THE NATIONAL CANCER INSTITUTE

The Nation's Investment in Cancer Research

A BUDGET PROPOSAL FOR FISCAL YEAR 2000

Prepared by the Director
National Cancer Institute

National Institutes of Health

The Bypass Budget communicates the needs and plans of the National Cancer Institute, in accordance with the legislative mandate contained within the National Cancer Act of 1971 [Public Law 92-218, Sec. 407 (b)(9)(A)]. This budget request is provided directly to the President in the Fall of each year as he formulates his budget request to the Congress for the entire Federal government and more specifically for cancer research. The amount exhibited within the President's Budget may differ from the level included in this document. The Congress, through the appropriations process, is empowered to determine the final funding amount that is appropriated to the National Cancer Institute.

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Director's Message

When our children and grandchildren look back at the late twentieth century, it is certain that they will view it as a Golden Age of scientific discovery, and as an era in which we finally began to unravel the deadly mysteries of cancer. Thirty years ago, Peyton Rous noted in his Nobel Lecture that, despite more than 70 years of intensive study, cancer was a poorly understood disease. As such, physicians could offer little to patients who were battling it. Today — only three decades later — Dr. Rous would be amazed at the impressive body of knowledge we have gathered about this disease. The revolution in molecular biology and genetics, along with the emergence of powerful new technologies, are allowing us to identify the circuits in a cell that go awry in cancer, to explain how a tumor cell behaves, and to determine how this abnormal cell can prosper, evading the body's natural defenses. This basic knowledge about the nature of cancer is providing us with critical insights into how we can prevent and detect cancer more effectively. And, it is giving us the opportunity to improve treatment by designing therapies that target the machinery of a cancer cell.

Our Nation is making progress in the fight against cancer, thanks in large measure to the dedication of legions of scientists devoted to eradicating this stubborn set of diseases. Between 1990 and 1995, our cancer incidence and death rates dropped significantly, reversing an almost 20-year trend of increasing cancer cases and deaths in the United States. This encouraging trend continued in 1996. Indeed, the incidence rate for all cancers combined declined an average of nearly 1 percent per year between 1990 and 1995. These welcome trends were seen for most age groups, for both men and women, and for most racial and ethnic groups. The exceptions were black males, in whom the rates continued to increase, and Asian and Pacific Islander females, in whom the rates were level. And, these exciting statistics do not capture the prolonged survival and improved quality of life experienced by many of the millions of cancer survivors in this country.

These promising declines indicate to us that our efforts are bearing tangible fruit. Nonetheless, we recognize that we have a long way to go. We desperately need better prevention, detection, and treatment strategies, so that this trend, while encouraging, is accelerated and extended so that all Americans benefit.

How can we continue to build on our recent accomplishments to reduce the burden of cancer — or even eliminate it from the lives of most Americans? First, we must sustain the proven research programs that have enabled us to pursue a path of scientific excellence and discovery in cancer research. At the National Cancer Institute, we have created an infrastructure that promotes discovery, worked with some

of the most innovative and productive scientists in the Nation, and initiated ground-breaking programs that have yielded critical knowledge, improved patient care, saved lives, and improved the quality of life for many cancer survivors. We must continue to offer these programs our full measure of support.

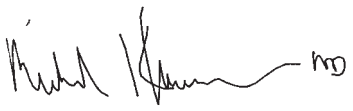
At the same time, we cannot hesitate to seize extraordinary opportunities to further the progress that is brought about by our previous research successes. Two years ago in this document, we identified four areas of investment that, if exploited, could produce dramatic progress against cancer. I am pleased that we can highlight in this year's Bypass Budget the exciting research programs that we have initiated in each of these areas and the progress that we are making as a result of these efforts.

Finally, we must ensure that the full promise of our research findings is realized by creating and sustaining mechanisms that will allow us to rapidly translate our findings from the laboratory into practical solutions that will benefit everyone. To meet this challenge, NCI is pursuing a plan that creates bridges between all components of the cancer research enterprise. These bridges will ensure that we close the gap between scientific discovery and cancer care.

In our efforts to improve our research programs, to identify and exploit promising investment opportunities, and to determine how best to build our translational bridges, we have tapped hundreds of individuals for advice and review. We have reviewed and examined virtually all of our research programs and have acted to reform those programs to best meet the needs and opportunities in cancer control and behavior, cancer prevention, clinical trials, cancer centers, our intramural research program, cancer therapeutics, and cancer communication. In this document, we describe new funding mechanisms for a variety of programs, including those for research, technology, and training; for development of animal models of cancer; and for offering researchers rapid access to the development of cancer interventions.

