects of Climate Change ... 2-255  
 Health Maintenance Consortium ... 2-130, 2-163  
 Health Maintenance Organizations ... 2-24, 3-12, 3-129  
 Health Partnership Program ... 2-236, 3-241  
 Health Personnel ... 2-24, 2-243, 3-12, 3-212  
 Health Plans ... 2-234  
 Health Promotion ... 1-19, 2-240, 3-141, 3-231, 4-30, B-3:B-4, F-10  
 Health Resource ... 2-152, 3-8, 3-49  
 Health Resources and Services Administration (see United States Health Resources and Services Administration)  
 Health Services Accessibility ... 2-153, 2-214, 3-14  
 Health Services Needs and Demand ... 2-1, 2-4, 2-75, 2-93, 2-139, 2-213:2-214, 2-223, 2-237, 3-95, 3-134, 3-142, 3-184, 3-225, 3-227, 4-23, 4-25, 4-28:4-29, B-4  
 Health Services Research ... 2-82, 2-99, 2-243, 3-89, 3-134, 3-197, 3-200, 3-206, 3-208, 3-211, E-11  
 Health Statistics ... 1-4, 2-3, 2-66, 2-75, 2-105, 2-120, 2-174, 2-180, 2-214  
 HEALTHY ... 1-9, 1-12, 1-19, 1-23:1-25, 2-5, 2-9, 2-16, 2-18, 2-20, 2-35, 2-38, 2-44, 2-54, 2-65, 2-80, 2-125, 2-128, 2-140:2-142, 2-145, 2-147, 2-152, 2-179, 2-185, 2-187:2-188, 2-198, 2-200, 2-205, 2-209, 2-214, 2-218, 2-221, 2-224, 2-227:2-228, 2-239, 3-3, 3-16, 3-18, 3-20, 3-23, 3-51, 3-53, 3-56, 3-72, 3-82, 3-96, 3-102, 3-111:3-112, 3-125, 3-139, 3-141, 3-183, 3-229, 3-231, 3-235, 3-243, 3-245:3-246, 4-13, 4-30, B-3  
 Healthy Aging in Neighborhoods of Diversity Across the Life Span ... 2-218, 2-227  
 Healthy People 2010 ... 1-19, 2-221, 2-239, 3-141, 3-229, 3-245:3-246, 4-30  
 Hearing ... 2-32, 2-38, 2-50:2-51, 2-66, 2-123, 2-176, 3-20, 3-166, 3-175, 3-237, 4-11, B-3, F-10  
 Hearing Aids ... 2-66:2-67, 3-175  
 Hearing Impaired Persons ... 2-46, 2-210, 3-168, 3-174  
 Hearing Impairment (see Hearing Loss)  
 Hearing Loss ... 1-15, 2-32, 2-37, 2-46, 2-57, 2-66:2-67, 2-71, 2-123, 2-153, 2-176, 2-196:2-197, 2-210:2-211, 2-229, 3-14, 3-19:3-20, 3-57, 3-61, 3-81:3-82, 3-168, 3-174:3-175, 3-185, 3-225, 3-237, B-3, F-10  
 Hearing Loss, Noise-Induced ... 3-237  
 Heart ... 1-14:1-15, 2-2, 2-9, 2-47, 2-121, 2-124:2-125, 2-128:2-129, 2-134, 2-140, 2-152, 2-159, 2-164:2-165, 2-171, 2-195, 2-230, 3-4, 3-32, 3-47, 3-49, 3-80, 3-87, 3-110, 3-121, 3-126, 3-134, 3-144, 3-156, 3-166, 3-227, 3-239, 4-14, 4-18, 4-32, B-1, E-2, F-6  
 Heart Disease ... 1-9, 2-3, 2-33, 2-109, 2-111, 2-117, 2-119, 2-121, 2-123, 2-125, 2-127:2-128, 2-133:2-135, 2-140, 2-147, 2-151:2-154, 2-174, 2-184, 2-187, 2-215, 2-217:2-218, 2-229:2-230, 2-234, 2-255, 3-3, 3-9, 3-14, 3-18, 3-28, 3-30, 3-32, 3-42, 3-51, 3-53, 3-57, 3-67, 3-139, 3-173, 3-181, 3-186, 3-225, 3-227, 3-239, 4-3, 4-12, F-7, F-11  
 Heart Disease: Coronary Heart Disease ... 2-255  
 Heart Failure ... 2-121, 2-133, 2-164, 2-167, 2-174, 3-87, 3-144, 3-157  
 Heart Septal Defects, Atrial ... 4-37:4-40  
 Heart Truth, The ... 2-128, 2-140, 3-227, 3-239  
 Heart Valve Prosthesis ... 3-190

- Heart Valves ... 2-83, 3-40, 3-190  
Heart, Artificial ... 3-190  
HELLP Syndrome ... 2-142, 2-198:2-199, 3-115  
Hematologic Diseases ... B-2, F-8  
Hematologic Neoplasms ... 2-2  
Hematology ... 2-255, D-8  
Hemiplegia ... 2-208  
Hemochromatosis ... 2-122  
Hemodialysis ... 2-132, 2-161, 3-71, 3-140, 3-186  
Hemophilia ... 2-122, 2-147, 2-175, 3-51  
Hemorrhagic Fever, Ebola ... 2-74, 2-76, 2-80:2-81, 2-90, 2-92, 2-100, 3-216  
Hemorrhagic Fevers, Viral ... 2-74  
Hepacivirus ... 2-129, 2-166, 2-175, 3-122  
Hepatitis ... 2-47, 2-78, 2-122, 2-129, 2-159, 2-166, 2-175, 2-255, 3-57, 3-122, 3-126, 4-28  
Hepatitis - A ... 2-255  
Hepatitis - B ... 2-175, 2-255, 3-57, 4-28  
Hepatitis - C ... 2-78, 2-129, 2-166, 2-175, 2-255, 3-122  
Hepatitis B Vaccines ... 2-175, 2-255  
Hepatitis B Virus ... 4-28  
Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial ... 2-166, 3-122  
Hepatitis C Virus (see Hepacivirus)  
Hepatitis, Chronic ... 2-122  
Hepatitis, Viral, Human ... 2-175  
Hepatology ... 2-166, 3-122  
Herbal Therapy ... F-5  
Herbal Treatments ... 3-85, 3-131  
Heroin Addiction ... 2-98, 2-154, 3-123  
Herpes ... 2-260, 3-57, F-7  
Heterosexual ... 2-79, 2-85, 2-90  
Heterosexual activity ... 2-85  
HHS (see United States Department of Health and Human Services)  
High Density Lipoprotein Cholesterol ... 2-165, 3-121  
High School ... 1-25, 3-204, 3-240  
High-Density Lipoprotein (see Lipoproteins, HDL)  
High-End Instrumentation ... 3-65, 3-138, 3-190:3-191  
High-Risk Pregnancies ... 2-195  
High-Throughput Screening ... 2-13, 2-16, 2-92, 3-70, 3-77, 3-180  
Highly Active Antiretroviral Therapy (see Antiretroviral Therapy, Highly Active)  
Hip ... 2-127, 2-141, 2-148, 2-186, 2-209, 2-225, 3-9, 3-72, 3-102, 4-13  
Hip Fractures ... 2-186, 2-209, 4-13  
Hippocampus ... 2-31  
Hispanic Americans ... 2-80, 2-147, 2-201, 2-228, 3-10, 3-34, 3-51, 3-152, 3-158, 3-224, 3-227, 3-234, 3-236, 3-240, D-7  
Hispanic Community Health Study ... 2-127, 2-153, 2-218, 2-229, 2-235, 3-8, 3-14, 3-50  
Hispanic Cultural Values ... 2-240  
Hispanic or Latino ... E-9:E-10, E-15:E-18  
Hispanics ... 2-14, 2-20, 2-22, 2-66, 2-68, 2-87, 2-127, 2-141, 2-147, 2-153, 2-198, 2-201, 2-213, 2-215, 2-217:2-220, 2-223, 2-225:2-227, 2-229, 2-231:2-236, 2-238, 2-240, 2-242:2-243, 3-8, 3-14, 3-17, 3-19, 3-50, 3-152, 3-199, 3-227, 3-234, 3-236, 3-240, 3-242, 4-7, 4-25:4-26, 4-28:4-29, E-9:E-10, E-15:E-18, E-34, E-37, E-40, E-44, E-46  
Histology ... 2-21, 2-28, 3-25, 3-39, 3-73, 3-154, D-1  
Historically Black Colleges and Universities ... 2-222, 2-242, 4-24:4-25, 4-27  
HIV (see Human Immunodeficiency Virus)  
HIV Dementia ... 2-61, 2-99  
HIV Infections ... 1-10:1-11, 1-20, 2-2, 2-17:2-18, 2-33, 2-47, 2-61, 2-68, 2-73:2-79, 2-82, 2-84:2-90, 2-94:2-95, 2-97:2-100, 2-120, 2-153:2-154, 2-159, 2-167, 2-172, 2-184:2-185, 2-191, 2-193, 2-204, 2-213, 2-215, 2-219, 2-225:2-226, 2-233:2-234, 2-240, 2-249, 2-255, 3-2, 3-7:3-8, 3-21, 3-23:3-24, 3-32, 3-85, 3-96:3-98, 3-116:3-117, 3-123:3-124, 3-126, 3-131, 3-134, 3-136, 3-153, 3-162, 3-170, 3-189, 3-200, 3-208, 3-211:3-212, 3-216, 3-228, 3-236, 4-25, 4-30, B-1:B-2, F-6:F-7, F-11  
HIV Neuropathogenesis ... 2-61, 2-99  
HIV Prevention ... 2-79, 2-84, 2-88:2-90, 2-94, 2-130, 2-163, 2-240  
HIV Prevention Trials Network ... 2-94  
HIV Protease Inhibitors ... 3-181  
HIV Rapid-Screen Technologies ... 2-84, 2-227, 3-124  
HIV Screening ... 2-84, 2-226:2-227, 3-124  
HIV Seropositivity ... 1-11, 1-20, 2-2, 2-17:2-18, 2-33, 2-47, 2-61, 2-68, 2-73:2-79, 2-82, 2-84:2-90, 2-94:2-95, 2-97:2-100, 2-120, 2-153:2-154, 2-159, 2-167, 2-172, 2-184:2-185, 2-191, 2-193, 2-204, 2-213, 2-215, 2-219, 2-225:2-226, 2-233:2-234, 2-240, 2-249, 2-255, 3-2, 3-7:3-8, 3-21, 3-23:3-24, 3-32, 3-85, 3-96:3-98, 3-116:3-117, 3-123:3-124, 3-126, 3-131, 3-134, 3-136, 3-153, 3-162, 3-170, 3-189, 3-200, 3-208, 3-211:3-212, 3-216, 3-228, 3-236, 4-25, 4-30, B-1:B-2, F-7  
HIV Transmission ... 2-79, 2-86, 2-97, 2-184, 2-191, 3-23, 3-116  
HIV Types ... 2-79  
HIV Vaccine Candidates ... 2-79, 2-98  
HIV Vaccine Trial ... 2-79, 2-87, 2-94, 2-98, 3-236  
HIV Vaccine Trials Network ... 2-79, 2-94  
HIV Vaccines ... 2-79  
HIV-1 ... 2-95, 3-106, 3-181  
HIV-Associated Co-Infections ... 2-78  
HIV-Associated Malignancies ... 2-78  
HIV-Infected Individuals ... 2-18, 2-78, 2-86  
HIV/AIDS (see Acquired Immunodeficiency Syndrome/Human Immunodeficiency Virus)  
HIV/AIDS Clinical Trials Units ... 2-94  
HIV/AIDS Epidemiological and Long-Term Cohort Studies ... 2-97, 2-191, 3-23, 3-116  
HIV/AIDS Pandemic ... 2-79  
HLA-C Antigens ... 2-107  
Hodgkin's Disease ... 2-255  
Homeostasis ... 2-113, 3-61, 3-77  
Homosexual ... 2-97, 2-191, 3-24, 3-116  
Hormone ... 2-24, 2-33, 2-47, 2-103, 2-133, 2-137, 2-188, 2-225, 3-3:3-4, 3-12, 3-32, 3-34, 3-129, 3-147, 3-149, F-4, F-6, F-8, F-10  
Hormone Replacement Therapy ... 2-24, 2-225, 3-3, 3-12, 3-129  
Hormone Therapy ... 3-3:3-4, 3-147, 3-149, F-4, F-6, F-10  
Host-Pathogen Interactions ... 2-135, 3-61, 3-78  
HPV (see Human Papillomavirus)  
HPV and/or Cervical Cancer Vaccines ... 2-7, 2-255  
HPV Vaccine (see HPV and/or Cervical Cancer Vaccines)  
HPV-16 ... 2-7  
HRSA (see United States Health Resources and Services Administration)  
Human Fetal Tissue ... 2-255  
Human Genes and the Environment Training Program ... 3-200, 3-213  
Human Genetics ... 2-21, 2-58, 3-34, 3-39, 3-48, 3-73, 3-148, 3-155, 3-213  
Human Genome ... 1-4, 1-12:1-15, 2-5, 2-9, 2-12, 2-14, 2-70, 2-104, 2-126, 2-143, 2-151, 2-255, 3-6, 3-13:3-14, 3-27:3-30, 3-35, 3-38, 3-40:3-42, 3-44, 3-46, 3-49:3-50, 3-52:3-53, 3-65:3-66, 3-139, 3-154, 3-165, 3-167, 3-169, 3-176:3-178, B-4, C-3, C-8, F-6  
Human Genome Project ... 2-9, 2-12, 2-104, 2-126, 2-143, 3-6, 3-13, 3-27:3-28, 3-40:3-42, 3-44, 3-49, 3-52, 3-65, 3-154, 3-165, 3-169, 3-176:3-178, B-4, C-3, F-6  
Human Immunodeficiency Virus ... 1-10:1-11, 1-20, 2-2, 2-17:2-18, 2-28, 2-33, 2-47, 2-61, 2-68, 2-73:2-79, 2-82, 2-84:2-90, 2-94:2-95, 2-97:2-100, 2-120, 2-153:2-154, 2-159, 2-167, 2-172, 2-184:2-185, 2-191, 2-193, 2-204, 2-213, 2-215, 2-219, 2-225:2-226, 2-233:2-234, 2-240, 2-249, 2-255, 3-2, 3-7:3-8, 3-21, 3-23:3-24, 3-32, 3-85, 3-96:3-98, 3-116:3-117, 3-123:3-124, 3-126, 3-131, 3-134, 3-136, 3-153, 3-162, 3-170, 3-189, 3-200, 3-208, 3-211:3-212, 3-216, 3-228, 3-236, 4-25, 4-30, B-1:B-2, F-7



- 2-159, 2-163, 2-167, 2-172:2-173, 2-184:2-185, 2-191, 2-193, 2-204, 2-213, 2-215, 2-219, 2-225:2-227, 2-233:2-234, 2-240, 2-249, 2-255, 3-2, 3-7:3-8, 3-21, 3-23:3-24, 3-28, 3-32, 3-85, 3-96:3-98, 3-106, 3-116:3-117, 3-123:3-124, 3-126, 3-131, 3-134, 3-136, 3-153, 3-162, 3-170, 3-181, 3-189, 3-200, 3-208, 3-211:3-212, 3-216, 3-228, 3-236, 4-25, 4-30, B-1:B-2, F-6:F-7, F-11
- Human Immunology Centers ... 2-82
- Human Microbiome ... 3-40, C-2, C-5:C-7
- Human Microbiome Project ... 1-12, 1-23, 3-40, C-2, C-5:C-8
- Human Papilloma Virus Vaccine (see Papillomavirus Vaccines)
- Human Papillomavirus ... 1-10, 2-2, 2-7, 2-17:2-18, 2-28, 2-86, 2-255, 3-25, 3-89, 3-136, 3-154, F-4
- Human Subjects Protection ... 1-18, 1-27, 1-30
- Huntington's Disease ... 2-69, 2-256, 3-27, 3-57, 3-60, 3-70, 3-109, 3-162, 3-189
- Hurricane Katrina ... 2-144, 2-220, 2-229, 3-125, 3-148, 3-228
- Hurricanes ... 2-237
- Hutchinson-Gilford Progeria Syndrome ... 2-195, 3-30, 3-47, 3-110
- Hyaluronic Acid ... 1-9
- Hydrocephalus ... 2-33
- Hyperbaric Oxygen ... 2-256
- Hyperinsulinism ... 2-136, 2-142, 2-199, 3-87
- Hyperparathyroidism ... F-8
- Hypersensitivity ... 3-21:3-22, 3-118
- Hypersensitivity, Delayed ... 2-116, 2-143, 3-71, 3-132
- Hypersensitivity, Immediate ... 2-116, 2-143, 2-161, 2-220, 3-21, 3-71, 3-118, 3-132
- Hypertension ... 2-69:2-70, 2-84, 2-121:2-122, 2-148, 2-157, 2-164:2-165, 2-170, 2-182, 2-184, 2-216, 2-220, 2-223, 2-227, 2-230, 2-234, 2-256, 3-2, 3-25, 3-59, 3-62, 3-68, 3-79, 3-114, 3-121, 3-124, 3-128, 4-3, 4-14:4-15, 4-31, F-6
- Hypertension prevention ... 2-234
- Hypoglycemia ... 2-117, 2-154, 2-199:2-200, 3-18, 3-182
- Hypothyroidism ... 2-179, 2-196, 3-185, F-8
- Hypoxemia ... 2-129, 2-158, 3-115:3-116
- IBD (see Inflammatory Bowel Disease)
- IBS (see Irritable Bowel Syndrome)
- Idiopathic Pulmonary Fibrosis ... 2-121, 2-129
- Image-Guided Interventions ... 3-171, 3-182
- Imaging Sciences Training Program ... 3-205
- Imaging Technique ... 2-7, 2-25, 2-27, 2-125, 2-134, 2-143, 2-191, 2-217, 2-230, 3-57, 3-171
- Imaging Technologies ... 2-9, 2-13, 2-16, 2-31, 2-35, 2-38, 2-43:2-44, 2-183, 2-188, 2-190, 3-11, 3-16, 3-180, F-7
- Immediate Hypersensitivity (see Hypersensitivity, Immediate)
- Immigrants ... 2-193, 2-216, 2-230, 3-10, 3-25
- Immigration ... 2-192, 2-230, 3-9, 3-25
- Immune Diseases ... 2-73, 2-115, 3-110
- Immune Disorders ... 2-110, B-2
- Immune System ... 1-11, 2-10, 2-36, 2-76, 2-84, 2-92, 2-95, 2-103, 2-105, 2-108, 2-110:2-111, 2-115:2-116, 2-138, 2-143, 2-157, 3-32, 3-56, 3-61, 3-69, 3-71, 3-76, 3-103, 3-110, 3-132
- Immune System Diseases ... 3-21
- Immune Tolerance ... 2-103, 2-105, 2-110, 2-116, 2-118, 2-172, 3-22, 3-61, 3-71, 3-132
- Immune Tolerance Network ... 2-110, 2-116, 3-61, 3-71, 3-132
- Immune-Related Diseases ... 2-73
- Immunization ... 2-91, 2-93, 2-99, 2-256, 3-192
- Immunoassays ... 2-91
- Immunology ... 2-79, 2-82, 2-88, 2-98, 2-103, 2-115, 2-158, 2-161, 3-21, 3-55, 3-110, 3-118, 3-134, D-2, D-8
- Immunosuppressants ... 2-156, 3-114
- Immunosuppression ... 2-110, 4-22
- Immunosuppressive Agents ... 2-110, 2-116, 2-157, 3-103
- Immunotherapeutics ... 2-80
- Immunotherapy ... 2-10, 2-19, 2-161, 3-21, 3-56, 3-118
- Immunotoxins ... 2-10
- InCHIANTI ... 4-13
- Inclusion of Women and Minorities as Subjects in Clinical Research ... 1-6, 1-8, 3-122, E-1:E-6
- Indians, North American ... 2-14, 2-20, 2-127, 2-146, 2-213, 2-215:2-217, 2-220, 2-223, 2-225, 2-231, 2-234:2-237, 2-250, 3-10, 3-91, 3-199, 3-227, 3-231, 4-7, 4-19, 4-21, 4-27, 4-43, D-7:D-8
- Indoprofen ... 2-63, 3-108
- Industrial Accidents ... 2-62, 2-96
- Infant ... 2-35, 2-43, 2-77, 2-79, 2-87, 2-97, 2-142, 2-156, 2-179, 2-181, 2-184:2-186, 2-190:2-191, 2-195:2-196, 2-198:2-199, 2-210, 2-213, 2-215, 2-231, 2-256, 2-261, 3-20, 3-22, 3-24:3-25, 3-82, 3-115:3-117, 3-168, 3-174, 3-185, 3-231, 4-11, 4-25, 4-30
- Infant Care ... 2-185
- Infant Mortality ... 2-174, 2-213, 2-215, 2-231, 2-256, 3-231, 4-25, 4-30
- Infant, Newborn ... 2-146, 2-179, 2-184, 2-190, 2-196, 2-198:2-199, 2-215, 3-19:3-20, 3-23:3-24, 3-82, 3-115, 3-185, 4-11
- Infant, Premature ... 2-181
- Infantile Neuroaxonal Dystrophy ... 3-125
- Infants, Premature ... 2-198:2-199
- Infections, Urinary Tract ... 2-135
- Infections, Wound ... 2-137
- Infectious Disease Research Training ... 2-99, 3-212
- Infectious Diseases ... **2-73:2-103**, 1-3, 1-5, 1-7, 1-10:1-11, 1-15, 1-29, 2-2, 2-5, 2-7, 2-17:2-19, 2-28, 2-31:2-33, 2-40, 2-61:2-62, 2-68, 2-108, 2-110, 2-118:2-120, 2-123, 2-129, 2-135, 2-151, 2-154, 2-156, 2-172, 2-175, 2-185:2-186, 2-191, 2-193, 2-204, 2-227, 2-232, 2-248, 2-253, 2-256, 2-262, 3-3, 3-7, 3-19, 3-21, 3-24:3-25, 3-27, 3-29, 3-34:3-35, 3-39:3-41, 3-44:3-45, 3-50, 3-52, 3-55:3-57, 3-60:3-61, 3-66, 3-76:3-78, 3-89, 3-106, 3-116:3-117, 3-124, 3-133:3-136, 3-154, 3-160, 3-165, 3-170, 3-174, 3-177, 3-184:3-185, 3-192, 3-199:3-200, 3-208, 3-212, 3-216, 3-236, 3-240, 4-28, A-5, B-2, C-8, D-8, F-6:F-7
- Infectious Diseases, Emerging ... 2-76:2-77, 2-82, 2-91, 2-94, 2-101, 3-76
- Infertility ... 2-184:2-185, 2-194, 2-256, 3-205, 3-209, F-7
- Inflammation ... 2-5, 2-19, 2-70, 2-114:2-115, 2-121:2-123, 2-125, 2-133:2-134, 2-137, 2-156, 2-162, 2-185, 2-205:2-206, 2-234, 3-31, 3-59, 3-64, 3-68, 3-75, 3-77, 3-105, 3-110, 3-114, 3-128, 3-188, F-9
- Inflammatory Bowel Disease ... 2-103, 2-105, 2-107:2-108, 2-126, 2-143, 2-161, 2-256, 3-42
- Inflammatory Bowel Disease Genetics Consortium ... 2-126, 2-143, 3-42
- Influenza ... 1-11, 2-73:2-77, 2-80:2-83, 2-91:2-93, 2-95:2-96, 2-98, 2-101, 2-119, 2-256, 2-259, 3-1:3-2, 3-7, 3-19, 3-28, 3-34, 3-39, 3-51:3-52, 3-60:3-61, 3-76, 3-78, 3-148, 3-154, 3-192, B-2
- Influenza A Virus ... 2-95, 3-34, 3-76
- Influenza Genome Sequencing Project ... 2-83, 2-96, 3-39, 3-52, 3-78, 3-148, 3-154
- Influenza Vaccines ... 2-76, 2-80:2-81, 2-91:2-93, 2-95, 2-98, 3-7, 3-19, 3-39, 3-51, 3-61, 3-76, 3-192
- Influenza Virus ... 1-11, 2-80, 2-82, 2-93, 2-96, 2-98, 3-7, 3-19, 3-51:3-52, 3-60:3-61, 3-78, 3-148, 3-154
- Influenza Virus Resource ... 2-96, 3-51, 3-60, 3-78, 3-148, 3-154
- Influenza Virus Sequence Database ... 2-96, 3-52, 3-78, 3-154
- Influenza virus vaccine (see Influenza Vaccines)
- Influenza Viruses ... 2-77, 2-95, 3-76
- Influenza, Avian ... 2-74, 3-34, 3-39

- Informatics ... 2-11:2-12, 2-15, 2-39, 2-41, 2-57, 2-202, 3-74, 3-92, 3-95, 3-99, 3-104:3-105, 3-142, 3-147:3-148, 3-151:3-152, 3-159, 3-161:3-163, 3-173, 3-185, 3-187, 3-190, 3-198:3-200, 3-207, 3-212, 3-215:3-217, B-5, C-3, C-5, C-7  
 Informatics Research Training Programs ... 3-163, 3-215  
 Informatics Training For Global Health ... 3-162, 3-200, 3-212  
 Information Campaigns ... 1-4:1-5, 1-7, 2-21:2-22, 2-24, 2-26, 2-43, 2-66, 2-68, 2-88, 2-126, 2-128, 2-131, 2-139:2-141, 2-149:2-150, 2-153, 2-156, 2-159, 2-201, 2-219, 2-231:2-233, 2-237, 2-239, 3-15, 3-51, 3-126:3-127, 3-129, 3-142, 3-153, 3-221:3-246, A-5  
 Information Clearinghouses ... 2-230, 3-235:3-236, A-5  
 Information Dissemination ... 2-104, 2-214, 3-221:3-246, 4-12, B-1, B-3, F-5, F-11  
 Information Service ... 2-26, 3-238  
 Information Systems ... 1-4:1-5, 1-7, 1-26, 2-25:2-28, 2-41, 2-53:2-54, 2-56, 2-58:2-59, 2-62, 2-93, 2-96:2-97, 2-113, 2-133, 2-140, 2-152, 2-164, 2-202, 2-228, 3-5, 3-10, 3-13, 3-25, 3-36:3-37, 3-48:3-49, 3-52, 3-78, 3-91:3-92, 3-120, 3-130:3-131, 3-145:3-148, 3-150:3-154, 3-158, 3-161:3-162, 3-185, 3-187, 3-189, 3-193, 3-204, 3-212, 3-216, 3-234, 3-239  
 Information Technology ... 1-14:1-15, 1-26, 2-245, 2-258, 3-141, 3-150, 3-160, 3-162, 3-165, 3-192, 3-212, B-5  
 Informed Consent ... 3-100  
 Informed Consent Documents ... 3-229  
 infoSIDA ... 2-219  
 Initiatives in Global HIV Trials ... 2-94  
 Injection ... 2-88, 2-98, 2-154, 3-123  
 Injection Drug Use ... 2-88, 2-98, 2-154, 3-123  
 Injury ... 1-11, 2-5, 2-19, 2-31:2-37, 2-40, 2-46, 2-48:2-49, 2-54, 2-92, 2-103, 2-122, 2-124:2-125, 2-131, 2-134, 2-139, 2-155, 2-165, 2-179:2-180, 2-186, 2-194, 2-207, 2-210, 2-256, 2-260, 3-76, 3-95, 3-106, 3-114, 3-130:3-131, 3-157, 3-190, 3-200, 3-212:3-213, 4-14:4-15, 4-25, 4-30  
 Injury (total) Accidents/Adverse Effects ... 2-256  
 Inner-City Asthma Consortium ... 2-130, 2-161, 3-21, 3-118  
 Institute of Medicine ... 2-67, 2-239, 3-53, 3-120, 4-27  
 Institutes and Centers ... 1-4:1-6, 1-8, 1-10, 1-14:1-22, 1-26:1-27, 1-29:1-31, 2-2, 2-31:2-33, 2-57, 2-59, 2-61, 2-74, 2-89, 2-132, 2-166, 2-169, 2-214, 2-221:2-222, 2-234, 3-5, 3-56:3-57, 3-75, 3-90:3-92, 3-96, 3-98, 3-104, 3-148, 3-159, 3-187, 3-191, 3-196:3-201, 3-203:3-204, 3-222:3-224, 3-230:3-231, 4-1, 4-35, 4-37, B-1, B-5:B-7, C-2:C-4, E-5:E-6, E-8, F-2:F-4, F-8, F-11  
 Institutional Development Award ... 2-221:2-223, 2-236, 2-246, 3-136:3-137  
 Institutional Review Boards ... 1-30:1-31, E-5  
 Insulin ... 2-109, 2-121, 2-125, 2-128:2-129, 2-147, 2-160, 2-193:2-194, 2-200, 3-182  
 Insulin Resistance ... 2-136, 2-188, 3-62, 3-87  
 Insulin-Secreting Cells ... 2-114, 2-125, 2-135, 2-147, 3-78  
 Insurance ... 2-184, 3-52, 3-229, 4-28, 4-38  
 Insurance Coverage ... 2-189, 3-15  
 Insurers ... 2-156, 3-127, 3-150, 3-235, 3-244  
 Integrative Cancer Biology Program ... 2-6, 2-15, 3-61, 3-74, 3-192  
 Integumentary System ... 2-136  
 Intellectual Disability ... 2-34, 2-180:2-181, 2-183, 2-185, 2-197, 2-249, 2-257  
 Intellectual Property ... 1-24, 1-27, 3-52  
 Intensive Care Units, Neonatal ... 2-198  
 Interagency Autism Coordinating Committee ... 4-36, 4-40:4-41  
 Interagency Coordinating Committee on Preventing Underage Drinking ... 2-42, 2-150, 2-203, 3-228, 3-241  
 Interagency Edison System ... 1-24  
 Interagency Registry for Mechanically Assisted Circulatory Support ... 2-133, 3-157  
 Interdisciplinary Research ... 1-20, 2-167, 3-46, 3-167, 3-171, 3-192:3-193, 3-198:3-199, 3-203, 3-206:3-207, 3-214:3-215, 3-217, 4-10, C-6, F-3  
 Interferon-Beta ... 2-112, 3-112  
 International Breast Screening Network ... F-4  
 International Centers for Research on CAM ... 3-85, 3-130  
 International Clinical, Operational and Health Services Research and Training Award for HIV/AIDS and TB ... 3-134:3-135, 3-208, 3-211:3-212  
 International Collaboration ... 2-18, 2-78, 2-82, 2-98, 2-145, 2-246, 3-137  
 International Collaborative Trauma and Injury Research Training Program ... 2-210, 3-212  
 International Epidemiologic Databases to Evaluate AIDS ... 2-97, 2-191, 3-2, 3-7, 3-23, 3-116  
 International Health Terminology Standards Development Organization ... 3-150, 3-160  
 International Maternal Pediatric Adolescent AIDS Clinical Trials ... 2-94  
 International Partnerships ... 2-74, B-5  
 International Research Scientist Development Award ... 2-100, 3-216  
 International Tobacco and Health Research and Capacity Building Program ... 2-12, 2-17, 2-145  
 International Training ... 2-99, 2-243, 3-20, 3-134, 3-211, 3-213  
 International Training and Research in Environmental and Occupational Health ... 3-213  
 International Training and Research Program in Population and Health ... 3-20, 3-213  
 Internationality ... 2-61, E-3, E-20:E-21, E-35, E-38, E-43, E-45  
 Internet ... 1-26, 1-28, 3-145, 3-171, 3-222, 3-227, 3-239, E-4  
 Interstitial Cystitis ... 2-122, 2-150, 2-167, 2-175, 2-231, 2-256, 3-19, 3-235, F-8  
 Intervention Research Grants ... 2-233  
 Intramural Program on Research on Women's Health ... 3-210  
 Intramural Programs ... 1-3, 1-7, 1-14, 1-16, 1-18:1-19, 1-22, 1-24:1-26, 1-30:1-33, 2-2, 2-12, 2-14, 2-19, 2-31, 2-35, 2-41, 2-44, 2-48, 2-53, 2-61, 2-68, 2-82, 2-109, 2-111:2-112, 2-115, 2-132, 2-167, 2-187:2-188, 2-221, 2-223, 2-244, 2-249, 3-8, 3-13, 3-16, 3-33, 3-35, 3-38, 3-63, 3-90, 3-101, 3-110, 3-112, 3-138, 3-152, 3-174, 3-181, 3-196, 3-204:3-206, 3-209:3-210, 3-215, 3-223, 3-233, 3-238, C-3, E-3:E-5, E-8, E-13:E-21, E-24:E-25, E-28:E-29, E-33:E-46, F-4  
 Intramural Research ... 1-3, 1-7, 1-14, 1-16, 1-18:1-19, 1-31:1-32, 2-12, 2-19, 2-41, 2-44, 2-53, 2-68, 2-82, 2-111, 2-115, 2-132, 2-187:2-188, 2-223, 2-244, 2-249, 3-8, 3-16, 3-35, 3-63, 3-101, 3-110, 3-138, 3-152, 3-174, 3-196, 3-205:3-206, 3-209, 3-215, 3-233, 3-238, E-5, E-8, E-13:E-14, E-16, E-18, E-20  
 Intramural Research Program ... 1-3, 1-7, 1-16, 1-18:1-19, 1-33, 2-44, 2-53, 2-115, 2-188, 2-244, 3-16, 3-110, 3-138, E-8  
 Intramural Research Training Award ... 3-205, 3-209  
 Intravenous Drug Use (see Substance Abuse, Intravenous)  
 Inuits ... 2-14, 2-213, 2-215:2-216, 2-220, 2-223, 2-233:2-236, 2-250, 3-231, 3-240, 4-25:4-26, D-8, E-10, E-15:E-18, E-34, E-40, E-44, E-46  
 Ionizing Radiation ... 2-92, 3-106, 3-153  
 IPlex ... 4-19, 4-21  
 IRBs (see Institutional Review Boards)  
 Irritable Bowel Syndrome ... 2-122, 2-127, 2-132, 2-143, 2-150, 2-169, F-8  
 Islets of Langerhans Transplantation ... 2-112, 3-107  
 Jackson Heart Study ... 2-125, 2-127, 2-134, 2-145, 2-153, 2-217, 2-224, 2-230, 2-235, 3-7:3-8, 3-20, 3-50  
 Jaw ... 2-209, 3-72, 3-102, 3-140

- John E. Fogarty International Center ... 1-15, 1-18, 2-7, 2-28, 2-33, 2-72, 2-74, 2-100:2-101, 2-118, 2-173, 2-248, 3-197, 3-200, 3-216, 3-228, B-5, F-4
- Joint Diseases ... 2-170
- Jointly Sponsored Predoctoral Training Program in the Neurosciences ... 3-198
- Joints ... 1-9, 2-122, 2-209, 3-72, 3-102, 3-232
- K-12 ... 1-24:1-25, 2-232, 3-240, 3-243
- Kallmann Syndrome ... 3-124
- Keratoconjunctivitis Sicca ... 3-79
- Keratoconus ... F-6
- Kidney ... 2-2, 2-122, 2-159, 2-162, 2-174, 3-15, 3-119, 3-134, 4-25, B-2, F-8
- Kidney Disease ... 1-15, 2-2, 2-109, 2-116:2-117, 2-122, 2-126:2-127, 2-129, 2-146, 2-153, 2-162, 2-171, 2-220, 2-229:2-230, 2-256, 2-259, 3-14:3-15, 3-17:3-18, 3-45, 3-71, 3-91:3-92, 3-107, 3-119, 3-132, 3-227, 3-235, 4-25, 4-30, 4-32, B-2, F-8
- Kidney Failure ... 2-110, 2-121, 2-146, 2-237, 3-11
- Kidney Failure, Chronic ... 2-122, 2-174, 3-17, F-8
- Kidney Stones ... 2-175
- Kidney Transplantation ... 2-122, 2-163
- Kirschstein-NRSA (see Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research)
- Knee ... 1-9, 2-69, 2-127, 2-146, 2-148, 2-165, 2-170, 2-186, 2-208:2-209, 2-225, 3-72, 3-102, 3-120:3-121
- Knee Joint ... 2-148, 2-225, 3-120
- Knockout Mouse Project ... 3-48, 3-50:3-51, 3-101, 3-179:3-180
- Know Stroke in the Community ... 2-68, 2-219, 2-238, 3-242
- Knowledge Management ... 3-79
- KOMP Repository ... 3-48, 3-101
- Labor, Obstetric ... 2-198
- Lamin A ... 2-195, 3-47, 3-110
- Language ... 1-3, 2-22, 2-32, 2-67, 2-70, 2-219, 2-222, 2-233, 2-246, 3-35, 3-81, 3-83, 3-137, 3-191, 3-230, 3-237, 3-243, 4-3, B-3, E-6, F-10
- Language Development ... 2-46, 2-210, 3-168, 3-175
- Large-Scale Efficacy Trials ... 2-79
- Large-Scale Sequencing Program ... 3-35, 3-41, 3-65, 3-177
- Lariat ... 2-246, 3-137
- Laser Eye Surgery ... 3-166
- Lasers ... 3-173
- Late-Onset Alzheimer's Disease ... 2-54, 3-156, 4-6
- Latin American Epidemiology Network ... 2-228, 3-10, 3-158
- Latinos ... 2-229, 3-13
- Lead Poisoning ... 2-257
- Leadership ... 1-3, 1-14, 1-16, 1-22, 2-94, 2-247, 3-77, 3-123, 3-181, 3-199, 3-214, 3-217, 3-223, 4-10, 4-29, B-1:B-3, B-6, C-6, F-6:F-7
- Learning and Memory ... 2-31, 2-35:2-36
- Learning Disabilities ... 2-33, 2-36, 2-185, 2-202
- Leber's Congenital Amaurosis ... 2-155, 3-96:3-97, 3-114
- Legs ... 2-134, 2-208, 3-75, 3-221, 4-18
- Leishmaniasis ... 2-78
- Leukemia ... 3-46, 3-56
- Leukemia, Lymphoid ... 2-5
- Leukemia, Myeloid, Acute ... 2-6, 2-19
- Librarians ... 1-26, 2-231, 3-151, 3-162, 3-200, 3-212, 3-244
- Licensure ... 2-93
- Life Expectancy ... 1-10, 2-78, 2-119, 2-158, 2-169, 2-218, 3-134, 3-168, 4-11, F-9
- Life Stages ... **2-179:2-212**, 1-3, 1-7, 2-17, 2-23, 2-25:2-27, 2-32, 2-41, 2-43:2-44, 2-46, 2-49, 2-51, 2-54, 2-61, 2-85, 2-97, 2-133:2-134, 2-141:2-142, 2-146, 2-148:2-150, 2-160, 2-162:2-163, 2-166, 2-168, 2-228, 3-9:3-11, 3-15:3-16, 3-19, 3-22:3-25, 3-47, 3-67, 3-72, 3-76, 3-82, 3-102, 3-110:3-111, 3-115, 3-117, 3-119:3-120, 3-162, 3-175, 3-182, 3-185, 3-189:3-190, 3-213, 3-215, 3-240:3-241, 3-244, A-5
- Lifespan ... 2-33, 2-35, 2-39, 2-60:2-61, 2-167, 2-182, 2-193:2-194, 3-42, 3-61, 3-74, 4-29
- Lifestyle intervention ... 2-128, 2-140, 2-144, 2-205, 2-221, 2-235, 3-7, 3-18, 3-96, 3-111, 3-116, 4-14
- Lifestyles ... 2-7, 2-33, 2-40, 2-127:2-128, 2-140:2-141, 2-144:2-145, 2-193, 2-205, 2-221, 2-224, 2-235, 3-7, 3-9:3-10, 3-18, 3-20, 3-96, 3-111, 3-116, 3-168, 4-13:4-14, F-6, F-8
- LifeWorks ... 1-25
- Ligaments ... 3-190
- Light Exposure ... 3-83
- Limb Amputation ... 2-121
- Limb-Girdle Muscular Dystrophy ... 4-19, 4-21
- Lip and Oral Cavity Carcinoma (see Lip Neoplasms)
- Lip Neoplasms ... 2-9, 2-20:2-21, 2-232, 3-125, 3-183, 3-231, 3-238
- Lipid Metabolism ... 2-136, 3-87
- Lipids ... 3-59
- Lipoproteins, HDL ... 2-165, 3-121
- Lipoproteins, LDL ... 2-165
- Literacy ... 1-13, 1-24, 2-219:2-221, 2-231, 2-239, 3-91, 3-141:3-142, 3-223, 3-229:3-230, 3-244:3-246
- Literature ... 1-26, 2-54, 2-234, 3-23, 3-145:3-148, 3-150, 3-152, 3-191
- Liver ... 2-2, 2-19, 2-54, 2-116, 2-121:2-122, 2-124:2-125, 2-134, 2-139, 2-159, 2-165, 2-193:2-194, 3-71, 3-76, 3-122, 3-132, 3-134, 4-33
- Liver Cancer ... 2-5, 2-257
- Liver Disease ... 1-20, 2-122, 2-129:2-130, 2-153, 2-160, 2-166, 2-173, 2-175, 2-193, 2-229, 2-252, 2-257, 3-14, 3-122, 4-25, 4-30, 4-33
- Liver Failure, Acute ... 2-125, 2-165:2-166, 2-193:2-194
- Liver Toxicity ... 2-125, 2-139
- Loan Repayment Program ... 2-222, 2-243:2-244, 3-205, 3-209, F-5
- Loan Repayment Program for Health Disparities Research ... 2-243
- Local Partnership Program ... 2-88, 3-236
- Long QT Syndrome ... 2-121, 2-124
- Long-Term Antiretroviral Therapy ... 2-78
- Long-Term Care ... 2-24, 2-158, 2-206, 2-209, 3-12, 3-115:3-116, 3-129, 4-4
- Long-Term Oxygen Treatment Trial ... 2-129, 2-158, 3-115:3-116
- Longevity ... 2-34, 2-194, 2-218, 3-42, 4-11
- Longevity Assurance Gene ... 3-42
- Longitudinal Assessment of Bariatric Surgery ... 2-130, 2-162, 2-201, 3-119
- Longitudinal Study of Mexican American Elderly Health ... 4-14
- Look AHEAD (see Action for Health in Diabetes)
- Low Density Lipoprotein Inhibitor ... 2-165
- Low-Density Lipoproteins (see Lipoproteins, LDL)
- Lung ... 1-15, 2-2:2-3, 2-5, 2-7:2-8, 2-10, 2-14, 2-19, 2-24, 2-81, 2-121, 2-152, 2-156, 2-159, 2-165, 2-171, 2-174, 2-215, 2-242, 2-257, 3-6, 3-12, 3-14, 3-33, 3-38, 3-49, 3-80, 3-96, 3-121, 3-129, 3-134:3-136, 3-156, 3-169:3-170, 3-235, 4-25, 4-30, 4-32:4-33, B-1, E-2, F-4, F-6
- Lung Cancer ... 2-3, 2-7:2-8, 2-10, 2-19, 2-257, 3-33, 3-96, 3-135:3-136, F-4
- Lung Diseases ... 2-121, 4-25, 4-33
- Lung Transplantation ... 2-159, 3-134
- Lupus Erythematosus, Cutaneous ... 2-106
- Lupus Erythematosus, Discoid ... 2-106:2-110, 2-112:2-113, 2-117, 2-217, 2-225:2-226, 3-11, 3-32, 3-156, F-7
- Lupus Erythematosus, Systemic ... 2-103, 2-105:2-110, 2-112:2-113, 2-117:2-118, 2-120, 2-126, 2-167, 2-217, 2-224:2-226, 2-257, 3-11:3-12, 3-32, 3-92, 3-106, 3-147, 3-156, F-7