This document describes the budget we believe will be needed to fund our research, training, and communications programs; and serves as our central planning document, laying out clearly our funding priorities. Through it, we have tried to fulfill one of NCI's critical responsibilities — to communicate fully the needs and plans of the Institute and to articulate a vision for the direction of this Nation's Cancer Research Program.

Anyone who has ever battled cancer, or lost a loved one to the disease, knows the frustration and heartbreak cancer causes to countless families each year. But now, as we enter a new millennium, we can truly say that change is imminent — indeed, it is happening. This budget represents the investment needed to take the next crucial steps toward the day when cancer is no longer a burden. It is an investment in the future — a future in which we, and our children and grandchildren, no longer need to live in dread of cancer.



Richard D. Klausner, M.D.
Director, National Cancer Institute

Table of Contents

Overview

Cancer is a disease that must be conquered — the health of our Nation depends on this. At the National Cancer Institute (NCI), we are leading our Nation's fight against this challenging disease, supporting and conducting groundbreaking research on all aspects of the cancer problem. This research — in cancer biology, cause, prevention, detection, treatment, and survivorship — is moving us ever closer to reaching our ultimate goal: preventing and curing all forms of cancer.

In charting a course toward this goal, NCI has developed a plan to:

1. Sustain at full measure our proven research programs that have enabled us to come this far;
2. Seize extraordinary opportunities to further progress made possible by our previous research discoveries; and,
3. Create and sustain mechanisms that will enable us to meet the challenge of rapidly translating our findings from the laboratory into practical applications.

The Bypass Budget is an integral part of this plan, communicating the needs, objectives, and pursuits of the Institute and elaborating a vision for the direction

What's inside

Infrastructure mechanisms yield results:

- **Harnessing new technologies to meet the needs of cancer researchers is the aim of two new programs.** The Phased Innovation Award, which supports technology research from inception to full-scale development, and the Unconventional Innovation Program, which focuses on high-impact, long-range opportunities, will give scientists the tools they need to meet extraordinary research opportunities.
see p.21

- **NCI's new strategic plan for training and career development of basic, clinical, and population scientists is designed to support researchers throughout their careers.** These strategies focus on attracting the best young scientists into cancer research and on providing stability and protected time for those disciplines critical to the translational research enterprise.
see p.29

of the Nation's Cancer Research Program. Through it, we articulate our research activities, describe the resources needed to support our research, training, and communications programs, our vision of extraordinary opportunities for investment, the challenges that we must meet in order to translate rapidly and efficiently discoveries from the laboratory to medical practice, and the infrastructure that underlies all of our initiatives.

All of NCI's pursuits — our research programs, extraordinary opportunities, and challenges — are interdependent and supported by our infrastructure. Recent scientific breakthroughs have laid the foundation for our extraordinary opportunities. In turn, our investment in these opportunities has helped to redirect and shape many of our current research efforts and many of our current research results will serve as the basis for future extraordinary opportunities. Through all of these research activities we continually generate important findings that must be converted into advances in cancer prevention and treatment. The challenge section of this document identifies the steps that we need to take to accomplish this translation.

SUSTAIN AT FULL MEASURE OUR PROVEN RESEARCH PROGRAMS THAT HAVE ENABLED US TO COME THIS FAR.

NCI'S Research Programs:
In support of the entire community of cancer researchers, NCI has developed research programs supported by an infrastructure for discovery composed of support mechanisms, organizations, and networks that link scientists, facilities, and information. This is the underpinning for activities that encompass all aspects of cancer prevention, detection, diagnosis, treatment, control, and survivorship. Each year, the efforts of thousands of scientists in the extramural and intramural communities supported by our infrastructure yield scientific advances in all areas of cancer research. Our infrastructure supports basic, translational, and clinical cancer research. In addition, it is an investment in new research programs to address the needs of cancer patients and survivors, and to support cancer centers, community-based clinical oncology programs and specialized programs of research excellence, training and education opportunities, and communicating research results to our constituents.