- Lupus Vulgaris ... 2-106:2-110, 2-112:2-113, 2-117:2-118, 2-217, 2-225:2-226, 3-11, 3-32, 3-156, F-7
- Lutein ... 2-53, 2-160, 3-117
- Lyme Disease ... 2-74, 2-257
- Lymphangiogenesis ... 2-17, 3-64
- Lymphangioma ... 4-33, F-11
- Lymphatic Diseases ... 2-134, 3-75
- Lymphatic System ... 2-134, 3-62, 3-75:3-76
- Lymphatic Vessels ... 2-134, 3-75:3-76
- Lymphedema ... 2-134, 3-75
- Lymphoma ... 2-257, 3-56, 3-96, 3-145
- Lysosomal Storage Diseases ... 2-32, 2-68
- Macromolecules ... 3-55, 3-180
- Macular Degeneration ... 1-9, 2-18, 2-38, 2-53, 2-71, 2-123, 2-126, 2-129, 2-139:2-140, 2-148, 2-160, 2-172, 2-176, 2-226, 2-233, 2-257, 3-6, 3-17, 3-31, 3-35, 3-112, 3-117, 3-155, 3-236, 4-17, 4-19, 4-43:4-44, E-2, F-5:F-6
- Macular Edema ... 2-160, 3-138
- Magnetic Resonance Imaging ... 2-35, 2-44, 2-51, 2-53, 2-112, 2-116, 2-130, 2-157, 2-162, 2-187:2-188, 2-204:2-205, 2-230, 3-5:3-6, 3-15:3-16, 3-103, 3-112, 3-119, 3-170:3-171, 3-173, 3-180:3-181, 3-186, 4-6, 4-39
- Magnetic Resonance Spectroscopy ... 3-181
- Major Depressive Disorder ... 2-204, 2-216, 3-36
- Major Histocompatibility Complex ... 2-110
- Malaria ... 1-11, 2-61, 2-73:2-78, 2-82:2-85, 2-100, 2-172, 2-193, 2-257, 3-29, 3-96, 3-200, B-2
- Malaria Microscopy ... 2-85
- Malaria Parasite ... 2-77, 2-84
- Malaria Vaccine ... 1-11, 2-73:2-78, 2-82:2-85, 2-100, 2-172, 2-257, 3-29, 3-96, 3-200, B-2
- Malaria, Avian ... 3-29
- Malaria, Cerebral ... 2-61
- Male Circumcision ... 2-79, 2-90
- Malignancies ... 2-18:2-19, 2-21, 2-74, 2-78, 2-86, 2-89, 2-184, 2-225, 3-39, 3-73, F-4, F-11
- Malnutrition ... 2-38, 2-40, 2-122, 3-84, 3-179
- Malocclusion ... 2-237, 3-140
- Mammalian Gene Collection ... 3-34
- Mammography ... 2-24, 2-163, 3-12, 3-129, 3-171, F-7
- Marburg Hemorrhagic Fever ... 2-81
- Marburg Virus Disease ... 2-81
- Marfan Syndrome ... 2-121, 2-165, 3-62, 3-79:3-80, 3-121
- Marijuana ... 2-50, 3-5, 3-80
- Mark D. Hatfield Clinical Research Center ... 1-4, 1-15, 1-18, 1-31, 2-11, 2-14, 2-72, 2-101, 2-157, 2-212, 2-223, 2-235, 2-248, 3-30, 3-90, 3-114, 3-135, 3-226, B-5, D-8, E-2
- Massage ... 3-85, 3-103, F-5
- Materials Science ... 2-125, 2-132, 3-71, 3-165, 3-186
- Maternal Health ... 2-195, 2-198, 3-115
- Maternal Oral Therapy to Reduce Obstetric Risk ... 2-198, 3-115
- Mathematics ... 2-6, 2-114, 2-135, 2-202, 3-45, 3-56, 3-74, 3-192, 3-243, D-5:D-6
- Matrix Model ... 2-47, 2-130, 2-159, 3-126
- Medical Countermeasures ... 2-62, 2-75, 2-80:2-81, 2-92:2-93, 2-96, 2-102, 3-106, 3-160
- Medical Device ... 3-79, 3-93, 3-189
- Medical Imaging ... 3-180
- Medical Informatics ... 3-147, 3-199, B-5
- Medical Records Systems, Computerized ... 2-164, 3-145, 3-161
- Medical Scientist Training Program ... 3-199, 3-211
- Medical Subject Headings ... 1-26
- Medicine, Traditional ... 3-85, 3-131
- Meditation ... 2-131, 2-164, 3-62, 3-85, 3-87, 3-128, 3-131, 3-144, F-5
- MEDLINE ... 1-26, 3-145:3-147, 3-152, 3-233
- MedlinePlus ... 3-147, 3-152:3-153, 3-160, 3-225, 3-233:3-234
- MedlinePlus en Espanol ... 3-152, 3-233
- Meesmann's Dystrophy ... 3-79
- Megavitamin Therapy ... 2-131
- Melanoma ... 3-56
- Membrane ... 2-114, 3-60, 3-179, 3-181
- Membrane Proteins ... 2-51, 2-69:2-70, 3-67:3-68, 3-74, 3-178:3-179, 3-181, C-6
- Memory ... 2-31, 2-35:2-36, 2-67, 3-83, 4-3, F-10
- Memory Deficits ... 2-31
- Memory Loss ... 2-47, 2-159, 3-126
- Men ... 2-3, 2-21, 2-61, 2-79, 2-87, 2-90, 2-97, 2-103, 2-141, 2-167, 2-175:2-176, 2-185, 2-189, 2-191, 2-193, 2-215, 2-219, 2-232, 3-9:3-10, 3-24, 3-116, 3-210, 3-231, 3-236, 3-238, 4-18, 4-26, E-6, E-8, E-14:E-19, F-2:F-5, F-9:F-11
- Men's Health ... F-2
- Mendelian Inheritance in Man ... 3-239
- Menopause ... 2-133, 2-183, 2-188:2-189, 3-3, F-6, F-10
- Menstrual Cycle ... F-9
- Mental Disorders ... 2-33:2-34, 2-36:2-37, 2-39:2-43, 2-48, 2-52, 2-58, 2-60, 2-64, 2-67, 2-72, 2-123, 2-130, 2-138, 2-141, 2-147, 2-154, 2-176, 2-180, 2-184, 2-187, 2-190, 2-193, 2-202, 2-204, 2-216, 2-218, 2-227, 2-229:2-230, 3-11, 3-13, 3-19, 3-25, 3-36, 3-48, 3-83, 3-85, 3-95, 3-101, 3-113, 3-117, 3-120, 3-155, 3-183, 3-232:3-233, 4-36:4-37, 4-39:4-41, B-3, F-8:F-10
- Mental Exercises ... 2-205
- Mental Health ... 1-10, 1-15, 2-32:2-33, 2-35, 2-38, 2-52, 2-54:2-55, 2-71, 2-126:2-127, 2-139, 2-141, 2-150, 2-167, 2-172, 2-176, 2-189, 2-198, 2-210, 2-218, 2-227, 2-229:2-230, 2-237, 2-257, 3-13, 3-15, 3-19, 3-23, 3-25, 3-97:3-98, 3-127, 3-141, 3-212, 3-228:3-229, 3-243, 4-25, 4-30, 4-36, B-3, F-3, F-8:F-9
- Mental Retardation ... 2-72, 2-196, 2-202, 2-211, 3-6, 3-16, 3-57, 3-82, 3-185, 4-37
- Mental Retardation and Developmental Disabilities ... 2-72, 2-211
- Mentored Clinical Scientist Research Career Development Award ... 3-204
- Mentored Quantitative Research Career Development Award ... 3-204
- Mercury ... 2-41, 2-107, 2-112, 3-12
- Mesenchymal Stem Cells ... 2-197, 3-82
- Mesenchyme ... 2-197, 3-82
- MeSH (see Medical Subject Headings)
- Metabolic Diseases ... 1-20, 2-111, 2-115, 2-117, 2-121:2-123, 2-127:2-130, 2-137, 2-140, 2-142, 2-144:2-146, 2-148, 2-154, 2-160, 2-163, 2-171, 2-174, 2-199:2-200, 2-215:2-216, 2-218:2-220, 2-224, 2-228:2-230, 2-235, 2-237, 3-7, 3-10:3-11, 3-18, 3-22:3-23, 3-25, 3-32, 3-45, 3-69, 3-77, 3-91, 3-96, 3-98, 3-107, 3-111, 3-116, 3-119, 3-127, 3-138, 3-182, 3-225, 3-235, 4-13, 4-25, 4-29, B-2, F-8
- Metabolic Poisons ... 2-81
- Metabolic Syndrome ... 2-136, 2-142, 2-199, 3-87
- Metabolism ... 2-112, 3-11, 3-45, 3-105, 3-170, D-8
- Metabolomics ... 3-7, 3-85, 3-103
- Metastasis ... 2-4:2-5, 2-9, 2-17, 3-59:3-60, 3-64, 3-105, 3-188
- Metformin ... 2-127, 2-130, 2-140, 2-160, 2-193, 3-18, 3-96, 3-111
- Methadone ... 2-98, 2-154, 3-123
- Methamphetamine ... 2-47, 2-130, 2-159, 2-257, 3-5, 3-126:3-127
- Methicillin-Resistant Staphylococcus Aureus ... 2-76, 2-91, 3-133
- Mexican Americans ... 4-14, 4-26
- Mice, Knockout ... 3-50:3-51, 3-179:3-180
- Mice, Obese ... 3-73
- Mice, Transgenic ... 2-45, 3-57, 3-84
- Microarray ... 2-81, 2-91, 2-114, 2-135, 3-78
- Microarray Analysis ... 2-91

- Microbial Genome Sequencing Centers ... 2-83, 3-28, 3-39  
 Microbial Genomics ... 2-82, 3-39, 3-41, 3-66  
 Microbial Pathogens ... 2-73, 3-57  
 Microbicide Innovation Program ... 2-89  
 Microbicide Trials ... 2-79, 2-85, 2-94, 2-204  
 Microbicide Trials Network ... 2-79, 2-94  
 Microbicides ... 2-79, 2-85, 2-88:2-90, 2-95, 2-148, 3-106, 3-133  
 Microbiology ... 2-92, 3-181, D-2  
 Microbiome ... 1-12, 1-22:1-23, C-8  
 Microneedle-based immunization ... 2-91, 3-192  
 MicroRNAs ... 3-69  
 Microscopy ... 2-85, 3-70, 3-170, 3-181:3-182  
 Migraine ... 2-33  
 Migration, Cell ... 2-17, 3-60, 3-64  
 Mild Cognitive Impairment ... 2-51, 2-204:2-205, 4-5:4-6, 4-9  
 Military ... 1-11, 2-48, 2-127, 2-147, 3-120  
 Milk Hypersensitivity ... 2-142, 2-199  
 Millimeter Wave Therapy ... 3-85, 3-131  
 Mind-Body ... 2-164, 2-166, 3-62, 3-87, 3-144, F-5  
 Minorities ... 1-6, 1-8, 2-14, 2-27, 2-66, 2-77, 2-144, 2-163, 2-200, 2-213:2-216, 2-218:2-220, 2-222, 2-225, 2-229, 2-232, 2-235, 2-239, 2-241:2-242, 2-244, 2-246:2-247, 3-22, 3-94, 3-120, 3-122, 3-125, 3-138, 3-196, 3-199, 3-230:3-231, 4-7, 4-24:4-25, 4-28:4-29, A-5, E-1:E-9, E-14:E-17, E-19, E-23, E-27, F-2:F-3  
 Minority Access to Research Careers ... 2-221, 2-241, 3-199, 3-211  
 Minority Groups ... 1-3, 1-6:1-8, 1-15, 2-3, 2-10, 2-14, 2-19:2-22, 2-27, 2-65:2-66, 2-68, 2-77, 2-84, 2-117, 2-135, 2-141:2-142, 2-144:2-146, 2-148, 2-153, 2-157, 2-161, 2-163, 2-200, 2-213:2-216, 2-239:2-248, 2-250, 2-257, 3-10:3-11, 3-13:3-14, 3-17, 3-19:3-20, 3-22, 3-25, 3-91, 3-94, 3-98, 3-100, 3-106, 3-114, 3-117, 3-120, 3-122, 3-124:3-125, 3-128, 3-136:3-142, 3-158, 3-196, 3-198:3-199, 3-205, 3-214, 3-227, 3-230:3-231, 3-233, 3-238, 3-240:3-242, 3-244, 3-246, 4-1:4-2, 4-4, 4-7, 4-13, 4-15, 4-24:4-30, 4-33, A-5, B-2, B-5, E-1:E-10, E-14:E-31, E-33:E-46, F-2:F-3, F-5, F-8  
 Minority Health ... **2-213:2-248**, 1-3, 1-6:1-7, 1-15, 2-3, 2-10, 2-14, 2-20:2-22, 2-27, 2-66, 2-68, 2-73:2-102, 2-117, 2-135, 2-141:2-142, 2-144:2-146, 2-148, 2-153, 2-157, 2-161, 2-163, 2-200, 2-257, 3-10:3-11, 3-13:3-14, 3-17, 3-19:3-20, 3-25, 3-106, 3-114, 3-117, 3-124:3-125, 3-128, 3-137:3-142, 3-158, 3-196, 3-198, 3-205, 3-235, 3-238, 3-240, 3-242, 3-244, 3-246, 4-1:4-2, 4-15, 4-24:4-25, 4-27:4-30, A-5, B-5, F-5  
 Minority Health and Health Disparities International Research Training Program ... F-5  
 Minority Institution/Cancer Center Partnership ... 2-27, 2-245  
 Minority Institutional Research Training Program ... 2-242  
 Minority Institutions' Drug Abuse Research Development Program ... 2-242  
 Minority Nurses ... 2-219, 2-247  
 Minority Outreach ... 4-7  
 Minority Participation in Clinical Trials ... 2-240  
 Minority Scientists ... 2-247, 3-138  
 Minority-Serving Institutions ... 2-27, 2-222, 2-245, 2-247  
 Mitochondria ... 3-238  
 Miyoshi Myopathy ... 4-18, 4-21  
 Molecular Libraries Initiative ... 3-150  
 Molecular Libraries Screening Centers Network ... 3-70  
 Molecular Libraries Small Molecule Repository ... 3-70  
 Molecular Structures ... 3-178, C-5  
 Molecular Weight ... 3-59  
 Monitoring the Future Survey ... 2-228, 3-4, 3-10, 3-149, 3-157  
 Monkeypox ... 2-100, 3-216  
 Monoclonal Antibodies ... 2-10, 2-14, 2-19, 3-135  
 Mood ... 2-36, 2-63, 2-141, 2-150, 2-227, 3-19, 3-47  
 Mood Disorders ... 2-40, 2-71, 2-172  
 Morbidity ... 2-7, 2-23, 2-25, 2-47, 2-54, 2-99, 2-112, 2-120, 2-133:2-134, 2-191, 2-206, 2-213, 2-239, 3-11, 3-20, 3-43, 3-76, 3-132, 3-200, 3-212:3-213, 4-12, 4-14, 4-31, F-10  
 Morris K. Udall Centers for Excellence in Parkinson's Disease Research ... 2-39, 2-55  
 Mortality ... 2-7, 2-23, 2-25, 2-34, 2-47, 2-54, 2-65, 2-73, 2-82, 2-98:2-99, 2-112, 2-120, 2-134, 2-174:2-175, 2-177, 2-191, 2-213, 2-215, 2-218, 2-232, 2-239, 3-7, 3-11, 3-19:3-20, 3-43, 3-76, 3-132, 3-200, 3-212:3-213, 4-14, 4-31, F-4, F-10  
 Mother-to-Child Transmission ... 2-79, 2-90  
 Mothers ... 2-43, 2-73, 2-79, 2-90, 2-142, 2-185, 2-190, 2-195:2-196, 2-198:2-199, 3-20, 3-22, 3-24:3-25, 3-82, 3-115, 3-153, 4-17  
 Motivation ... 2-50, 2-196, 3-82, 3-84, 3-222  
 Motivational Incentives for Enhanced Drug Abuse Recovery ... 2-47, 2-130, 2-159, 3-127  
 Motor Activity ... 2-49, 3-83:3-84, 3-102  
 Motor Behaviors ... 2-49:2-50, 3-83:3-84  
 Motor Neuron Diseases ... 2-58, 3-155  
 Motor Neurons ... 2-40  
 Mouse, Knockout ... 3-48, 3-101  
 Mouth ... 2-9, 2-20:2-22, 2-83, 2-180, 2-183, 2-187, 2-197, 2-209, 3-21, 3-40, 3-67, 3-72, 3-115, 3-118, 3-125, 3-172, 3-183, F-7  
 Movement ... 2-31, 2-49, 2-67, 2-92, 3-83, 3-165:3-166, 4-6, 4-14, 4-17, E-5  
 Mr. OS ... 2-127, 2-141, 3-9  
 MRI (see Magnetic Resonance Imaging)  
 MRI Study of Normal Brain Development ... 2-44, 2-187  
 MRSA (see Methicillin-Resistant Staphylococcus Aureus)  
 MS (see Multiple Sclerosis)  
 Mucopolysaccharidoses ... 2-257, 3-124  
 Multi-Ethnic Study of Atherosclerosis ... 2-226, 3-17  
 Multicenter AIDS Cohort Study ... 2-97, 2-191, 3-24, 3-116  
 Multicenter Uveitis Steroid Treatment ... 2-129, 2-156, 3-114  
 Multidisciplinary ... 2-6, 2-15, 2-18, 2-23, 2-31, 2-34, 2-43, 2-45, 2-47, 2-53, 2-60:2-61, 2-79, 2-89, 2-94, 2-99, 2-105, 2-131, 2-144, 2-150, 2-161, 2-164, 2-166:2-168, 2-189, 2-195, 2-203, 2-209, 2-214, 2-216:2-217, 2-222, 2-224:2-225, 2-246, 3-5, 3-15, 3-22, 3-43, 3-53, 3-61:3-63, 3-66, 3-74, 3-87, 3-99:3-100, 3-132, 3-134, 3-137:3-139, 3-143:3-144, 3-148, 3-165, 3-167, 3-172:3-173, 3-182, 3-185, 3-192:3-193, 3-198, 3-205, 3-207:3-208, 3-211, 3-241, 4-1, 4-10, 4-29, 4-38, C-3, F-5, F-10  
 Multidrug-Resistant Strains of HIV ... 2-78  
 Multidrug-Resistant TB ... 2-76:2-77  
 Multinational Influenza Seasonal Mortality Study ... 2-98, 3-7, 3-19  
 Multiple Myeloma ... 2-6, 2-19, 3-58  
 Multiple Sclerosis ... 2-32, 2-36, 2-39, 2-53, 2-103, 2-105, 2-108, 2-110, 2-112, 2-120, 2-257, 3-32, 3-112, F-5, F-9  
 Multiplex Initiative ... 2-151:2-152, 3-53, 3-139  
 Muscle ... 2-56, 2-121, 2-123, 2-132, 2-170, 2-261, 3-37, 3-83, 3-159, 3-232, 3-236, 4-14, 4-18, 4-20, 4-22  
 Muscle Cells ... 4-17  
 Muscle Contraction ... 4-18  
 Muscle Disorders ... 2-123, 3-22, 3-118, 4-20, F-7  
 Muscle Fibers ... 4-22  
 Muscle Protein ... 2-22, 3-39, 3-73, 4-14, 4-20  
 Muscle Satellite Cell (see Myoblasts)  
 Muscle Spasms ... 2-37  
 Muscle Weakness ... 4-14, 4-18  
 Muscle, Skeletal ... 2-56, 2-209, 3-37, 3-72, 3-159, 4-14  
 Muscles, Skeletal ... 4-12, 4-18  
 Muscular Atrophy ... 4-18  
 Muscular Atrophy, Spinal ... 2-32, 2-40, 2-62, 2-260, 3-108:3-109  
 Muscular Diseases ... 4-14, 4-18  
 Muscular Dystrophies, Limb-Girdle ... 4-18

- Muscular Dystrophy ... 1-6:1-7, 1-20, 2-32, 2-39, 2-55:2-56, 2-69, 2-72, 2-253:2-254, 2-258, 3-37, 3-108:3-109, 3-112, 3-147, 3-159, 4-2, 4-17:4-23, 4-43
- Muscular Dystrophy Community Assistance Research and Education ... 4-17, 4-19
- Muscular Dystrophy Coordinating Committee ... 2-55, 3-108, 3-112
- Muscular Dystrophy, Duchenne ... 4-17:4-19, 4-22
- Musculoskeletal Diseases ... 2-122, 2-124
- Music Therapy ... 2-131
- Mutant Mouse Regional Resource Centers ... 3-48, 3-101
- Mutations ... 2-20, 2-108, 2-196, 3-27:3-28, 3-33:3-34, 3-38, 3-41:3-42, 3-50:3-51, 3-81, 3-175, 3-179, 3-238, 4-18, F-6
- Myasthenia Gravis ... 2-258
- Myelin ... 2-39, F-9
- Myelodysplastic Syndrome ... 4-33
- Myoblasts ... 4-22
- Myocardial Infarction ... 2-121, 2-182
- Myosins ... 4-14
- Myotonia ... 4-18
- Myotonic Dystrophy ... 2-56, 2-258, 3-37, 3-159, 4-18:4-19, 4-21
- Naltrexone ... 2-98, 2-154, 3-123
- Nanomedicine ... 1-12, 3-59, 3-66, 3-167, 3-193, C-5
- Nanomedicine Development Centers ... 3-59, 3-66, 3-193
- Nanostructures ... 3-66, 3-193
- Nanotechnology ... 2-4, 2-8:2-9, 2-11:2-13, 2-16, 2-53, 2-55, 2-63, 2-87, 2-187, 2-258, 3-66:3-67, 3-70, 3-75, 3-104, 3-108:3-109, 3-112, 3-139, 3-146, 3-150, 3-154, 3-165, 3-169, 3-180, 3-186:3-187, 3-193, C-5
- Narcotics ... 2-65, 2-155, 3-113
- National Academy of Sciences (U.S.) ... 3-201
- National Advisory Child Health and Human Development ... 2-72, 2-101, 2-211
- National Advisory Council on Minority Health and Health Disparities ... 2-214, 2-248
- National Alzheimer's Coordinating Center ... 4-5, 4-7, 4-9
- National Biocontainment Laboratories ... 2-82, 2-94
- National Cancer Institute ... 1-15, 1-20, 2-2, 2-6:2-7, 2-9, 2-11, 2-13:2-17, 2-22, 2-25:2-26, 2-28, 2-72, 2-74, 2-86, 2-101:2-102, 2-104, 2-118, 2-171, 2-173, 2-180, 2-191, 2-211:2-212, 2-233, 2-245, 2-248, 3-28, 3-56, 3-89, 3-93, 3-104, 3-135:3-136, 3-151, 3-167, 3-178, 3-181, 3-186, 3-226, 3-232, B-1, F-4
- National Cancer Institute's Developmental Therapeutics Program ... 2-9
- National Cancer Program ... 2-245, B-1
- National Cell Repository for Alzheimer's Disease ... 4-4, 4-6, 4-9
- National Center for Biotechnology Information ... 2-96, 3-52, 3-78, 3-148, 3-154
- National Center for Complementary and Alternative Medicine ... 1-15, 2-28, 2-71:2-72, 2-101, 2-118, 2-166, 2-173, 2-212, 2-248, 3-203, 3-216, 3-219, 3-226:3-227, 3-239, B-4, F-5
- National Center for Health Statistics ... 2-66
- National Center for Medical Rehabilitation Research ... 2-32, 2-72, 2-211
- National Center for Research Resources ... 1-4, 1-15, 1-18, 2-72, 2-74, 2-101, 2-118, 2-173, 2-212, 2-246:2-248, 3-105, 3-138, 3-167, 4-32, B-4, F-5
- National Center on Minority Health and Health Disparities ... 1-6:1-7, 1-15, 1-18, 2-72, 2-101, 2-118, 2-144, 2-173, 2-212, 2-214, 2-222:2-223, 2-233:2-235, 2-245:2-246, 2-248, 3-125, 4-2, 4-24:4-25, 4-27:4-31, 4-44, B-5, F-5
- National Center on Minority Health and Health Disparities Centers of Excellence Program ... **4-24:4-31**
- National Centers for Biomedical Computing ... 3-151, 3-162, 3-188
- National Children's Study ... 2-184, 2-189, 2-229, 3-7, 3-13, 3-24
- National Clinical Research Associates ... C-7
- National Coalition of Ethnic Minority Nurses Associations ... 2-219
- National Commission on Orphan (or Rare) Diseases ... 4-32
- National Comorbidity Survey Replication ... 2-229, 3-13
- National Database for Autism Research ... 2-41, 2-202, 3-148, 3-162, 4-40:4-41
- National Diabetes Education Program ... 2-171, 2-219, 2-230, 3-235
- National Drug Abuse Clinical Trials Network ... 2-130
- National Drug Abuse Treatment Clinical Trials Network ... 2-66, 2-159, 3-126, 3-245
- National Electronics Clinical Trials and Research ... 3-151, C-7
- National Epidemiologic Survey on Alcohol and Related Conditions ... 2-141, 2-227, 3-18:3-19
- National Eye Health Education Program ... 3-235:3-236
- National Eye Institute ... 1-15, 2-32, 2-71:2-72, 2-101, 2-118, 2-172:2-173, 2-212, 2-248, 3-17, 3-75, B-2, F-5
- National Health and Nutrition Examination Survey ... 3-17, 3-91
- National Health Interview Survey ... 2-66, 3-175
- National Heart, Lung, and Blood Institute ... 1-15, 1-20, 2-2, 2-7, 2-33, 2-72, 2-74, 2-101:2-102, 2-118, 2-133, 2-152, 2-165, 2-171, 2-173, 2-212, 2-226, 2-235, 2-244, 2-248, 3-17, 3-28, 3-49, 3-80, 3-121, 3-156:3-157, 3-167, 4-23, 4-32, B-1, E-2, F-6
- National Human Genome Research Institute ... 1-4, 1-15, 2-72, 2-101, 2-104, 2-118, 2-173, 2-195, 2-212, 2-248, 3-28, 3-41, 3-47, 3-56, 3-110, 3-176, 3-200, 3-226, B-4, F-6
- National Institute of Allergy and Infectious Diseases ... 1-15, 2-2, 2-72, 2-74, 2-78, 2-82, 2-84, 2-87, 2-92, 2-96, 2-100:2-102, 2-104, 2-118, 2-172:2-173, 2-212, 2-248, 3-24, 3-28, 3-52, 3-56, 3-78, 3-148, 3-154, 3-216, 3-228, 3-236, B-2, F-6
- National Institute of Arthritis and Musculoskeletal and Skin Diseases ... 1-15, 2-101, 2-104, 2-118, 2-172:2-173, 2-248, 3-147, 3-203, 3-218, 3-231:3-232, 3-236, 4-17, 4-23, 4-32, B-3, F-6:F-7
- National Institute of Biomedical Imaging and Bioengineering ... 1-4, 1-15, 1-20, 2-3, 2-72, 2-101, 2-118, 2-173, 2-180, 2-212, 2-248, 3-56:3-57, 3-167, 3-181, B-4, F-7
- National Institute of Child Health and Human Development ... 1-15, 2-3, 2-32:2-33, 2-72, 2-74, 2-101, 2-118, 2-173, 2-180, 2-190, 2-194, 2-198, 2-210:2-212, 2-248, 3-5, 3-24, 3-102, 3-123, 3-181, 3-215, 3-231, 4-17, 4-23, 4-32, 4-36:4-37, B-2, D-8, F-3, F-7
- National Institute of Dental and Craniofacial Research ... 1-15, 2-2, 2-28, 2-33, 2-72, 2-101, 2-118, 2-171, 2-173, 2-180, 2-211:2-212, 2-248, B-1, F-7:F-8
- National Institute of Diabetes and Digestive and Kidney Diseases ... 1-15, 1-20, 2-2, 2-33, 2-72, 2-101, 2-104, 2-118, 2-162, 2-171, 2-173, 2-212, 2-248, 3-119, 4-32, B-2, F-8
- National Institute of Environmental Health Sciences ... 1-4, 1-15, 2-2, 2-33, 2-41, 2-52, 2-72, 2-101:2-102, 2-104, 2-118, 2-144, 2-173, 2-180, 2-190, 2-212, 2-235, 2-248, 3-24, 3-56, 3-125:3-126, 3-149, 3-158, 3-184, 3-200, 4-36, B-3, F-8
- National Institute of General Medical Sciences ... 1-4, 1-15, 1-18, 2-3, 2-72, 2-101, 2-118, 2-173, 2-212, 2-221, 2-235, 2-248, 3-56:3-57, 3-178, 3-199, 3-211, 3-214, B-2, F-8
- National Institute of Mental Health ... 1-15, 2-32, 2-58, 2-71:2-72, 2-74, 2-101, 2-118, 2-172:2-173, 2-212, 2-248, 3-5, 3-48, 3-101:3-102, 3-148, 3-155, 3-228, 3-232, 3-246, 4-36:4-37, 4-39, 4-41, B-3, F-8:F-9
- National Institute of Neurological Disorders and Stroke ... 1-15, 2-2, 2-32, 2-58, 2-62, 2-65, 2-68, 2-71:2-72, 2-74, 2-96, 2-101, 2-104, 2-118, 2-173, 2-180, 2-207, 2-212, 2-248, 3-5, 3-109, 3-112, 3-148, 3-155, 3-190, 3-227, 4-7, 4-17, 4-23, 4-32, 4-36, B-2, F-9

- National Institute of Nursing Research ... 1-15, 2-2, 2-72, 2-101, 2-118, 2-172:2-173, 2-180, 2-211:2-212, 2-243, 2-247:2-248, 3-215, B-4, F-9:F-10
- National Institute of Standards and Technology ... 3-188
- National Institute on Aging ... 1-15, 1-20, 2-2, 2-28, 2-33, 2-71:2-72, 2-101, 2-118, 2-172:2-173, 2-180, 2-189, 2-211:2-212, 2-248, 3-148, 3-227, 3-236, 3-241, 4-4, 4-7, 4-9:4-10, 4-15, B-3, F-10
- National Institute on Aging Information Center ... 3-227, 3-236
- National Institute on Alcohol Abuse and Alcoholism ... 1-15, 2-7, 2-32, 2-71:2-72, 2-101, 2-118, 2-172:2-173, 2-180, 2-211:2-212, 2-248, 3-228:3-229, B-3:B-4, F-10
- National Institute on Deafness and Other Communication Disorders ... 1-15, 2-32, 2-71:2-72, 2-101, 2-118, 2-173, 2-211:2-212, 2-248, 3-237, 4-36, B-3, F-10
- National Institute on Drug Abuse ... 1-15, 2-3, 2-7, 2-32, 2-71:2-72, 2-74, 2-101, 2-118, 2-130, 2-172:2-173, 2-211:2-212, 2-219, 2-242, 2-248, 2-253, 3-5, 3-149, 3-226, 3-228:3-229, B-3, F-10:F-11
- National Latino and Asian American Study ... 2-218, 2-229, 3-13
- National Library of Medicine ... 1-4, 1-6, 1-15, 1-26, 2-72, 2-101, 2-118, 2-173, 2-212, 2-231, 2-248, 3-70, 3-145:3-147, 3-150, 3-152, 3-154, 3-160, 3-163, 3-197, 3-200, 3-215, 3-224, 3-226:3-227, 3-230, 3-233, 3-237, 3-239, 3-241, 3-244, B-5, C-2, D-1
- National Long-Term Care Survey ... 2-206, 2-209
- National Longitudinal Survey of Youth ... 2-193, 3-4, 3-10
- National Lung Screening Trial ... 2-8
- National Marfan Foundation ... 2-165, 3-80, 3-121
- National Network of Libraries of Medicine ... 2-220, 2-231, 3-230:3-231, 3-244, 3-246
- National Ophthalmic Disease Genotyping Network ... 3-75
- National Organization for Rare Disorders ... 4-33
- National Public Health Institute ... 2-184, 2-190, 3-24
- National Registry for Myotonic Dystrophy and FSHD Patients and Family Members ... 3-37, 3-159
- National Research Service Awards ... 2-221, 2-241:2-242, 3-197:3-202, 3-214, 3-216, 3-218, A-5, D-1, D-7
- National Science Advisory Board for Biosecurity ... 1-29, 2-74, 2-94
- National Science Foundation ... 1-30, 2-91, 2-242, 3-172, 3-188
- National Survey of American Life ... 2-218, 2-229, 3-13
- National Toxicology Program ... 3-98, 3-126, 3-146
- Native Americans ... 3-227
- Native Hawaiians ... 2-213, 2-220, 2-223
- Natural Language Processing ... 3-150, 3-160
- Natural Products ... 2-52, 3-62
- NCBI (see National Center for Biotechnology Information)
- NCBI Conserved Domain Database ... 3-50
- NCCAM (see National Center for Complementary and Alternative Medicine)
- NCI (see National Cancer Institute)
- NCI Community Cancer Centers Program ... 2-11, 2-14, 3-135
- NCI Vaccine Program ... 2-17, 2-86, 3-136
- NCMHD (see National Center on Minority Health and Health Disparities)
- NCMRR (see National Center for Medical Rehabilitation Research)
- NCRR (see National Center for Research Resources)
- Near-Term Development for Genome Sequencing grants ... 3-41, 3-176
- Neck ... 2-208
- Needs Assessment ... 4-29
- NEI (see National Eye Institute)
- Neighborhoods ... 2-184, 2-188, 2-218, 2-227, 3-5, 3-16, 3-29:3-30, F-6
- Neonatal Onset Multisystem Inflammatory Disease ... 3-128
- Neonatal Screening ... 2-179, 2-196, 3-19:3-20, 3-185
- Neoplasm Staging ... 3-158
- Neoplasms ... 3-98
- Neoplastic Processes ... 2-4:2-5, 2-17, 3-60, 3-64
- Nerve Cells ... 2-40, 2-59, 2-70, 3-61, 3-68, 3-73, 3-83, 4-3, 4-8
- Nerve Degeneration ... 2-33, 2-38, 2-51, 2-53, 2-56:2-57, 2-71, 2-136, 2-172
- Nerve Gas ... 2-73
- Nerve Regeneration ... 2-51
- Nervous System ... 1-7, 2-19, 2-23, 2-31:2-72, 2-96:2-97, 2-100, 2-112, 2-120, 2-134, 2-136, 2-138, 2-144, 2-147, 2-150, 2-155, 2-158:2-160, 2-167, 2-169:2-170, 2-188, 2-190, 2-193, 2-202, 2-208, 2-210, 2-232, 2-249, 3-11, 3-16, 3-22:3-23, 3-36:3-37, 3-43:3-44, 3-46:3-48, 3-61:3-63, 3-68, 3-72:3-74, 3-76, 3-80:3-81, 3-83:3-84, 3-86:3-87, 3-102, 3-107:3-109, 3-112:3-114, 3-117, 3-120:3-121, 3-126:3-127, 3-131:3-133, 3-139, 3-153, 3-155:3-156, 3-158:3-160, 3-162, 3-175, 3-179, 3-184, 3-190, 3-208, 3-241, 3-245, 4-8, B-2
- Nervous System Diseases ... 1-3, 2-39, 2-44, 2-61, 2-65, 2-68, 2-100, 2-187, 3-16, 3-112
- Nervous System Neoplasms ... 2-1:2-22, 2-24:2-26, 2-28, 2-32:2-33, 2-68, 2-86, 2-191:2-192, 2-220, 2-231, 2-233, 2-236, 2-245, 3-6, 3-12, 3-14, 3-33:3-34, 3-37:3-39, 3-44, 3-56, 3-60, 3-63:3-64, 3-69, 3-73, 3-95, 3-102:3-104, 3-129, 3-135, 3-151, 3-158, 3-170, 3-175, 3-178, 3-180, 3-186, 3-190, 3-226, 3-238, 3-240, B-1, F-4
- Neural Prosthesis Program ... 2-49, 2-207, 3-190
- Neural Tube Defects ... 2-33
- Neuralgia ... 2-59, 2-169
- Neurexin Gene ... 2-42, 3-44, 3-183
- Neuritis ... 2-68
- NeuroAIDS ... 2-61, 2-97, 3-153
- NeuroAIDS Tissue Consortium ... 2-61, 2-97, 3-153
- Neurobiology ... 1-24, 2-23, 2-46:2-47, 2-133, 2-202, 3-43, 3-132, 3-198, 4-38
- Neuroblastoma ... 2-5
- Neurocognitive Function ... 2-200, 3-182
- Neurodegenerative ... 2-32, 2-38:2-39, 2-51, 2-95, 2-258, 3-36, 3-60, 3-70, 3-106, 4-3, 4-5, 4-8:4-9
- Neurodegenerative Diseases ... 2-95, 3-60, 3-70, 3-106, 4-3, 4-5, 4-8:4-9
- Neurodegenerative Disorders ... 2-38:2-39, 2-51, 3-36, 3-60, 3-70, 4-3, 4-5, 4-8:4-9
- Neuroendocrine ... 2-33, 2-167
- Neurofibrillary Tangles ... 4-3
- Neurofibromatoses ... 2-32, 2-258
- Neurogenesis ... 2-37
- Neuroimaging Informatics Tools and Resources Clearinghouse ... 2-57, 3-159
- Neurological Disorders ... 1-15, 2-2, 2-32:2-33, 2-41, 2-61, 2-63, 2-69:2-71, 2-76, 2-193, 3-46, 3-109, 3-149, 4-7, B-2, F-9
- Neurological Emergencies Treatment Trials ... 2-65, 3-112
- Neurology ... 2-56, 2-65, 3-5, 3-36:3-37, 3-112, 3-159, 3-167, 3-173
- Neuromuscular Diseases ... 2-39
- Neurons ... 2-31:2-32, 2-35:2-39, 2-44:2-45, 2-47, 2-49:2-50, 2-133, 2-168, 3-62:3-63, 3-80, 3-83:3-84, 3-170, 3-179
- Neuropathy ... 2-68, 2-258
- Neuropathy, Diabetic ... 2-68
- Neuroplasticity ... 2-32, 2-34, 2-36:2-37, 2-45
- Neuropsychology ... 3-5
- Neurosciences ... **2-31:2-72**, 1-3, 1-7, 1-32, 2-19, 2-23, 2-96:2-97, 2-100, 2-112, 2-120, 2-134, 2-136, 2-138, 2-144, 2-147, 2-150, 2-155, 2-158:2-160, 2-167, 2-169:2-170, 2-188, 2-190, 2-193, 2-202, 2-208, 2-210, 2-219, 2-232, 2-249, 2-258, 3-11, 3-16, 3-22:3-23, 3-28, 3-36:3-37, 3-43:3-44, 3-46:3-48, 3-55, 3-62:3-63, 3-68, 3-73:3-74, 3-76, 3-80:3-81, 3-83:3-84, 3-86:3-87, 3-102, 3-107:3-109, 3-112:3-114, 3-



- 117, 3-120:3-121, 3-126:3-127, 3-131:3-133, 3-139, 3-153, 3-155:3-156, 3-158:3-160, 3-162, 3-175, 3-179, 3-184, 3-190, 3-198, 3-205, 3-208:3-209, 3-241, 3-245, 4-4:4-5, 4-14, 4-23, A-5, B-2, B-4, D-2, D-4, E-7, F-3  
 Neurosurgery ... 2-65, 3-112  
 Neurotoxicity Syndromes ... 2-38  
 Neurotrophic Factors ... 2-53, 3-139  
 Nevus ... 3-79  
 New Innovator Award ... 1-13, 1-28, C-5:C-6  
 New Pathways to Discovery ... 3-166:3-167, C-3, C-5, C-7:C-8  
 New York Consortium for Alzheimer's Research and Education ... 4-7  
 Newborn Intensive Care Units ... 2-199  
 Newsletters ... 2-152, 2-234, 3-53, 3-139, 3-236, 4-28  
 NHGRI (see National Human Genome Research Institute)  
 NHLBI (see National Heart, Lung, and Blood Institute)  
 NHLBI Pediatric Heart Network ... 2-165, 3-80, 3-121  
 NIA (see National Institute on Aging)  
 NIAAA (see National Institute on Alcohol Abuse and Alcoholism)  
 NIAID (see National Institute of Allergy and Infectious Diseases)  
 NIAID category A-C priority pathogens ... 2-92  
 NIAID Rocky Mountain Laboratories ... 2-82  
 NIAMS (see National Institute of Arthritis and Musculoskeletal and Skin Diseases)  
 NIBIB (see National Institute of Biomedical Imaging and Bioengineering)  
 NICHD (see National Institute of Child Health and Human Development)  
 Nicotine ... 2-12, 2-17:2-18, 2-23, 2-25, 2-27, 2-32, 2-47, 2-145, 2-148, 2-177, 2-191, 3-43, 3-132  
 Nicotine Dependence (see Tobacco Use Disorder)  
 Nicotine Vaccine ... 2-23, 2-47, 3-43, 3-132  
 NIDA (see National Institute on Drug Abuse)  
 NIDCD (see National Institute on Deafness and Other Communication Disorders)  
 NIDCR (see National Institute of Dental and Craniofacial Research)  
 NIDDK (see National Institute of Diabetes and Digestive and Kidney Diseases)  
 NIEHS (see National Institute of Environmental Health Sciences)  
 Niemann Pick Disease ... 2-68, 3-124  
 NIGMS (see National Institute of General Medical Sciences)  
 NIGMS/NCI Collaborative Access Team ... 3-178  
 NIH Academy ... 2-221, 2-244  
 NIH Autism Coordinating Committee ... 4-36  
 NIH Center for Scientific Review ... 1-15:1-16, 1-18, 1-27, 2-72, 2-101, 2-118, 2-173, 2-212, 2-248, B-5  
 NIH Clinical Center (see Mark D. Hatfield Clinical Research Center)  
 NIH Countermeasures Against Chemical Threats Research Network ... 2-62, 2-81, 2-96  
 NIH Director's New Innovator Award ... 1-28, C-5:C-6  
 NIH Director's Pioneer Award ... 2-100, 3-216  
 NIH HIV Vaccine Research Education Initiative ... 2-87, 3-236  
 NIH Influenza Genome Sequencing Project ... 2-83, 3-39  
 NIH Innate Immune Receptors and Adjuvant Discovery ... 2-92, 3-76  
 NIH Magnetic Resonance Imaging Study of Normal Brain Development ... 2-35  
 NIH Manuscript Submission ... 3-152  
 NIH MedlinePlus The Magazine ... 3-152, 3-233  
 NIH Mission ... 1-3, 1-14, 1-16, 2-131, 2-221, 3-3, 3-56, 3-197, 3-206, B-5  
 NIH Pain Consortium ... 2-33, 2-59, 2-120, 2-132, 2-169  
 NIH Pharmacogenetics Research Network ... 3-46  
 NIH Pipeline to Partnerships ... 1-24  
 NIH Public Access Policy ... 3-146  
 NIH Reform Act of 2006 ... 1-3, 1-6, 1-12, 1-14, 1-21, 4-1, B-6  
 NIH Research on Social Work Interventions and Health Summer Institute ... 3-141  
 NIH Revision Awards ... 3-54  
 NIH Revitalization Act of 1993 ... E-5, F-3  
 NIH Roadmap for Medical Research ... 1-12, 1-19, 1-28, 1-30, 2-42, 2-63, 2-105, 2-164, 3-40, 3-44, 3-59, 3-66, 3-70:3-71, 3-90, 3-99, 3-109, 3-142, 3-146, 3-150, 3-161:3-162, 3-166:3-167, 3-178:3-179, 3-184, 3-188:3-189, 3-193, 3-198, 3-206:3-207, C-1:C-3, C-5  
 NIH Special Emphasis Panel on the Coordination of Rare Diseases Research ... 4-32  
 NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities, Fiscal Years 2002-2006 ... 2-248  
 NIH Toolbox for Assessment of Neurological and Behavioral Function ... 2-63, 3-86  
 NIH Tracking and Inclusion Committee ... E-7:E-8, E-14  
 NIH Tumor Biology and Metastasis Program ... 3-60  
 NIHSeniorHealth.gov ... 3-241  
 NIMH (see National Institute of Mental Health)  
 NIMH Center for Collaborative Genetic Studies ... 4-39, 4-41  
 NIMH Genetics Repository ... 3-48, 3-148, 3-155  
 NIMH Human Genetics Initiative ... 2-58, 3-48, 3-155  
 NINDS (see National Institute of Neurological Disorders and Stroke)  
 NINDS Neurological Emergency Clinical Trials Network ... 2-62, 2-96  
 NINR Mentored Research Scientist Development Award for Underrepresented or Disadvantaged Investigators ... 2-243  
 NLM (see National Library of Medicine)  
 NLM Institutional Training Grants and Fellowships ... 3-200  
 Nobel Prize ... 2-103, 3-55, 3-57, 3-195  
 Nociception ... 2-70, 3-68  
 Noise ... 2-50, 2-176, 3-237, 4-12  
 Noise-Induced Hearing Loss (see Hearing Loss, Noise-Induced)  
 Non-Small Cell Lung Cancer (see Carcinoma, Non-Small-Cell Lung)  
 Nonalcoholic Steatohepatitis ... 2-129, 2-160, 2-193  
 Nonalcoholic Steatohepatitis Clinical Research Network ... 2-129:2-130, 2-160, 2-193  
 Nonhuman Primates ... 2-95, 3-29  
 NOS1 Protein, Human ... 2-37, 2-45, 2-168, 3-62:3-63, 3-80  
 Nose ... 3-40, 3-195  
 Nuclear and Radiological Threats ... 2-92, 3-106  
 Nuclear/Radiological Countermeasures ... 2-81  
 Nucleic Acids ... 2-96, 3-50, 3-52, 3-55, 3-78, 3-154, 3-172, 3-183  
 Nucleosomes ... 3-46:3-47  
 Nucleotides ... 3-27  
 Nurse Investigators ... 2-243  
 Nurse Scientists ... 2-243, 3-215, B-4  
 Nurses ... 1-25, 2-84:2-85, 2-139, 2-219, 2-243, 2-247, 3-215, 3-229, 3-243, B-4  
 Nursing ... 1-14, 2-243, 3-200, 3-215, B-4, D-3, F-9:F-10  
 Nursing Research ... 1-15, 2-2, 2-72, 2-101, 2-118, 2-172:2-173, 2-180, 2-211:2-212, 2-243, 2-247:2-248, 3-215, B-4, F-9:F-10  
 Nutrition ... 1-12, 1-23, 2-61, 2-69, 2-128, 2-141, 2-188, 2-193:2-194, 2-227, 2-231, 2-258, 3-5, 3-16:3-17, 3-67, 3-91, 3-231, 3-235, B-2, C-8, D-2, F-8  
 Nutrition Disorders ... 2-40  
 Nutritional Status ... 2-198, 3-36  
 Nutritional Support ... 4-14  
 Obesity ... 1-10, 1-12, 1-20, 2-7, 2-25, 2-33, 2-46:2-47, 2-69:2-70, 2-119, 2-121, 2-127:2-131, 2-133:2-134, 2-136, 2-