We have made important progress against cancer through research supported by our infrastructure. However, as long as people continue to struggle with this disease, our work is not done. Many questions

- Forming consortia to share resources, techniques, and data necessary to gain new insights and generate new cancer research questions is the objective of a **new, innovative pilot known as Activities to Promote Research Collaborations. Through this initiative, NCI-funded laboratories around the country can apply for supplemental resources and are encouraged to collaborate with communities that have not traditionally been involved in cancer research, or to work with individuals in multidisciplinary fields.**
see p.19

- A new international agreement will **improve the ability of NCI's Cooperative Groups to collaborate with the European Organization for Research and Treatment of Cancer and other international cancer research groups.** The agreement, created to strengthen the protection of patients in international clinical trials, will help speed the transfer of laboratory findings to clinical practice.
see p.28

still must be fully answered before we can conquer cancer. In light of this, NCI is pursuing a myriad of research activities aimed at answering the central questions of cancer research. These questions and their related research, discussed in the NCI publication, *NCI's Research Programs: Pursuing the Central Questions of Cancer Research*, cover the whole scope of the cancer research field, from understanding how a normal cell becomes cancerous, to monitoring the effects of cancer on our population, to learning about the causes of cancer and how it spreads within the body, to developing the best methods of detection and prevention, to creating effective treatments, and to improving survivors' lives.

SEIZE EXTRAORDINARY OPPORTUNITIES TO FURTHER PROGRESS MADE POSSIBLE BY OUR PREVIOUS RESEARCH DISCOVERIES

Extraordinary Opportunities for Investment: In 1996, NCI began a systematic examination of the field of cancer research to identify areas where focused efforts and increased resources could produce dramatic progress toward reducing the burden of cancer. Through this effort, we selected four areas of extraordinary opportunity for investment. Our pursuit of these opportunities is providing profound insights into how cancer develops and progresses, paving the way for new techniques to prevent, detect, diagnose, and treat the disease.

Cancer Genetics. The most direct and theoretically the most effective approach to preventing, detecting, diagnosing, and treating cancer is to identify and characterize the genes involved in the development of cancer and modulate their function. In the past year, we have taken several steps toward achieving this goal by:

• Launching the Cancer Genetics Network, a program that will link centers that test, monitor, and counsel individuals for genetic susceptibility, evaluate genetic and environmental factors that contribute to cancer, and speed the application of findings for clinical use.

• Establishing cooperative family registries for colon, breast, and ovarian cancers to provide researchers with information they need to study the inherited genetic mutations that predispose individuals to developing these cancers.

• Starting the Genetic Annotation Initiative, a large effort to develop a comprehensive catalog of variations in the DNA sequences of each cancer-related gene.

Preclinical Models of Cancer. To understand how a cancer gene disrupts the normal processes of a cell, we need to manipulate genes in a living system and then study the biological effects of the alterations that have been introduced. Obviously, such research cannot be done in humans. Rather, we need to develop and use experimental models that mimic the wide variety of human cancers. The scarcity of these models has been

What's inside

Progress in pursuing our Extraordinary Opportunities for Investment:

- **The Cancer Genetics Network** has been launched and will link participating centers that test, monitor, and counsel individuals for cancer susceptibility. **The network will serve as a resource for collaborative investigations exploring the genetic basis of cancer susceptibility.**
see p.45
- **The Cancer Genome Anatomy Project (CGAP)** is an effort to uncover all cancer-related genes found in normal, precancerous, and cancerous human cells. **To date, more than 11,800 new genes have been found and 302,500 sequences entered in CGAP's public database,** the Tumor Gene Index.
see p.64
- Accelerating the discovery of genes and gene pathways involved in human cancer by discovering those of the mouse is the aim of the **Mouse Cancer Genome Anatomy Project (m-CGAP). This effort parallels that of CGAP**

a major roadblock to cancer discoveries. New technologies and recent scientific advances are now enabling us to develop useful preclinical models. Our progress in this pursuit this year includes:

• Launching the Mouse Cancer Genome Anatomy Project, a large initiative that will accelerate the discovery of genes and gene pathways involved in human cancer development by taking advantage of our ability to manipulate mouse genes, thus, enabling us to compare mouse cancer stages with those of human cancers at equivalent body sites.

• Creating the Mouse Models of Human Cancer Consortium, a partnership of scientific laboratories and teams dedicated to developing, validating, and characterizing mouse models of human cancers.

• Providing funding to encourage the use of simple organisms, such as yeast, in cancer studies and drug development research.

Imaging Technologies. Imaging technology promises to improve greatly our capacity to search out tiny colonies of cancer cells within the body and monitor the effectiveness of our treatments. To tap the potential of imaging tools NCI is:

• Establishing a single national network of investigators to perform multi-institutional clinical trials in diagnostic imaging. This network will expedite early clinical testing of promising imaging devices.

• Creating mechanisms to fund facilities to evaluate new imaging agents in small animals, particularly mice.