- 141:2-142, 2-145:2-146, 2-153, 2-160, 2-162:2-163, 2-170, 2-173:2-174, 2-180, 2-182, 2-185, 2-187, 2-189, 2-191, 2-193:2-194, 2-198:2-201, 2-209, 2-216, 2-218, 2-220:2-221, 2-224:2-225, 2-228:2-229, 2-231:2-232, 2-234:2-235, 2-237, 2-258, 3-1, 3-4, 3-11, 3-14, 3-24, 3-59, 3-62, 3-67:3-68, 3-77, 3-84, 3-87, 3-98, 3-116, 3-119, 3-121, 3-127:3-128, 3-146, 3-179, 3-181, 3-231, 3-235, 3-240, 4-14, 4-25:4-26, 4-30, F-7:F-8, F-11
- Obesity Prevention ... 2-141, 2-234, 3-235
- Obstetric Delivery (see Delivery, Obstetric)
- Obstetrics ... 2-198, 3-115
- Obstetrics and Periodontal Therapy Trial ... 2-198, 3-115
- Occipital Lobe ... 2-67, 3-83
- Occupation ... 2-153, 2-229, 3-14
- Occupational Exposure ... 2-106:2-107, 2-112, 3-11
- Oceanic Ancestry Group ... 2-14, 2-213, 2-215, 2-220, 2-223, 2-233:2-234, 2-236, 3-199, 3-240, 4-25, D-7, E-9:E-10, E-15:E-18, E-34, E-37, E-44, E-46
- Ocular Motility Disorders ... 4-8
- Office of AIDS Research ... 1-15, 2-28, 2-72, 2-74, 2-89, 2-101, 2-173, 2-225, 2-248, B-7, F-11
- Office of Animal Care and Use ... 1-32
- Office of Behavioral and Social Sciences Research ... 1-4, 1-15, 1-20, 2-101, 2-173, 2-248, 3-230, B-6, F-11
- Office of Biotechnology Activities ... 1-29:1-30
- Office of Communications and Public Liaison ... 3-223:3-224, 3-230
- Office of Dietary Supplements ... 1-15, 2-173, 2-211, B-6, F-11
- Office of Disease Prevention ... 1-15, 2-173, B-6
- Office of Extramural Research ... 1-14, 1-16, 1-24, 1-31:1-32, 3-122, 3-201, 3-203:3-204, E-2, E-5:E-7
- Office of Intramural Research ... 1-14, 1-18, 1-24, 1-31:1-32, 2-101, 2-248, E-5:E-6
- Office of Laboratory Animal Welfare ... 1-31:1-32
- Office of Management and Budget ... 1-21, 3-201:3-202, 3-218, E-7, E-9, E-18
- Office of Medical Applications of Research ... 1-15, 3-98, B-6
- Office of National Drug Control Policy ... 2-228, 3-4, 3-10, 3-157
- Office of Portfolio Analysis and Strategic Initiatives ... 1-14:1-15, 1-20:1-22, B-6
- Office of Rare Diseases ... 1-15, 2-68, 2-101, 2-118, 2-248, 3-228, 3-239, 4-32, 4-35, B-6, F-11
- Office of Research Facilities ... 1-25
- Office of Research on Minority Health ... 2-246
- Office of Research on Women's Health ... 1-4, 1-15, 2-61, 2-101, 2-118, 2-150, 2-167, 2-173, 2-194, 2-248, 3-122, 3-203, 3-210, 3-215, 3-226, 3-230, B-7, E-2, E-5:E-7, E-14, F-1:F-4
- Office of Science Policy ... 1-26, 1-29, 2-74, 2-173
- Office of Technology Transfer ... 1-24
- Office of the Assistant Secretary for Preparedness and Response ... 2-81, 2-93, 3-160
- Office of the Director, NIH ... 1-4, 1-8, 1-14:1-16, 1-20:1-22, 1-25, 1-27, 1-29, 1-32, 2-89, 2-225, 3-98, 3-223, 3-230, B-1, B-6, C-2, C-4, E-7, F-2, F-11
- Older Adults ... 2-6, 2-28, 2-168, 2-176, 2-182, 2-205:2-207, 2-209, 2-247, 3-227, 3-236, 3-241, 4-10:4-11, 4-13:4-15
- Older Americans Independence Centers (see Claude D. Pepper Older Americans Independence Centers)
- Oligonucleotide Array Sequence Analysis ... 3-169, 3-183
- OMAR (see Office of Medical Applications of Research)
- OMB (see United States Office of Management and Budget)
- Omega-3 Fatty Acids ... 2-52:2-53, 2-160, 3-59, 3-117
- Opiate Addiction ... 2-98, 2-153, 3-123
- Opioids (see Analgesics, Opioid)
- Opportunistic Infections ... 2-61, 2-89, 2-99, 2-225, F-11
- Optic Atrophies, Hereditary ... 2-155:2-156, 3-114
- Optic Nerve ... 2-56, 2-71, 2-123, 2-125, 2-136, 2-172, F-5
- Optic Neuritis ... F-5
- Optics ... 3-74:3-75, 3-104, 3-173, 3-187, D-6
- Oral Cancer ... 2-9, 2-20:2-21, 2-219, 2-232, 2-237, 3-125, 3-140, 3-172, 3-183, 3-231, 3-238
- Oral Cavity ... 2-21:2-22, 2-83, 2-187, 2-197, 2-209, 3-67, 3-72, 3-115, 3-125, 3-183
- Oral Clefting ... 2-216
- Oral Contraception ... 2-225
- Oral Health ... 2-198, 2-219, 2-237, 3-99, 3-115, 3-140
- Oral Health Disparities Centers Initiative ... 2-237, 3-140
- Organ Survival ... 2-158, 3-134
- Organ Systems ... 1-3, 1-7, 2-18, 2-26:2-27, 2-31, 2-33, 2-43, 2-45:2-48, 2-53:2-54, 2-56, 2-58:2-61, 2-64:2-66, 2-69, 2-96, 2-98, 2-104, 2-114:2-117, 2-119:2-120, 2-122:2-125, 2-131, 2-134, 2-166, 2-171, 2-179:2-180, 2-194, 2-196:2-197, 2-199:2-201, 2-207, 2-223:2-225, 2-228:2-230, 2-235, 2-237, 3-8:3-9, 3-11, 3-14:3-15, 3-18:3-23, 3-25, 3-36:3-37, 3-42:3-43, 3-45, 3-49:3-51, 3-53, 3-56, 3-63, 3-68:3-69, 3-71, 3-73:3-74, 3-76, 3-78, 3-80, 3-87, 3-103, 3-107, 3-111, 3-113:3-114, 3-116:3-122, 3-124:3-128, 3-133:3-134, 3-138:3-140, 3-144, 3-155:3-157, 3-161, 3-170, 3-174, 3-177, 3-184, 3-186, 3-235, 3-239, 3-241, 3-243:3-245, 4-33, A-5
- Organ Transplantation ... 2-111, 2-116, 2-118, 2-120, 2-122, 2-130, 2-157:2-158, 2-172:2-173, 2-258, 2-262, 3-103, 3-134, B-2
- Organization and Administration ... 1-3, 1-29, 2-17, 2-72, 2-77, 2-89, 2-145, 2-194, 2-246, 3-137, 3-200, 3-218, 3-221, 3-223, 3-233, 3-236, C-1, E-3, E-12, E-23, E-27, E-30
- Organizations ... 1-16, 1-19, 1-25, 1-27, 2-55, 2-77, 2-79, 2-82, 2-88, 2-98, 2-104, 2-131, 2-139, 2-141, 2-156, 2-219, 2-231, 2-234:2-236, 2-246, 3-100, 3-108, 3-113, 3-123, 3-136:3-137, 3-152, 3-217, 3-229:3-232, 3-235:3-237, 3-243:3-246, 4-24, 4-27, 4-33, 4-41, A-4, B-4, C-5, F-6
- Orofacial Pain ... 2-132, 2-170, 3-22, 3-118
- Orofacial Pain: Prospective Evaluation and Risk Assessment ... 2-132, 2-170, 3-22, 3-118
- Orphan Drug ... 2-258
- Orthopaedic trauma care ... 2-224, 3-106
- Orthopedic Surgery ... 3-200, 4-18
- Orthotic Devices ... 2-229, 3-120
- Osteitis Deformans ... 2-122
- Osteoarthritis ... 2-69, 2-121:2-122, 2-127, 2-131, 2-145, 2-148, 2-165, 2-170, 2-175, 2-225, 3-120:3-121, 4-11:4-12, F-5, F-7
- Osteoarthritis Initiative ... 2-127, 2-145:2-146
- Osteoarthritis, Hip ... 2-225
- Osteoarthritis, Knee ... 2-127, 2-146
- Osteoblasts ... 2-115, 2-137, 3-69
- Osteogenesis Imperfecta ... 2-122, 2-149, 2-176, 2-201, 2-258
- Osteonecrosis ... 3-140
- Osteoporosis ... 2-122, 2-124, 2-127, 2-133, 2-141, 2-176, 2-180, 2-201, 2-258, 3-9, 3-42, 3-236:3-237, 3-240, 4-11:4-12, F-5, F-7:F-8, F-10
- Otitis Media ... 2-123, 2-176, 2-258
- Ovarian Cancer ... 2-258, 3-33, F-6
- Ovarian Failure, Premature ... 2-167
- Ovaries ... F-4
- Overweight ... 2-121, 2-128, 2-142, 2-145, 2-174, 2-194, 2-198, 2-200, 2-228, 2-235, 3-73, 3-98, 3-116
- Oxygen ... 2-129, 2-158, 3-115:3-116
- Oxygen Inhalation Therapy ... 2-158, 3-115:3-116
- Oxygen Therapy ... 2-129, 2-158, 3-95, 3-115:3-116
- Paclitaxel ... 2-14, 3-96, 3-135
- Paget's Disease ... 2-122, 2-176, 2-258
- Pain ... 1-19, 2-33, 2-36:2-37, 2-45, 2-59, 2-69:2-70, 2-120, 2-122:2-123, 2-129, 2-131:2-132, 2-150, 2-161, 2-164:2-165, 2-168:2-170, 2-184, 2-208, 2-224, 2-259, 3-22, 3-59, 3-62:3-63, 3-68, 3-73, 3-86, 3-118, 3-120:3-121, 3-128, 3-139, 3-161, 4-13, A-5, F-5, F-9

- Pain Conditions, Chronic ... 2-259
- Pain Control (see Analgesia)
- Pain Disorder ... 2-170, 3-22, 3-118
- Pain Management (see Analgesia)
- Pain Relief (see Analgesia)
- Pain, Burning ... 2-46, 2-155, 3-114
- Pain, Postoperative ... 2-131
- Painful Bladder Syndrome (Also see Interstitial Cystitis) ... 2-122, 2-175, 3-19, F-8
- Palate ... 2-69, 2-183, 2-187, 2-196, 3-67, 3-81:3-82
- Palate, Soft ... 2-21
- Palliative Care ... 2-28, 2-120, 2-131:2-132, 2-168, 3-86, 3-215, A-5
- Palliative Medicine ... 2-207
- Pan American Health Organization ... 2-210, 3-213
- Pancreas ... 2-5, 2-14, 2-103, 2-110, 2-114, 2-121:2-122, 2-125, 2-130, 2-135, 3-14, 3-38, 3-78
- Pancreatic Cancer ... 3-6
- Pancreatic Cancer Cohort Consortium ... 3-6
- Pancreatic Diseases ... 2-111, 2-114:2-115, 2-117, 2-121:2-122, 2-129, 2-140, 2-146, 2-148, 2-154, 2-163, 2-171, 2-200, 2-220, 2-230, 2-237, 3-11, 3-18, 3-22, 3-25, 3-45, 3-69, 3-107, 3-111, 3-182, 3-235, B-2, F-8
- Pancreatitis ... 2-122
- Pancreatitis, Chronic ... 2-122
- Pandemic Influenza ... 2-80:2-81, 2-91, 2-93, 2-95, 3-76, 3-192
- Pandemic Influenza Plan ... 2-91
- Pandemics ... 1-11, 2-79:2-80, 2-89, 2-91:2-93, 2-95, 2-98, 2-100, 3-7, 3-19, 3-28, 3-34, 3-76, 3-192, 3-216, F-11
- Papillomaviridae ... 2-7, 2-17:2-18, 2-28, 2-86, 2-255, 3-25, 3-89, 3-136, 3-154
- Papillomavirus Infection ... 3-25, 3-89, 3-154
- Papillomavirus Vaccines ... 2-7, 2-17:2-18, 2-28, 2-86, 2-255, 3-136
- Paralysis ... 2-37, 2-49, 2-56, 2-186, 2-207, 3-87, 3-190, 4-14
- Parasites ... 2-77, 2-83:2-84, 3-29, 3-39, 3-56
- Parasitology ... D-2
- Parenting ... 2-44, 2-185, 2-190, 2-193, 2-199, 3-9, 3-11, F-7
- Parents ... 1-25, 2-119, 2-141, 2-183:2-185, 2-193, 2-196:2-199, 2-201, 2-230, 3-9, 3-21, 3-25, 3-33, 3-72, 3-118, 3-210, 3-225, 3-228, 3-230, 3-233, 3-235, 3-240, 4-38
- Parkinson Disease ... 2-32, 2-36, 2-39, 2-49, 2-51:2-52, 2-55, 2-58:2-59, 2-69, 2-72, 2-120, 2-207, 2-259, 3-6, 3-36, 3-60:3-61, 3-70, 3-73, 3-83, 3-109, 3-145, 3-148:3-149, 3-155, 3-158, 3-170, 3-190, 4-7
- Parkinson's Disease Registry ... 2-52, 3-149, 3-158
- Parkinsonism ... 3-6
- PART (see Program Assessment Rating Tool)
- Participation in Clinical Trials ... 2-8, 2-240, 3-94
- Participation in Research ... 3-141, 4-30
- Partnership for AIDS Vaccine Evaluation ... 2-79, 2-99
- Partnerships to Promote Innovation ... 3-173, 3-186
- Patents ... 1-24
- Pathogen Functional Genomics Resource Center ... 2-83, 3-39
- Pathogenic Agents ... 2-73
- Pathology ... 2-24, 2-38, 2-110:2-111, 3-12, 3-129, 3-151, 3-171, D-1:D-3, D-8
- Pathway to Independence ... 1-13, 1-28, 3-203, 3-209
- Patient Advocacy ... 2-104, 2-219, 4-33:4-34
- Patient Care ... 1-25, 2-157, 2-180, 2-223, 3-114, 3-141, 3-145, 3-168, 3-192, 4-6, B-5, F-10
- Patient Education ... 2-21, 2-232, 3-238
- Patient Navigation Research Program ... 2-20, 2-220, 2-231
- Patient Recruitment ... 4-38
- Patient-Reported Outcomes ... 2-129, 2-164, 3-161, C-6
- Patient-Reported Outcomes Measurement Information System ... 2-129, 2-164, 3-161, C-6
- Pediatric ... 2-35, 2-43:2-44, 2-94, 2-97, 2-101, 2-150, 2-156, 2-165, 2-171, 2-185, 2-187, 2-191, 2-193, 2-199, 2-203, 2-211, 2-259, 3-5:3-6, 3-16, 3-24, 3-80, 3-94:3-95, 3-116, 3-121:3-123, 3-130, 3-142, 3-174, 3-199, 3-203, 3-205, 3-209, 3-228, 3-241, 4-33, A-7, D-8
- Pediatric AIDS ... 2-259
- Pediatric Clinical Research Centers ... A-7
- Pediatric HIV/AIDS Cohort Study ... 2-97, 2-191, 3-24, 3-116
- Pediatric Obesity ... 2-185
- Pediatric Research Initiative ... 2-259
- Pediatric, Adolescent, and Maternal AIDS Branch ... 2-101, 2-211
- Peer Review ... 1-16:1-17, 1-27, 1-29, 1-33, 3-146, 3-153, 3-191, 3-232, 4-3, 4-9, 4-16, B-5:B-6, E-6:E-7
- Pelvic Floor ... 3-95, 3-130
- Pelvic Inflammatory Disease ... 2-259
- Pemphigus Vulgaris ... 2-110
- People of Color ... 2-117, 2-226
- Peptic Ulcer ... 2-122, 2-253
- Peptide Fragments ... 2-18
- Peptides ... 2-53, 2-110, 2-112, 2-148, 3-112
- Perception ... 2-31, 2-234
- Perimenopause ... 2-188
- Perinatal ... 2-259, 3-199, F-9
- Perinatal Period ... 2-259, F-9
- Perinatal Period, Conditions Originating in Perinatal Period ... 2-259
- Perinatology ... 2-195, 2-210
- Periodontal Bone Loss ... 2-115, 2-137, 3-69
- Periodontal Disease ... 2-83, 2-115, 2-123, 2-137, 2-198, 3-4, 3-40, 3-68:3-69, 3-115, F-7
- Periodontitis ... 2-111, 2-115, 2-124:2-125, 2-137:2-138, 2-176, 2-216, 3-59, 3-68:3-69
- Peripheral Arterial Disease ... 2-121, 2-174
- Peripheral Nervous System ... 2-70, 2-97, 3-153
- Peripheral Neuropathies ... 2-68
- Personality ... 2-179, D-4
- Personality Disorders ... 2-141, 2-227, 3-19
- Personalized Medicine ... 2-1, 2-12, 3-2, 3-7, 3-13, 3-28, 3-35, 3-49, 3-155, 3-169
- Pesticides ... 2-107, 2-112, 2-183, 3-12
- PET (see Positron-Emission Tomography)
- Pharmacies ... 2-91, 3-192
- Pharmacists ... 1-25
- Pharmacogenetics ... 1-11, 3-46
- Pharmacogenetics Research Network ... 3-46
- Pharmacogenomics ... 3-123
- Pharmacokinetics ... 2-92
- Pharmacology ... 2-45, 2-168, 3-63, 3-95, 3-130, 3-170, 3-198, B-2, D-2
- Pharmacology, Clinical ... 3-205
- Pharmacotherapy ... 2-41, 4-39
- Pharmacy ... D-3
- Pharynx ... 2-21
- Phase 3 Clinical Trials (see Clinical Trials, Phase III as Topic)
- Phenols ... 2-136, 3-87
- Phenotype ... 2-42, 2-60, 2-71, 2-103, 2-139:2-140, 2-144, 2-152, 2-172, 2-183, 2-217, 3-6, 3-13, 3-35, 3-43:3-44, 3-49, 3-59, 3-70, 3-74, 3-146, 3-148, 3-154:3-156, 3-184, 3-214, 4-41, C-8
- Phenyl Ether ... 2-41
- Phenylketonuria ... 2-179, 2-196, 3-185
- Phoenix Epidemiology and Clinical Research Branch ... 2-146, 2-237, 3-10
- Photoactivated Localization Microscopy ... 3-170, 3-181
- Phototherapy ... 3-183
- Physical Activity ... 2-7, 2-25, 2-49, 2-119, 2-127:2-128, 2-141, 2-148, 2-151, 2-153, 2-163, 2-185, 2-191, 2-205, 2-225,

- 2-229, 3-14, 3-33, 3-37, 3-83:3-84, 3-102, 3-172, 3-177, 3-185, 3-231, 3-235, 4-11, 4-14  
Physical Therapy Modalities ... 1-17, 2-186  
Physicians ... 1-25, 2-11, 2-15, 2-25, 2-58, 2-115:2-116, 2-130, 2-139, 2-157, 2-163, 2-192, 2-194, 2-200, 3-22, 3-30, 3-86, 3-91, 3-98, 3-103, 3-110, 3-120:3-121, 3-123, 3-142, 3-145, 3-151, 3-153, 3-171, 3-174, 3-190, 3-198, 3-204, 3-206:3-207, 3-215, 3-222, 3-224:3-227, 3-229:3-230, 3-243, 4-1, 4-7, 4-20, 4-29, 4-34, D-8, F-6  
Physicians, Women ... 3-237  
Physiological Processes ... 2-35, 2-182, 3-59  
Pick's Disease ... 2-32, 2-254, 2-259, 4-5, 4-7:4-8  
Pilot Project ... 2-15, 2-69, 2-108, 2-113, 3-33, 3-77, 3-109, 3-190, 4-20, 4-27, 4-29  
Pilot Studies ... 1-22:1-23, 2-194, 2-233, C-7  
Pilot Study ... 2-142, 2-200, 2-205, 2-228, 4-13:4-15  
Pioneer Award ... 1-12, 2-100, 3-216, C-6  
PKD (see Polycystic Kidney Disease)  
PKU (see Phenylketonuria)  
Placebo Effect ... 2-65, 2-155, 3-113  
Placebos ... 2-65, 2-73, 2-155, 2-157, 2-160, 2-193, 2-223, 3-113:3-114, 3-133  
Placenta ... 2-261  
Planning Grants ... 2-233, 3-130  
Plant Extracts ... 2-136, 3-87, B-6  
Plant Physiology ... D-1  
Plasma ... 2-62, 2-97, 2-146, 3-45, 3-107, 3-153, D-6, F-8  
Plasma Membrane ... F-8  
Pneumonia ... 2-17, 2-75, 2-124, 2-145, 2-259, 3-133  
Point Mutation ... 3-30  
Point-of-Care Technologies ... 3-171:3-172, 3-182  
Point-of-Care Testing ... 3-172, 3-185  
Policies, Population ... 3-20, 3-213  
Policy Analysis ... 1-30, 3-100, C-7, D-4  
Policy Development ... 1-18, 3-232  
Policy Makers ... 1-13  
Polio ... 2-119, 3-146  
Politics ... D-4  
Polycystic Kidney Disease ... 2-122, 2-129, 2-162, 2-171, 2-259, 3-15, 3-119  
Polycystic Ovary Syndrome ... 2-150, 2-194, 3-115  
Polymer ... 2-116, 2-157, 3-103, D-6  
Polymerase Chain Reaction ... 3-55  
Polymorphism, Single Nucleotide ... 2-152, 3-8, 3-28:3-29, 3-41, 3-45, 3-49, 3-52, 3-169, 3-176  
Polyphenols ... 2-136, 3-87  
Polyradiculoneuropathy, Chronic Inflammatory Demyelinating ... 2-68  
Polysaccharides ... 3-59  
Population Groups ... 2-24, 2-52, 2-113, 2-192, 2-209, 2-213, 2-215, 3-4, 3-6, 3-10, 3-46, 3-79, 3-95, 3-122, 3-130, 3-142:3-143, 3-158, 4-7, 4-26, E-7:E-9, E-40, E-42, F-8  
Population Research ... 2-2, 2-192, 2-213, 2-217:2-218, 2-226, 3-9, 3-20, 3-213  
Population Sciences ... 2-115, 3-110, F-4  
Populations ... 1-6, 2-1, 2-15, 2-33:2-34, 2-39, 2-58, 2-65, 2-71, 2-73, 2-86, 2-98, 2-100, 2-106, 2-122, 2-127, 2-130, 2-141:2-142, 2-154, 2-163, 2-169, 2-172, 2-197, 2-200, 2-208, 2-214, 2-218:2-219, 2-221:2-223, 2-225, 2-227:2-233, 2-235, 2-243, 3-2, 3-7, 3-10, 3-13, 3-17, 3-19, 3-25, 3-74, 3-82, 3-92, 3-94, 3-98:3-99, 3-123, 3-128, 3-130, 3-149, 3-155, 3-157, 3-192, 3-195, 3-198, 3-216, 3-222, 3-224, 3-230, 3-244, 4-1, 4-5, 4-7, 4-9, 4-27, 4-30, 4-35, A-5, B-3:B-4, E-5, F-5, F-7, F-9  
Positron-Emission Tomography ... 2-51, 2-204:2-205, 3-170, 3-180, 4-6  
Post-Baccalaureate Research Education Program ... 2-221  
Post-Thoracotomy Pain Syndrome ... 2-46, 2-131, 2-155, 3-114  
Postdoctoral Intramural Research Training Award ... 3-205, 3-209  
Postdoctoral Training ... 2-242, 3-196, 3-200, 3-202, 3-207, 3-216, A-5  
Poverty ... 2-213, 3-229, F-10  
Practice Based Research Networks ... 3-139:3-140  
Practice Guidelines ... 3-98  
Prader-Willi syndrome ... 4-33  
Prayer ... 2-131  
Pre-Eclampsia ... 2-142, 2-198:2-199, 3-115, F-11  
Precancerous Conditions ... 2-9  
Preclinical Development ... 2-56, 2-77, 2-83, 2-92, 2-106, 2-112, 3-77, 3-107, 3-109  
Predoctoral Research Training in Biostatistics ... 3-214  
Predoctoral Training at the Interface of the Behavioral and Biomedical Sciences ... 3-199, 3-214  
Prefrontal Cortex ... 2-67, 3-83  
Pregnancy ... 1-9, 2-37, 2-43, 2-82, 2-142, 2-150, 2-179, 2-182:2-184, 2-190, 2-194:2-196, 2-198:2-199, 2-210, 2-215, 2-261, 3-22, 3-24, 3-63, 3-82, 3-115, 3-141, F-8, F-11  
Pregnant Woman ... 2-196, 2-198, 3-82, 3-115  
Pregnant Women ... 1-9, 2-82, 2-184, 2-190, 3-24  
Premature Birth ... 2-195, 2-198, 2-215, 3-115  
Prematurity ... 2-189, 3-24, 3-79  
Premenopause ... 2-188  
Prenatal Alcohol in SIDS and Stillbirth ... 2-195, 3-22  
Prenatal Care ... 2-43, 2-181, 2-195, 3-22  
Prenatal Diagnosis ... 2-197, 3-72  
Prescription ... 3-225  
Prescriptions, Drug ... 2-139, 3-122, 3-125  
President's Emergency Plan for AIDS Relief ... 2-78, 2-99, 3-135, 3-208, 3-212  
Preterm Birth ... 2-181, 2-184, F-7  
Preterm Labor ... 2-195  
Prevention Science Initiative ... 2-89  
Priapism ... 2-161, 2-224, 3-139  
Primary Biliary Cirrhosis ... F-8  
Primary Care ... 2-126, 2-139, 2-151, 3-53, 3-139, 3-229, 3-243  
Primary Sclerosing Cholangitis ... 2-122  
Primate Research Center ... 2-82, 2-95, 3-106  
Primates ... 2-95, 2-100, 3-41, 3-65, 3-106, 3-136, 3-177, 3-216  
Prison ... 2-98, 2-154, 3-123  
Prisoners ... 2-98, 2-154, 3-123  
Privacy ... 2-126  
Private Sector ... 1-10, 1-24, 2-11, 2-92, 2-98, 2-145, 3-123, 3-168, 3-201, B-6  
Probes ... 2-91, 3-70, 3-150, C-5, C-8  
Problem Solving ... 2-202, 2-227  
Progeria ... 2-195, 3-30, 3-47, 3-110  
Progestins ... 3-3  
Program Assessment Rating Tool ... 1-21, 3-201:3-202, 3-218  
Program Evaluation ... 2-246, 3-137, 3-143, 3-202, 3-218  
Program for Research on Black Americans ... 2-218  
Program in HIV/AIDS & Cancer Virology ... 2-18, 2-86  
Prospective Studies ... 2-143, 2-170, 3-2, 3-22, 3-118, 4-39  
Prospective Study ... 3-6:3-7  
Prostate ... 2-2, 2-14, 2-20, 2-215, 2-231, 3-6, 3-14, 3-33, 3-38, 4-26  
Prostate Cancer ... 2-2:2-3, 2-5, 2-11, 2-14, 2-109, 2-259, 3-6, 3-13, 3-32, 3-38, 3-162, 3-189, 3-225  
Prostatitis ... 2-122  
Prostheses ... 1-9  
Prostheses and Implants ... 2-49, 2-207, 3-71, 3-190  
Prosthesis ... 2-208, 3-111, 3-189:3-190  
Protease Inhibitors ... 3-181, 4-22  
Protein Biosynthesis ... 2-9, 3-44, 3-178  
Protein Structure Initiative ... 3-169, 3-178

- Protein Structure, Tertiary ... 3-50  
Protein Transport ... 3-84  
Proteins ... 2-9, 2-21:2-22, 2-47, 2-69, 2-83, 2-108:2-110, 2-114, 2-135:2-136, 2-196, 2-225:2-226, 3-4, 3-27, 3-39, 3-44:3-45, 3-47, 3-50, 3-55:3-56, 3-59:3-60, 3-64, 3-67, 3-70, 3-75, 3-77, 3-82, 3-104:3-105, 3-115, 3-162, 3-166, 3-169:3-170, 3-178:3-182, 3-187, 4-5, 4-8, 4-14, 4-18, C-6, C-8  
Proteome ... C-8  
Proteomics ... 1-26, 2-2, 2-9, 2-11:2-13, 2-16, 2-81, 2-83, 2-105, 2-109, 2-114, 2-133, 2-135, 2-202, 3-7, 3-9, 3-27, 3-39, 3-42, 3-44:3-45, 3-55:3-56, 3-173, 3-178, 3-180  
Proteomics Research Centers ... 2-83, 3-39  
Pruritus ... 2-122  
Psoriasis ... 2-107:2-108, 2-113, 2-259, 3-33, 3-156, 4-25, 4-30  
Psychiatry ... 2-40, 2-168, 3-127, D-8  
Psycholinguistics ... D-3  
Psychological Factors ... 2-170, 3-22, 3-118  
Psychology ... 2-31, 2-142, 2-185, 2-188, 2-199, 3-5, 3-16, D-3:D-4  
Psychometrics ... D-4  
Psychomotor Disorders ... 4-40  
Psychoses ... 2-32  
Psychosocial Factors ... 2-153, 2-179:2-180, 2-229, 3-14  
Psychotherapy ... 2-39, 3-97  
Psychotic Disorders ... 2-55  
Pub. L. No. 107-280 (see Rare Diseases Act of 2002)  
Pub. L. No. 109-416 (see Combating Autism Act of 2006)  
PubChem ... 3-70, 3-146, 3-150, 3-154, 3-162  
Puberty ... 2-43, 2-150, 2-203, 3-58, 3-63, 3-241, F-9  
Public Access ... 2-151, 3-44, 3-146, 3-152  
Public Access Policy ... 3-146  
Public Domain ... 1-20, 1-22, C-4, F-6  
Public Health ... 1-3, 1-6, 1-10, 1-12, 1-14, 1-16, 1-20:1-22, 1-24, 1-26, 1-28, 1-31, 2-5, 2-7, 2-12, 2-23, 2-47:2-48, 2-65:2-66, 2-73:2-74, 2-77:2-78, 2-80:2-84, 2-88, 2-91, 2-93:2-95, 2-98:2-99, 2-119, 2-123, 2-131, 2-145, 2-159, 2-165, 2-184, 2-190, 2-192:2-193, 2-198, 2-201, 2-206, 2-214, 2-216, 2-219:2-221, 2-223:2-224, 2-227, 2-233, 2-237, 2-239:2-240, 2-244:2-245, 3-1:3-4, 3-7:3-9, 3-19:3-20, 3-24, 3-43, 3-76, 3-79, 3-96:3-97, 3-107, 3-112, 3-115, 3-124, 3-126:3-127, 3-130, 3-132:3-134, 3-140, 3-142, 3-145:3-147, 3-149, 3-152:3-153, 3-160, 3-163, 3-191, 3-193, 3-195:3-196, 3-200, 3-206, 3-208, 3-211, 3-215, 3-221:3-222, 3-224:3-225, 3-231:3-232, 3-234, 3-240, 3-242:3-243, 3-245:3-246, 4-1, 4-3, 4-10, A-1:A-3, A-5, A-7, B-5:B-6, C-3:C-4, C-7, D-2, E-5, E-11, F-6, F-10  
Public Health Informatics ... 3-200  
Public Health Interventions ... 2-77, 3-4, 3-145  
Public Health Service Act ... 1-3, 1-6, 1-16, 2-221, 2-244:2-245, 4-3, 4-10, A-1:A-2, A-7  
Public Health Threats ... 2-73:2-74, 2-80, 2-82  
Public Service Announcements ... 2-21, 2-156, 2-232, 3-225, 3-231, 3-235, 3-238  
Public-Private Partnership ... 1-26:1-27, 2-7, 2-11, 2-25, 2-27, 2-51, 2-64, 2-77:2-78, 2-127, 2-138, 2-148, 2-151, 2-191, 2-204, 3-33, 3-36:3-37, 3-79, 3-93, 3-101, 3-105, 3-107, 3-142, 3-177, 3-201, 3-217, 4-39, C-6  
PubMed ... 1-26, 3-146:3-147, 3-150, 3-152, 3-160, 3-239  
PubMed Central ... 3-146:3-147, 3-152  
Pulmonary Embolism ... 3-3  
Pulmonary Hypertension ... 2-157, 2-223, 3-114  
Pyrimidines ... 2-60  
Qi Gong ... F-5  
Quality of Care ... 2-11  
Quality of Life ... 1-10, 2-1, 2-4, 2-12:2-13, 2-24:2-25, 2-46, 2-48, 2-65, 2-67, 2-69, 2-78, 2-104, 2-119:2-120, 2-123:2-124, 2-129:2-132, 2-158, 2-164, 2-169:2-170, 2-184, 2-210, 2-217, 3-12:3-13, 3-17, 3-19, 3-86:3-87, 3-107, 3-112, 3-121, 3-129:3-130, 3-134:3-135, 3-144, 3-161, 3-165, 3-168, 3-174:3-175, 3-230, 4-13:4-14, 4-18, B-2, B-4, F-7, F-9:F-10  
Rabies Virus ... 2-44, 3-84  
Race ... 2-65, 2-127, 2-149, 2-201, 2-215, 2-218, 2-221, 2-232, 2-239, 3-27, 3-52, 3-122, 3-149, 3-199, 3-225, 4-25, 4-27, D-7, E-3:E-4, E-6:E-10, E-14:E-19, E-22, E-24, E-26, E-28, E-31, E-33:E-46  
Race and ethnicity ... 3-122, 3-199, E-3:E-4, E-7:E-9, E-14:E-17, E-19, E-22, E-24, E-26, E-28, E-31, E-33:E-38  
Racial and Ethnic Approaches to Community Health (REACH 2010) ... 2-235  
Radiation ... 2-10, 2-16, 2-21, 2-25, 2-81, 2-93, 2-192, 3-135:3-136, 3-160  
Radiation Event Medical Management ... 2-81, 2-93, 3-160  
Radiation Event Medical Management Program ... 2-81  
Radiation exposure ... 2-81, 3-64  
Radiation Injuries ... 2-81  
Radiation injury ... 2-92, 3-106  
Radiation Oncology ... 2-10  
Radio ... 2-156, 3-56, 3-222, 3-224, 3-227, 3-233, 3-235, 4-28  
Radioactive substances ... 2-73  
Radiological or nuclear threat ... 2-81  
Radiotherapy ... 2-10, 2-16, 2-21, 2-25, 2-192, 3-135:3-136  
Ragweed ... 2-116, 3-71, 3-132  
Raloxifene ... 2-8, 2-13, 3-135  
Randomized controlled trial ... 2-206, 4-14  
Rapid Access to Intervention Development Pilot Program ... 2-111, 3-93, 3-107, 3-109  
Rapid DNA Sequencing ... 3-165  
Rapid Response Program ... 2-128, 2-149, 2-203, 3-14, 3-244  
Rare Diseases ... 1-6:1-7, 1-15, 2-33, 2-68, 2-121, 2-124, 2-147, 2-151, 2-179, 2-202, 3-45, 3-51, 3-90, 3-93, 3-96, 3-124, 3-195, 3-228, 3-239, 4-1:4-2, 4-32:4-35, 4-45, B-2, B-6, F-5, F-11  
Rare Diseases Act of 2002 ... 4-32, 4-34:4-35  
Rare Diseases Clinical Research Network ... **4-32:4-35**, 1-6:1-7, 4-2, 4-45, B-6  
Rat Resource and Research Center ... 3-48, 3-101  
Rates, Survival ... 2-25, 2-192, 2-215, F-4  
Rats ... 2-36, 2-116, 2-157, 3-34, 3-103  
Re-Entry Program ... 3-210  
REACH 2010 (see Racial and Ethnic Approaches to Community Health (REACH 2010))  
Reagents ... 2-9, 2-12, 2-83, 2-161, 3-39, 3-44, 3-92, 3-140, 3-178  
Really Simple Syndication (RSS) ... 3-160, 3-225  
Reasons for Geographic and Racial Differences in Stroke Study ... 2-65, 2-218  
Receptors, T-Cell ... 2-110  
Recombinant DNA ... 1-29  
Recombinant DNA Advisory Committee ... 1-29:1-30  
Recombinant DNA Research ... 1-30  
Red Blood Cells ... 2-122  
Reengineering the Clinical Research Enterprise ... 1-20, 3-99, C-3, C-6, C-8  
Referral ... 1-16, 1-28, 3-226:3-227, 3-236, 4-7, B-6  
RefSeq database ... 3-50  
REGARDS (see Reasons for Geographic and Racial Differences in Stroke Study)  
Regeneration ... 2-50:2-51, 2-114, 2-135, 2-209, 3-60, 3-72, 3-78, 3-102  
Regenerative Medicine ... 2-259, 3-57, 3-60, 3-78, 3-173, 3-188, 4-22  
Regional Biocontainment Laboratories ... 2-82, 2-94  
Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research ... 2-82, 2-94  
Regional Medical Libraries ... 2-231, 3-244  
Registries ... 2-24, 2-39, 2-106, 2-190, 3-12, 3-25, 3-129, 3-146:3-147, 3-149

- Registry ... 2-52, 2-56, 2-113, 2-133, 2-198, 3-37, 3-78, 3-120, 3-131, 3-153, 3-157:3-159, 4-5
- Regulations ... 1-16, 1-23:1-24, 1-30:1-32, 2-37, 2-50, 2-94, 3-34, 3-63, 3-80, 3-98, 3-100, 3-126, 3-166
- Rehabilitation ... 1-3, 1-7, 2-1, 2-4, 2-10:2-11, 2-13:2-14, 2-17, 2-20:2-21, 2-23:2-27, 2-32, 2-41, 2-43:2-44, 2-46, 2-48:2-49, 2-51, 2-54, 2-61, 2-63, 2-72, 2-85, 2-97, 2-106, 2-127, 2-133:2-134, 2-140:2-142, 2-146, 2-148:2-150, 2-160, 2-162:2-163, 2-166, 2-168, 2-179:2-212, 2-228, 2-231, 2-235, 2-240, 2-260, 3-7, 3-9:3-12, 3-15:3-19, 3-22:3-25, 3-47, 3-67, 3-72, 3-76, 3-82, 3-89, 3-91, 3-93, 3-95, 3-102, 3-109:3-111, 3-115, 3-117, 3-119:3-120, 3-129, 3-135, 3-158, 3-162:3-163, 3-175, 3-182, 3-185, 3-189:3-190, 3-212:3-213, 3-215, 3-233, 3-240:3-241, 3-244, 4-3, 4-12:4-14, 4-28, 4-34, A-5, B-1:B-2, D-3, F-11
- Reiki ... F-5
- Rejection ... 2-116, 2-130, 2-157, 3-71, 3-103, 3-132
- Renal Dialysis ... 2-122
- Renal Disease, End-Stage ... 2-174, 3-17, F-8
- Renal Insufficiency, Chronic ... 3-17
- Report on Carcinogens ... 3-98, 3-125:3-126
- Reproduction ... 2-194, 2-252, F-7
- Reproductive Health ... 2-142, 2-180, 2-184:2-185, 2-194, 2-199, 2-210, 3-215, F-3
- Reproductive Technologies ... 2-194
- Request for Applications ... 1-17, 2-61, 2-81, 2-203, 2-233, 3-14, 3-83, 3-85, 3-103, 3-120, 3-182, 4-15, 4-23, 4-35
- Request for Information ... 1-22, 1-27, 3-232
- Requests for Applications ... 1-20, 2-43, 2-81, 2-134, 2-150, 2-203, 3-241, 4-15, 4-29, F-3
- Research Agenda for MDR-TB/XDR-TB ... 2-88
- Research and Development Contracts ... 2-139, 3-184
- Research Centers ... 1-6:1-7, 2-2, 2-5, 2-7, 2-23, 2-25, 2-27, 2-39:2-40, 2-55, 2-62, 2-82:2-83, 2-95:2-96, 2-147, 2-150, 2-184, 2-191:2-192, 2-202, 2-222, 2-236, 2-246, 3-39, 3-41, 3-65, 3-91, 3-95, 3-100, 3-106, 3-108, 3-112, 3-130, 3-136:3-137, 3-177, 3-197, 4-2, 4-4, 4-17, 4-30, 4-32, 4-43, A-7, F-3
- Research Centers in Minority Institutions (RCMI) ... 2-222, 2-236, 2-246:2-247, 3-100, 3-136:3-138
- Research Centers in Minority Institutions (RCMI) Research Network ... 3-100
- Research Dissemination Grant ... 2-233
- Research Enhancement Awards Program ... 2-167
- Research Infrastructure ... 2-4, 2-12, 2-93:2-94, 2-168, 2-207, 2-222, 2-236, 2-246, 3-100, 3-137, 3-167, 4-1, 4-24, B-4:B-5, C-6, F-5:F-6
- Research Infrastructure in Minority Institutions ... 2-222, 2-246, F-5
- Research Infrastructure Initiative ... 3-100
- Research Initiative for Scientific Enhancement ... 2-221, 2-240:2-241
- Research Initiatives ... 1-12, 1-14, 2-17, 2-76, 2-180, 2-192, 3-133, 3-204, 3-232, 3-245, A-4, B-6, C-1:C-2, C-4:C-5, F-6, F-10
- Research Planning Grants ... 2-233
- Research Priorities ... 2-88, 2-180, 2-242, 2-244:2-245, 3-191, 3-196
- Research Protocols ... 2-66, 2-159, 2-236, 2-242, 2-245, 3-126, 3-137, 3-196, 3-245, 4-35, E-8, E-13:E-20
- Research Resources ... 1-4, 1-15, 1-19, 1-24, 2-74, 2-76, 2-81:2-82, 2-93, 2-106, 2-109, 2-114, 2-135, 2-202, 2-246, 3-13, 3-49, 3-64, 3-74, 3-78, 3-104:3-105, 3-154, 3-168, 3-173, 3-187:3-188, 4-19, 4-32, B-4, F-5
- Research Scientist Development Award ... 2-100, 2-243, 3-209, 3-216
- Research Subjects ... 1-29, 1-31, 3-94, 4-4, 4-7
- Research Supplements to Promote Diversity in Health-Related Research ... 2-221, 2-242
- Research Teams of the Future ... 1-12, 3-99, 3-206, C-3, C-6
- Research Workforce ... 2-221, 2-241:2-243, 2-245, 3-195:3-196, 3-198:3-199, 3-201, 3-205, 3-207, 3-219
- Research, Conditions, and Disease Categorization ... 1-5:1-6
- Resin Cements ... 2-224
- Resistance Genes ... 2-76, 2-91, 3-133
- Resistance to Antimicrobial Drugs ... 2-75:2-76
- Resource Center for Minority Aging Research ... 4-13
- Resource Centers for Minority Aging Research ... 2-247
- Resources ... 1-4, 1-12, 1-17:1-19, 1-22:1-23, 1-25:1-26, 1-31:1-32, 2-11, 2-16, 2-23, 2-27, 2-31, 2-39, 2-54, 2-56:2-58, 2-62:2-63, 2-83, 2-89:2-90, 2-93, 2-95, 2-106, 2-112, 2-123, 2-125:2-126, 2-139, 2-166, 2-169, 2-193, 2-206, 2-231, 2-235:2-236, 2-246, 3-5:3-6, 3-9, 3-34, 3-39, 3-48, 3-53, 3-75, 3-77, 3-90:3-93, 3-99, 3-101, 3-104:3-109, 3-129:3-130, 3-135, 3-137, 3-145:3-151, 3-156, 3-159, 3-161:3-162, 3-167:3-168, 3-173, 3-187:3-189, 3-200, 3-205, 3-208, 3-213, 3-222, 3-226, 3-228:3-230, 3-233, 3-243:3-244, 3-246, 4-1, 4-4:4-6, 4-9, 4-13, 4-20, 4-23, 4-36, 4-38, 4-41, 4-43, B-4, C-2, C-4, C-6:C-8, D-3, F-6
- Resources for Enhancing Alzheimer's Caregiver Health II ... 2-169
- Respiration Disorders ... 2-19, 2-116, 2-121, 2-128, 2-130, 2-143:2-144, 2-161, 2-220, 2-229, 3-21, 3-73, 3-118, 3-125, 3-132
- Respiratory Distress Syndrome, Newborn ... 2-259
- Respiratory infections ... 2-74:2-75
- Resuscitation ... 3-131, 3-157
- Resuscitation Outcomes Consortium ... 3-131, 3-157
- Resveratrol ... 3-73
- Retina ... 2-53, 2-123, 2-155:2-156, 2-160, 3-62, 3-79, 3-114, 3-138, F-6
- Retinal ... 2-53, 2-155:2-156, 2-226, 3-17, 3-79, 3-96:3-97, 3-114, 3-138
- Retinal Detachment ... 2-160, 3-138
- Retinal Diseases ... 2-53, 2-148, 2-160, 2-230, 3-25, 3-79, 3-138
- Retinopathy ... 2-18, 2-148, 2-160, 2-176, 2-230, 3-25, 3-79, 3-96, 3-138, F-5
- Retirement ... 2-189, 3-15
- Retrovirus ... 2-86, 3-21
- Retrovirus Epidemiology Donor Study ... 2-86, 3-21
- Retroviruses ... 2-100, 3-216
- Rett's Syndrome ... 2-32, 2-68, 2-260, 4-33, F-9, F-11
- Reverse Transcriptase ... 2-73
- Reye's Syndrome ... 2-260
- Rheumatic Diseases ... 2-114, 2-236:2-237, 3-241:3-242
- Rheumatoid Arthritis ... 2-103, 2-105:2-108, 2-110:2-111, 2-113:2-114, 2-117, 2-167, 3-32, 3-62, 3-147, 3-156, B-2, F-7
- Ribonucleic Acid (see RNA)
- Ricketts ... 2-224, 3-92, 3-106
- Rimonabant ... 2-60, 2-158, 3-133
- Risk Assessment ... 2-12, 2-132, 2-170, 3-22, 3-118
- Risk Reduction ... 2-88, 2-140, 2-231, 2-240, 3-18, 3-111, F-11
- Risky Behaviors ... 2-44, 2-78, 2-190, 3-11
- RNA ... 3-27:3-28, 3-50, 3-55, 3-57, 3-65, 3-69, 3-176
- RNA Virus ... 3-28
- RNA, Double-Stranded ... 3-57
- Roadmap Interdisciplinary Research Training Initiative ... 3-198
- Robert Wood Johnson Foundation ... 3-228:3-229
- Robotic devices ... 3-166
- Robotics ... 3-165, 3-171
- Rodents ... 2-143, 2-209, 3-48, 3-72, 3-101:3-102
- rosiglitazone ... 2-129, 2-161:2-162
- RSS (see Really Simple Syndication)
- Running ... 2-129, 2-133, 2-189, 3-2, 3-9, 3-32, 3-42
- Rural Communities ... 2-246
- Rural Health ... 2-237, 2-260
- Rural Population ... 2-232, 2-237, 2-239, 3-240

- Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research ... 2-221, 2-242
- Saliva ... 2-22, 2-109, 2-114, 2-135, 3-45, 3-115, 3-172, 3-183
- Salivary Gland ... F-7
- Salivary Gland Diseases ... 2-109
- SARS Virus ... 1-11, 2-74, 2-81
- Scalp ... 2-113, 3-159
- Schizophrenia ... 2-32, 2-36, 2-40, 2-58, 2-60, 2-64, 2-67, 2-130, 2-138, 2-154, 2-193, 2-260, 3-33, 3-36, 3-83, 3-95, 3-101, 3-113, 3-162, 3-189, 3-233, F-9
- Science Education ... 1-14, 1-23:1-25, 2-232, 3-240, 3-243
- Science Education Partnership Award ... 1-25, 2-232:2-233, 3-240
- Scientific Opportunity ... 1-13, 1-21, 2-89, 2-109, 2-225, A-3, C-8, F-11
- Scientific Review Group ... 1-16:1-17, B-5, E-8
- Scleroderma ... 2-106, 2-111, 2-224, 2-260, 3-92, 3-106, 4-25, 4-30, F-7
- Scleroderma, Localized ... 2-106, 2-111
- Scleroderma, Systemic ... 2-106, 2-111, F-7
- Scleroderma: Cyclophosphamide or Transplantation ... 2-111
- Screenings ... 3-229
- SEARCH for Diabetes in Youth Study ... 2-163, 2-200, 3-22, 3-119
- Seasonal Affective Disorder ... 2-64, 2-138, 2-150, 2-204, 3-47
- Seasonal Epidemics ... 2-80
- Second Cancer ... 3-58
- SEER (see Surveillance, Epidemiology, and End Results)
- Seizures ... 2-31, 2-37, 2-49, 2-62, 2-96, 2-186, 2-199, 2-207, 3-166, 3-182, 3-190, 4-37, F-9
- Senior Scientist Research and Mentorship Awards ... 3-203
- Sensation ... 2-33, 2-37, 2-63, 3-86
- Sensitivity ... 2-36, 2-50:2-51, 2-87, 2-184, 2-204, 3-61, 3-80, 3-180, 4-6
- Sepsis ... 3-133
- Septicemia ... 2-260, 3-133
- Serotonin ... 2-47, 2-133, 4-38, 4-40
- Serotonin Reuptake Inhibitors ... 2-204
- Severe Acute Respiratory Syndrome ... 1-11, 2-74, 2-81, 3-228
- Sex and Gender ... 2-95, 2-127, 2-135, 2-150, 2-167, 3-94, 3-123, F-3, F-9
- Sex Differences ... 2-44, 2-143, 2-188, 3-16
- Sex-Specific ... E-3, E-16, E-24:E-25, E-28:E-29
- Sexual Behavior ... 2-78, 2-87:2-88, 3-236, E-3, E-19
- Sexually Transmitted Diseases ... 2-75, 2-89, 2-260
- Sexually Transmitted Infections ... 2-74, F-6
- SHARe (see Framingham SNP-Health Association Resource)
- Shared Instrumentation Grant ... 3-65, 3-138, 3-190:3-191
- Shingles ... 2-76, 2-164, 3-87, 3-144
- Siblings ... 2-54, 2-108, 2-188, 3-4, 3-16, 3-156, 3-228, 4-39
- Sickle Cell Disease ... 2-63, 2-122, 2-147, 2-157, 2-161, 2-175, 2-217, 2-223:2-224, 2-260, 3-31, 3-51, 3-109, 3-114, 3-139
- Side Effects ... 2-1, 2-8, 2-13, 2-45, 2-64, 2-78, 2-90, 2-110, 2-137:2-138, 2-166, 2-168, 3-46, 3-59, 3-63, 3-66, 3-68, 3-89, 3-93:3-94, 3-102, 3-122, 3-135, 3-170, 3-193, 4-18, F-9
- Signal Pathways ... 2-17, 3-56, 3-60, 3-64
- Signal Transduction ... 2-70, 2-138, 2-197, 3-68, 3-78, 3-82, 3-188
- Sildenafil ... 2-157, 2-223, 3-114
- Silica Dust ... 2-106, 2-112, 3-11
- Silicon Dioxide ... 2-224
- Simian Immunodeficiency Virus ... 2-95, 3-106
- Single Nucleotide Polymorphisms (see Polymorphism, Single Nucleotide)
- Single Nucleotide
- Sirtuins ... 3-73
- SISTEr (see Stress Incontinence Surgical Treatment Efficacy Trial)
- Sjogren's Syndrome ... 2-109:2-110, 2-114, 2-135, 3-45
- Skeletal muscle (see Muscle, Skeletal)
- Skeletal muscle structure (see Muscle, Skeletal)
- Skin ... 2-111, 2-122, 2-136:2-137, 2-148, 3-40, 3-60, 3-82:3-83, 3-232, 3-236, 4-15
- Skin Cancers ... 2-2
- Skin Diseases ... 1-15, 2-104, 2-118, 2-122, 2-136, 2-148, 2-172, 2-176, 3-83, 3-201, 4-17, B-3, F-6
- SLE (see Lupus Erythematosus, Systemic)
- Sleep ... 1-24, 2-125, 2-133, 2-186, 2-206, 3-86
- Sleep Disorders ... 1-24, 2-33, 2-152:2-153, 2-229, 2-242, 2-260, 3-14, 3-49, 3-156, B-1
- Sling Surgical Procedure ... 2-162, 3-119
- SMA Project ... 2-40, 2-62, 3-108
- Small Business Innovation Research ... 1-24, 2-81, 3-64, 3-105, 3-188:3-189
- Small Business Technology Transfer ... 1-24, 3-64, 3-105, 3-188
- Smallpox ... 1-11, 2-73, 2-77, 2-80, 2-90, 2-92, 2-148, 2-260
- Smallpox Vaccine ... 1-11, 2-73, 2-90, 2-148, 2-260
- Smallpox Viruses (see Variola virus)
- SMART (see Strategies for Management of Anti-Retroviral Therapies)
- Smoking ... 1-10, 2-7, 2-12, 2-17:2-18, 2-25, 2-27, 2-126, 2-130, 2-140, 2-145, 2-147, 2-153, 2-163, 2-167, 2-191, 2-196, 2-198, 2-229, 2-240, 2-260, 3-2, 3-14, 3-33, 3-36, 3-82, 3-155
- Smoking and Health ... 2-260
- SNPs (see Polymorphism, Single Nucleotide)
- Social Behavior ... 2-185, 4-37
- Social Environment ... 2-42, 2-149:2-150, 2-183, 2-203, 2-218, 2-239, 2-242, 2-247, 3-4, 3-53:3-54, 3-186, 3-241, 4-30:4-31, B-3, B-6
- Social Networks ... 3-4
- Social Welfare ... 1-31, 2-24, 2-26:2-27, 2-54, 2-94, 2-128, 2-141, 2-214, 2-217, 2-219:2-221, 2-230:2-233, 2-235, 2-245, 2-247, 3-91, 3-94, 3-129, 3-142, 3-156, 3-209, 3-226, 3-229:3-233, 3-235, 3-238, 3-240, 3-244, 3-246, 4-1, 4-7, 4-24, 4-27, 4-34, B-4, E-5, E-7, F-11
- Societies ... 1-27, 2-239, 3-2, 3-6, 3-201, 3-232, F-6
- Socioeconomic Factors ... 1-12, 2-189, 2-214, 3-24
- Socioeconomic Status ... 2-44, 2-153, 2-190, 2-218, 2-229, 2-239, 3-1, 3-11, 3-14, 3-86, 3-229
- Sociology ... 2-188, 3-5, 3-16, D-4
- Sound ... 2-46, 2-50, 2-66:2-67, 2-69, 2-170, 2-210, 3-94, 3-121, 3-167:3-168, 3-174:3-175, 3-191, 3-224, 3-230, 3-234
- Spanish Flu ... 2-80, 3-34
- Spanish-Language ... 2-22, 2-219, 2-233
- Special Populations ... 2-77, 2-82, 2-101, F-10
- Specialized Center of Clinical Research ... 2-124
- Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health ... 2-127, 2-150, F-3
- Specialized Program of Translational Research in Acute Stroke ... 2-40, 2-62, 3-107:3-108
- Specialized Research and Diagnostic Centers of Excellence for Rare Diseases ... 4-32
- Spectroscopy ... 3-74, 3-104, 3-169, 3-187
- Speech ... 2-21:2-22, 2-32, 2-46, 2-67, 2-70, 2-210, 2-213, 3-81, 3-115, 3-168, 3-175, 3-221, 3-237, 4-37, B-3, F-9:F-10
- Speech-Language Pathology ... D-2
- Spina Bifida ... 2-33, 2-260
- Spinal Cord ... 2-2, 2-31:2-32, 2-37, 2-39:2-40, 2-59, 2-70, 3-68, 3-72
- Spinal Cord Injury ... 2-32, 2-37, 2-46, 2-49, 2-131, 2-155, 2-186, 2-207, 2-260, 3-60, 3-83, 3-114, 3-190
- Spinal Muscular Atrophy (see Muscular Atrophy, Spinal)
- Spine ... 2-131, 2-170, 2-256, 3-128



- Spine Patient Outcomes Research Trial ... 2-131, 2-170, 3-128
- Split-Brain Procedure ... 2-31
- Spondylolisthesis ... 2-171, 3-128
- Staphylococcal Infections ... 3-133
- Staphylococcus ... 3-133
- State-of-the-Science Conference ... 2-132, 2-168, 2-186, 2-207, B-6
- Steering Committee ... 1-31, 2-43, 2-65, 2-150, 2-203, 3-112, 3-143, 3-207, 3-241, 4-17, 4-23, 4-33:4-34
- Stem Cell Research ... 2-37, 2-260:2-261, 3-77, 3-200, 3-204
- Stem Cell Transplantation ... 2-37
- Stem Cell-Based Therapies ... 2-37, 2-95, 3-106
- Stem Cells ... 2-6, 2-19, 2-37:2-38, 2-68:2-69, 2-114, 2-135, 2-209, 2-232, 3-56, 3-60, 3-72, 3-77:3-78, 3-83, 3-91, 3-102, 3-109, 3-204, 3-240, 4-19, 4-22
- Stenosis ... 2-171, 3-128
- Stent ... 1-9, 3-190
- Stereotypic Movement Disorder ... 4-37
- Steroids ... 2-161, 3-21, 3-118, 4-18
- Stevens-Johnson Syndrome ... 3-79
- Stillbirth ... 2-43, 2-184, 2-195, 3-22
- Stillbirth Collaborative Research Network ... 2-195
- Stomach ... 2-5, 2-19, 2-47, 2-122, 2-133
- Strain ... 1-11, 2-59, 2-70, 2-77:2-78, 2-80, 2-93, 2-95:2-96, 2-98, 2-124, 3-19, 3-46, 3-50:3-51, 3-60, 3-72, 3-76, 3-78, 3-148, 3-154, 3-179
- Strategic Initiatives ... 1-14:1-15, 1-20:1-22, 2-94, A-3:A-4, B-6
- Strategic National Stockpile ... 2-90
- Strategic Partners ... 1-24, 2-77, 2-80
- Strategic Plan ... 1-4, 1-14, 1-18:1-21, 2-7, 2-25, 2-28, 2-71:2-72, 2-81, 2-100:2-102, 2-118, 2-131, 2-166, 2-171:2-173, 2-180, 2-191, 2-210:2-212, 2-214, 2-217, 2-223, 2-225, 2-245, 2-248, 3-181, 4-40:4-41, A-4, B-1, C-5, F-9, F-11
- Strategic Plan and Research Agenda on Medical Countermeasures Against Chemical Threats ... 2-81
- Strategic Plan to Combat Health Disparities ... 2-223
- Strategic Planning ... 1-3, 1-6:1-8, 1-14, 1-19:1-23, 2-71, 2-171:2-172, B-1, B-6, C-1:C-2
- Strategies for Management of Anti-Retroviral Therapies ... 3-97, 3-117
- Streptococcus Sanguis ... 2-83, 3-40
- Stress ... 2-52, 2-164, 2-185, 2-199, 2-206, 2-213, 3-31, 3-33, 3-128, 3-172, 3-186
- Stress Disorders, Post-Traumatic ... 2-32, 2-48, 2-127, 2-147, 3-120, F-9
- Stress Incontinence Surgical Treatment Efficacy Trial ... 2-162, 3-119
- Stroke ... 1-9, 1-15, 2-2, 2-32:2-33, 2-38, 2-40, 2-48, 2-58, 2-60, 2-62, 2-65:2-66, 2-68:2-69, 2-71, 2-121, 2-123, 2-153, 2-180, 2-182, 2-184, 2-186, 2-193, 2-208:2-209, 2-215, 2-218:2-219, 2-229, 2-232, 2-238, 2-261, 3-3, 3-14, 3-32, 3-58, 3-107:3-109, 3-155, 3-166:3-167, 3-172, 3-221:3-222, 3-227, 3-242, 4-3, 4-7, 4-10, 4-13:4-14, 4-25:4-26, 4-30, B-2, F-9
- Stroke Champions ... 2-68, 2-219, 2-238, 3-242
- Stroke, Acute ... 3-108
- Student Recruitment and Retention ... 2-245
- Studies to Advance Autism Research and Treatment ... 1-6, 4-2, 4-36:4-40, 4-46
- Study of Osteoporotic Fractures ... 2-127, 2-141, 3-9
- Study of Tamoxifen and Raloxifene ... 2-8, 2-13, 2-221, 2-241, 3-135
- Study of Women's Health Across the Nation ... 2-188, F-10
- Stuttering ... 2-70, 3-61, 3-81
- Sub-Saharan Africa ... 2-60, 2-75, 2-193
- Substance Abuse ... 2-42:2-43, 2-123, 2-150, 2-164, 2-167, 2-184:2-185, 2-190, 2-228, 2-261, 3-10:3-11, 3-44, 3-96:3-97, 3-128, 3-134, 3-141, 3-157, 3-184, 3-228, F-3, F-11
- Substance Abuse, Intravenous ... 2-84, 2-88, 2-226, 3-124
- Substance Use Disorders ... 2-67, 2-141, 2-227, 3-19, 3-120
- Substance-Related Disorders ... 2-23, 2-25, 2-27, 2-42, 2-45, 2-47, 2-50, 2-54, 2-119, 2-128, 2-149:2-150, 2-177, 2-203, 3-4, 3-14, 3-43, 3-76, 3-80, 3-126, 3-132, 3-241, 3-244
- Sudden Infant Death Syndrome ... 2-43, 2-184, 2-195, 2-210, 2-231, 2-261, 3-22, 3-231
- Suicide ... 2-67, 2-163, 2-185, 2-204, 2-216, 2-261, 3-120
- Summer Genetics Institutes ... 3-215
- Summer Training Institute in Genes, Environment and Behavior Research ... 3-54
- Surgeon General ... 2-42, 2-119, 2-147, 2-150, 2-203, 3-51, 3-228, 3-237, 3-241, 4-10
- Surveillance, Epidemiology, and End Results ... 2-2, 2-11, 2-26:2-27, 3-147, 3-149, 3-158
- Surveys ... 2-85, 2-218, 2-229, 3-4:3-5, 3-13, 3-17, 3-91
- Survivors ... 2-1, 2-4, 2-10:2-11, 2-17, 2-20, 2-25, 2-192, 2-208, 2-220, 2-231, 3-166
- Survivorship ... 2-6, 2-12, 2-184
- Sustained Release ... 2-226
- Sutures ... 2-197, 3-82, 3-189
- Swallowing ... 2-22, 3-115
- Symbiosis ... 2-138
- Synostosis ... 2-197, 3-82
- Systematic Treatment Enhancement Program for Bipolar Disorder ... 3-97
- Systemic Lupus Erythematosus (see Lupus Erythematosus, Systemic)
- Systemic Lupus Erythematosus Biomarkers Working Group ... 2-109
- Systemic Scleroderma (see Scleroderma, Systemic)
- T-Cells ... 3-77
- Tai Chi Chuan ... 2-164, 3-62, 3-87, 3-144
- Take Care of Yourself (see ¡Cuidate!)
- Tamoxifen ... 2-8, 2-13, 2-24, 3-12, 3-129, 3-135
- Tarsal Bones ... 2-230
- Task Force ... 1-20, 1-30, 2-7, 2-25, 2-149, 2-191, 2-203, 3-14, 3-77, 3-244, E-5
- Task Force on College Drinking ... 2-149, 2-203, 3-14, 3-244
- Taste Buds ... 2-69, 3-67
- Taste Disorders ... 2-69, 3-67
- Taurine ... 4-41
- TB Research Agenda ... 2-77
- TB Vaccines ... 2-77
- Technology Development ... **3-165:3-193**, 1-4:1-5, 1-7, 2-2:2-3, 2-11, 2-13, 2-15:2-16, 2-20:2-21, 2-42, 2-46, 2-49, 2-67, 2-91, 2-97, 2-132, 2-139, 2-151, 2-156, 2-196:2-197, 2-200, 2-208:2-210, 3-37:3-38, 3-41, 3-44, 3-50:3-51, 3-59, 3-64:3-66, 3-70:3-71, 3-74:3-75, 3-84, 3-92, 3-104:3-105, 3-111, 3-125, 3-138, 3-141, 3-157, 3-161:3-162, A-5, C-3
- Technology Transfer ... 1-14, 1-18, 1-23:1-24, 3-64, 3-105, 3-188, 4-3
- Teen-LABS ... 2-130, 2-162, 2-201, 3-119
- Teenage Pregnancy ... 2-261, 3-141
- Teens (see Adolescent)
- Teeth ... 2-123, F-7
- Telecommunications ... 3-171
- Telemedicine ... 2-40, 3-171
- Telepathology ... 3-171
- Telephone ... 2-26, 2-169, 3-236, 3-238
- Television ... 2-141, 2-234, 3-222, 3-229, 3-233, 3-235
- Temperature ... 2-32, 4-13
- Temporomandibular Joint ... 2-123, 2-209, 3-22, 3-72, 3-102, 3-118, F-7:F-8
- Temporomandibular Muscle/Joint Disorder ... 2-123, 2-261, F-7
- Terminal Care ... 2-168, 2-207
- Tetrachlorodibenzodioxin ... 2-249:2-250
- Thalassemia ... 2-175
- Thrombosis ... 3-108
- Thyroid Diseases ... F-8

- Tissue Engineering ... 2-125, 2-132, 2-208:2-209, 3-57, 3-71:3-72, 3-102, 3-111, 3-173, 3-186, 3-188:3-189, F-7
- Tissue Plasminogen Activator ... 2-62, 2-66, 2-232, 3-108
- TMJ (see Temporomandibular Muscle and Joint)
- TMJD (see Temporomandibular Muscle/Joint Disorder)
- TNF- $\alpha$  (see Tumor Necrosis Factor alpha)
- Tobacco ... 1-10, 2-3, 2-7:2-8, 2-12, 2-17:2-18, 2-24:2-25, 2-27, 2-119, 2-145, 2-147:2-148, 2-177, 2-191, 2-261, 3-1, 3-12, 3-98, 3-129
- Tobacco Cessation ... 2-24, 3-12, 3-129
- Tobacco Use ... 1-10, 2-7, 2-12, 2-25, 2-27, 2-119, 2-147, 2-191, 3-1, 3-98
- Tobacco Use Disorder ... 2-7, 2-12, 2-23, 2-47, 2-177, 3-1, 3-33, 3-43, 3-132
- Tobacco Use Research Centers ... 2-7, 2-25, 2-27, 2-147, 2-191
- TODAY (see Treatment Options for Type 2 Diabetes in Youth)
- Tongue ... 2-21, 2-69, 3-22, 3-67, 3-118
- Tonsils ... 2-21
- Tooth ... 2-115, 2-137, 3-69
- Tooth Decay ... 2-83, 3-40
- Tooth Loss ... 2-115, 2-123:2-124, 2-137, 3-59, 3-69
- Tooth Mobility ... 2-123
- Topical Microbicides ... 2-249, 2-262
- Tourette Syndrome ... 2-32, 2-262
- Tox Town ... 3-234
- Toxicology ... 2-56, 3-93, 3-98, 3-109, 3-126, 3-146, 3-148, 3-153, 3-234, B-5, D-2, F-8
- Toxicology Data Network ... 3-148, 3-153
- TOXNET (see Toxicology Data Network)
- Tracks ... 3-4
- Traditional Chinese Medicine ... 2-164, 3-85, 3-87, 3-131, 3-144, F-5
- Training Outcomes ... 3-202, 3-218
- Training Programs ... 1-6, 2-57, 2-99, 2-242:2-244, 3-131, 3-134, 3-157, 3-162:3-163, 3-197, 3-199:3-200, 3-203, 3-205:3-208, 3-210:3-212, 3-214:3-216, 3-218, 4-15, 4-34:4-35, A-5, A-7, B-5, F-4, F-7
- Trans-Institute Angiogenesis Research Program ... 2-6, 2-18
- Trans-NIH Initiative for Translational Research in Immunology, Autoimmunity, and Inflammation ... 2-115, 3-110
- Transdisciplinary Research ... 2-6:2-7, 2-25, 2-191
- Transdisciplinary Research on Energetics and Cancer ... 2-7, 2-25, 2-191
- Transforming Growth Factor Beta ... 2-165, 3-80, 3-121, 4-21
- Transfusion of Blood Products (see Blood Transfusion)
- Translation, Genetic (see Protein Biosynthesis)
- Translational Research ... **3-89:3-144**, 1-4, 1-7, 1-20, 1-23, 2-1, 2-10, 2-13:2-17, 2-20:2-26, 2-32, 2-37, 2-39:2-40, 2-46:2-48, 2-52:2-53, 2-55:2-58, 2-60, 2-62:2-67, 2-69, 2-74, 2-84, 2-86:2-87, 2-91, 2-93, 2-95, 2-98:2-99, 2-112, 2-115:2-117, 2-128, 2-138, 2-140, 2-144:2-147, 2-152, 2-154:2-166, 2-168, 2-170:2-171, 2-195, 2-198, 2-200:2-201, 2-204, 2-209, 2-217, 2-223:2-225, 2-227, 2-229, 2-235:2-237, 2-239, 2-246:2-247, 3-3, 3-13, 3-15, 3-18, 3-21:3-23, 3-43, 3-45, 3-47:3-48, 3-53, 3-64:3-66, 3-71:3-73, 3-75, 3-80, 3-85, 3-87, 3-153, 3-157, 3-163, 3-183, 3-187:3-189, 3-191:3-193, 3-195, 3-198, 3-205, 3-207:3-209, 3-212, 3-215, 3-233, 3-244:3-246, 4-1, 4-10, 4-23, 4-33, A-5, B-4, C-1, C-3, C-6:C-7, F-3
- Translational Research Working Group ... 2-26, 3-143
- Transmissible Spongiform Encephalopathy ... 2-68, 2-74, 2-262
- Transplant ... 2-37
- Transplant Rejection ... 2-130
- Transplantation ... 2-110:2-112, 2-116, 2-118, 2-120, 2-122, 2-130, 2-158:2-159, 2-163, 2-172:2-173, 2-258, 2-262, 3-71, 3-107, 3-132, 3-134, 4-31, B-2
- Transplantation, Homologous ... 2-116, 2-157, 3-103
- Transplantation, Islet ... 2-110, 2-130, 2-163
- Trauma ... 2-5, 2-19, 2-32, 2-48, 2-127, 2-147, 2-208:2-210, 2-256, 3-72, 3-102, 3-111, 3-120, 3-131, 3-157, 3-171, 3-182, 3-189, 3-200, 3-212:3-213, F-6
- Traumatic Brain Injury ... 2-32:2-34, 2-48:2-49, 2-256, 3-95, 3-130
- Treacher Collins Syndrome ... 2-197, 3-72
- Treatment Effectiveness ... 2-28, 2-58, 2-154, 2-162, 3-92, 3-95, 3-113, 3-119
- Treatment Efficacy ... 2-28, 2-162, 3-119
- Treatment Options for Type 2 Diabetes in Youth ... 2-130, 2-163, 2-200, 3-22, 3-119
- Treatment utilization ... 2-141, 2-227, 3-19
- Trial to Reduce the Incidence of Type 1 Diabetes for Those Genetically at Risk ... 2-142, 2-199
- TrialNet (see Type 1 Diabetes TrialNet)
- Tribal Epidemiology Centers Program ... 2-235
- Trichomonas vaginalis ... 2-77
- tropical diseases ... 2-78
- Trypanosomiasis ... 2-78
- Tuberculosis ... 1-11, 2-38, 2-46, 2-50, 2-61, 2-73:2-78, 2-82, 2-88:2-90, 2-100:2-101, 2-119, 2-172, 2-193, 2-201, 2-262, 3-39, 3-80, 3-84, 3-96, 3-134:3-135, 3-179, 3-200, 3-208, 3-211:3-212, 3-240, B-2
- Tuberculosis Vaccine ... 2-100, 2-262
- Tuberous Sclerosis ... 2-32, 2-69, 2-72, 2-262, 3-109
- Tumor ... 2-19, 3-169
- Tumor Microenvironment Network ... 2-5, 2-17, 3-64
- Tumor Necrosis Factor alpha ... 2-56, 2-125, 2-136:2-137
- Tumor Stem Cells ... 2-6, 2-19
- Turmeric ... 2-136, 3-62, 3-87
- Twins ... 2-198, 3-115
- Type 1 Diabetes (see Diabetes Mellitus, type 1)
- Type 1 Diabetes Genetics Consortium ... 2-108
- Type 1 Diabetes TrialNet ... 2-128, 2-147
- Type 1 Diabetes-Rapid Access to Intervention Development ... 2-106, 2-111, 3-107
- Type 2 Diabetes (see Diabetes Mellitus, type 2)
- Typhoid Fever ... 2-119
- Tyrosinemia ... 2-196, 3-185
- U-STAR (see Undergraduate Student Training in Academic Research)
- U.S. COPD Coalition ... 2-156, 3-235
- U.S. Surgeon General's Family History Initiative ... 2-147, 3-51
- U.S.-Born Children of Immigrants ... 2-230, 3-25
- Ulcerative Colitis ... 2-122, 2-129, 2-161:2-162
- Umbilical Cord Blood ... 2-261
- Underage Drinking Research Initiative ... 2-42, 2-128, 2-149, 2-203, 3-228, 3-241
- Undergraduate Scholarship Program ... 2-221, 2-244
- Undergraduate Student Training in Academic Research ... 2-221, 2-241, 3-199
- Underserved Population ... 2-14, 2-20, 2-22, 2-27, 2-213, 2-219:2-220, 2-231, 2-233, 2-236, 2-240, 3-240, F-9
- Understanding and Promoting Health Literacy ... 2-221, 2-239, 3-141, 3-245
- Unified Medical Language System ... 1-21, 1-26, 2-103, 2-185, 3-150, 3-160, F-3
- United Nations ... 2-82
- United States Agency for Healthcare Research and Quality ... 3-137
- United States Centers for Medicare and Medicaid Services ... 2-11, 2-158, 3-116
- United States Department of Health and Human Services ... 1-10, 1-19, 1-29:1-33, 2-7, 2-80:2-81, 2-90:2-93, 2-147, 2-

- 151, 2-214, 2-221, 2-225, 2-234, 2-236, 2-239, 2-242, 2-247, 3-37, 3-51, 3-91, 3-106, 3-137, 3-141, 3-160, 3-177, 3-192, 3-229:3-230, 3-245, 4-36, 4-41, C-1:C-2, E-2, F-2
- United States Food and Drug Administration ... 1-10, 1-24, 1-29:1-30, 2-7:2-9, 2-15, 2-17, 2-22, 2-40, 2-60, 2-62, 2-73, 2-86, 2-93, 2-96, 2-133, 2-145, 2-150, 2-158, 3-79, 3-89, 3-93:3-94, 3-96, 3-104, 3-108, 3-115, 3-120, 3-123, 3-133, 3-136, 3-153, 3-157, 3-160, 3-189, 4-33
- United States Health Resources and Services Administration ... 2-147, 2-236, 3-51, 3-137
- United States Public Health Service ... 1-3, 1-6, 1-16, 1-24, 1-28, 1-31:1-32, 2-221, 2-244:2-245, 3-199, 4-3, 4-10, A-1:A-2, A-5, A-7, B-5, E-5, E-7
- United States Substance Abuse and Mental Health Services Administration ... 3-97
- University Informatics Research Training Programs ... 3-163, 3-215
- Urinary Incontinence Treatment Network ... 2-162, 3-119
- Urinary Tract Infection ... 2-95, 2-122, 2-135, 2-175, F-8
- Urolithiasis ... 2-171
- Urologic Diseases ... 2-122, 2-175, 2-262, 4-10
- Uterine Cancer ... 2-262
- Uterine Cervical Neoplasms ... 2-2, 2-7, 2-17, 2-24, 2-28, 2-86, 2-255, 3-12, 3-25, 3-89, 3-129, 3-136, 3-154, 4-28
- Uterine Fibroids ... 2-137, F-8
- Uterus ... 2-137, F-8
- UTIs (see Urinary Tract Infection)
- Uveitis ... 2-123, 2-129, 2-156, 2-176, 3-114, F-5
- Vaccination ... 2-91, 2-93, 2-148, 2-164, 3-1, 3-87, 3-144, 3-192
- Vaccine Research Center ... 2-79, 2-100, 2-172
- Vaccine Therapy ... 2-19, 2-67
- Vaccines ... 1-10, 2-7, 2-17:2-18, 2-23, 2-47, 2-73:2-81, 2-83:2-86, 2-88, 2-90:2-93, 2-95, 2-97:2-99, 2-148, 2-191, 2-255, 2-262, 3-7:3-8, 3-19, 3-24, 3-28, 3-43, 3-56, 3-61, 3-76, 3-89, 3-92, 3-106, 3-116, 3-132, 3-136, 3-148, 3-192, F-11
- Vaccines, Attenuated ... 2-93
- Vaccinia ... 2-90
- Vaccinia virus ... 2-148
- Vagina ... 3-40
- Vaginal Delivery Procedure (see Delivery, Obstetric)
- Vaginal Smears ... 2-28, 3-25, 3-154
- Variola Virus ... 1-11, 2-73, 2-90, 2-92, 2-260
- Vascular Diseases ... 2-125, 3-79
- Vertebrate ... 3-29
- Vestibulocochlear Nerve ... 2-46, 2-210, 3-174
- Veterinarian ... 1-32, 3-100, 3-136
- Veterinary Medicine ... 1-32, D-3
- Violence ... 2-262, 3-233
- Violence Research ... 2-262
- Viral Diseases ... 2-18, 2-86
- Viral Hepatitis ... 2-122, 2-175
- Virulence ... 2-92, 2-96, 2-135, 3-51, 3-78, 3-154
- Viruses ... 1-23, 2-1:2-2, 2-73:2-74, 2-77, 2-80:2-81, 2-83, 2-86, 2-95, 2-100, 2-122, 2-225, 3-21, 3-29, 3-34, 3-39, 3-61, 3-76, 3-179, 3-216
- Vision Disorders ... 2-226, 3-17, F-5
- Vision impairment ... 2-181, 3-17
- Vision, Low ... 3-17, 3-235, B-2, F-5
- Visual Impairment (see Vision, Low)
- Visual Perception ... 2-67, 3-83, 4-39
- Vitamin C ... 3-191
- Vitamin D ... 3-191:3-192
- Vitamin E ... 2-129:2-131, 2-160, 2-165, 2-193, 3-121
- Vitamins ... 1-9, B-6
- Vitiligo ... 2-111, 2-117, 2-226
- Viverridae ... 3-43
- Vocabulary ... 1-26, 3-160, 4-34
- Voice ... 2-21, 3-229, 3-237, B-3, F-10
- von Willebrand Disease ... 2-122
- Walter Reed Army Institute of Research ... 2-84
- Warren Grant Magnuson Clinical Center ... 1-25
- Watson, James ... 3-27
- Ways to Enhance Children's Activity & Nutrition ... 2-128, 2-141, 3-235
- Weaning ... 2-142, 2-199
- Web sites ... 1-4:1-5, 1-14, 2-234, 3-152, 3-222, 3-224, 3-228, 3-234, 4-21, 4-28, B-1
- WeCan! (see Ways to Enhance Children's Activity & Nutrition)
- Weight Gain ... 2-140, 3-36, 3-155
- Weight Loss ... 2-128, 2-144, 2-221, 2-235, 3-96, 3-116, 4-10, 4-14
- Weight-Control Information Network ... 2-231, 3-235
- Wellstone Muscular Dystrophy Cooperative Research Centers ... **4-17:4-23**, 1-6:1-7, 2-39, 2-55, 3-108, 3-112, 4-2, 4-43
- West Nile Virus ... 2-74, 2-92, 2-262
- Wheezing ... 2-161, 3-21, 3-118
- WHI (see Women's Health Initiative)
- White ... 1-28, 2-49, 2-65, 2-84, 2-111:2-112, 2-141, 2-148, 2-214:2-216, 2-218, 2-225:2-227, 2-229:2-232, 2-240, 2-247, 3-11, 3-13, 3-17, 3-19, 3-25, 3-124, 3-199, 3-201, 3-231, 4-25:4-26, 4-28, E-9:E-10, E-15:E-18, E-34, E-37, E-40, E-44, E-46
- White (Hispanic) ... E-10
- WHO (see World Health Organization)
- WHO Initiative for Vaccine Research ... 2-83
- Whole-Genome Sequencing ... 2-82, 2-151, 3-40, 3-176
- Wireless Information System for Emergency Responders ... 2-96:2-97, 3-147:3-148, 3-185
- Woman ... 3-115, 3-165, 4-3
- Women ... 1-4, 1-6, 1-8, 1-10, 1-15, 2-2:2-3, 2-5, 2-7:2-8, 2-13, 2-15:2-18, 2-23:2-24, 2-43, 2-61, 2-79, 2-85:2-87, 2-90, 2-95, 2-97, 2-101, 2-103:2-104, 2-118, 2-127:2-128, 2-133, 2-135, 2-137, 2-140:2-141, 2-143, 2-150, 2-162, 2-166:2-167, 2-175:2-176, 2-183:2-185, 2-188:2-196, 2-198, 2-215, 2-217, 2-219, 2-225, 2-231, 2-234, 2-241, 2-248, 2-262, 3-3:3-4, 3-9:3-10, 3-12, 3-22:3-24, 3-42, 3-82, 3-89, 3-94:3-95, 3-115:3-116, 3-119, 3-122:3-123, 3-129:3-130, 3-135:3-136, 3-149, 3-171, 3-196, 3-199, 3-203, 3-205, 3-210, 3-215, 3-222, 3-226:3-227, 3-230:3-231, 3-236, 3-238:3-239, 4-13, 4-15, 4-18, 4-26, 4-28:4-29, A-5, B-1, B-6:B-7, E-1:E-8, E-12, E-14:E-19, F-1:F-11
- Women's Health ... 1-4, 1-6, 1-8, 1-15, 2-2, 2-61, 2-95, 2-101, 2-118, 2-127, 2-133, 2-135, 2-143, 2-150, 2-166:2-167, 2-188, 2-194, 2-248, 2-262, 3-3, 3-9, 3-42, 3-123, 3-149, 3-203, 3-205, 3-210, 3-215, 3-226, 3-230, 3-238, 4-13, B-1, B-6:B-7, E-2, E-5:E-6, F-1:F-8, F-10:F-11
- Women's Health and Aging Study ... F-10
- Women's Health and Functional Visceral Disorders Center ... 2-143
- Women's Health in the U.S.: Research on Health Issues Affecting Women (2004) ... 2-101, 2-118, 2-248
- Women's Health Initiative ... 2-2, 2-133, 3-3:3-4, 3-9, 3-42, 3-149, B-1, F-10
- Women's Health Initiative Study of Cognitive Aging ... F-10
- Women's Health Postdoctoral Fellowship ... 3-205
- Women's Health Special Interest Group ... 3-210
- Women's Interagency HIV Study ... 2-97, 2-191, 3-24, 3-116
- Women's Reproductive Health Research Career Development Centers ... F-3
- Women's Reproductive Health Research Career Development Program ... 2-194, 3-215
- Workforce development ... 2-222
- World Health Organization ... 2-82:2-83, 2-210, 3-213, 3-227, 3-239
- Wound ... 3-66, 3-193

Wound Healing ... 2-115, 2-122, 2-136:2-137, 3-69, 3-102, 3-190  
Wounds and Injuries ... 2-48, 2-52, 2-81, 2-93, 2-122, 2-136:2-137, 2-184, 3-66, 3-160, 3-193, 3-216  
X-rays ... 2-8, 3-178, F-7  
XDR-TB ... 2-76:2-77

Xerostomia ... 2-22, 3-115  
xTrain ... 3-202  
Yoga ... F-5  
Zidovudine ... 2-73  
Zinc ... 2-53, 2-61, 2-160, 2-193, 3-117  
Zoology ... D-2