• Establishing an initiative to fund studies that apply and develop new imaging techniques to determine whether a therapeutic agent reaches a cancer, and once there, how it acts upon the tumor.

Defining the Signatures of Cancer Cells: Detection and Diagnosis. Each cell has a signature — a unique, identifiable characteristic related to its role in the body. As a normal cell is transformed into a cancerous cell, the signature changes, and that change becomes a unique signal of the cell's presence and character. By reading such signals accurately, we will be better able to detect and diagnose individual cancers. Recognizing the importance of research in this area, NCI is supporting a number of initiatives, including:

• The Cancer Genome Anatomy Project (CGAP), the Institute's principal vehicle for achieving advances in molecular detection and diagnostics. An important goal of this project is to establish the Tumor Gene Index, a complete index of all expressed genes in cancer cells.

• The development of novel technologies to enable molecular analyses of tumor samples.

• The development of effective early detection techniques to identify abnormalities in cells shed from cancerous tumors.

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and will help us better understand human cancer development by employing the mouse — a primary animal model for cancer.
see p.55

• NCI is creating a single, **national network for evaluating diagnostic imaging technologies.** This cooperative group of academic centers and affiliated hospitals with imaging expertise will expedite the early clinical testing of promising devices and will be able to **rapidly move new promising devices into large-scale trials more quickly.**
see p.60

CREATE AND SUSTAIN MECHANISMS THAT WILL ENABLE US TO MEET THE CHALLENGE OF RAPIDLY TRANSLATING OUR FINDINGS FROM THE LABORATORY INTO PRACTICAL APPLICATIONS

NCI's Challenge:
In this golden age of scientific discovery, promising scientific breakthroughs and emerging innovative technologies are yielding exciting insights about the basic nature of cancer. Yet, we are faced with the tremendous challenge of converting these basic findings into advances in cancer prevention and treatment. To meet this challenge, we have begun to set in place a system of "bridges" among all aspects of research — between research and clinical practice, between research and industry, and between the cancer research enterprise and the American people. Our activities in the following six areas, will help to span the gap between discovery and clinic.

Investigator-Initiated Research. Enhancing the level of support for all types of investigator-initiated research remains a fundamental need. In light of this, we continue to work to increase our support of investigators through a variety of steps. Over the last year, we:

• Made important progress in increasing our percentage of grant applications funded, as we are funding the top 29 percent of the competing applications in the Research Project Grant (RPG) pool.

• Continued to increase support for first-time investigators to help ensure that a steady stream of new investigators and ideas flows into the Research Project Grant pool.

• Worked with NIH's Center for Scientific Review to establish, in FY 1999, a study section for translational research in clinical oncology. This group will specialize in the review of grant proposals that move findings from the laboratory into the clinic.

Cancer Centers: Restructuring and Expansion.
Cancer Centers are central to NCI's work and presence in communities across the country. These institutions carry out vital cancer research, bringing cutting-edge treatments, diagnostics, detection techniques, and prevention methods to the community. Because of the significance of these centers, NCI must continue to work to improve the Cancer Centers Program and increase the number of Cancer Centers. During the past year, we:

• Worked to revitalize the Cancer Centers Program by adopting more flexible program guidelines that allow more research institutions to qualify for funding.

• Increased the number of centers throughout the country to 58.

• Increased the number of NCI-designated Comprehensive Cancer Centers from 31 to 35. A Comprehensive Center must demonstrate

What's inside

Meeting NCI's Challenge:

- **Our Rapid Access to Intervention Development (RAID) program, and our new Chemistry-Biology Centers, will help us translate basic discoveries rapidly and efficiently into the development and testing of new drugs.** By RAID's enabling the translation to the clinic of novel interventions developed in academic settings and by the Centers' fostering chemists and biologists to work collaboratively on research projects, these two programs will speed the discovery of novel therapeutic and preventive agents.
see p.78
- Improving access to clinical trials information is one focus of the Cancer Informatics Infrastructure (CII). **NCI has been developing components of the CII, such as the Clinical Data Update System and Adverse Events Reporting System, which will assist researchers in reporting and sharing clinical trials information.** NCI is also redesigning the

significant scientific strength in basic, clinical, and population studies, interdisciplinary collaboration across scientific boundaries, and have in place effective cancer information, education, and outreach activities for the communities they serve.

National Clinical Trials Program. Clinical trials are a crucial component in the process of developing new treatments, preventive measures, and detection and diagnostic techniques. Yet, an astonishingly small number of adults with cancer — approximately two percent — participate in cancer-related clinical trials. We need to develop a robust National clinical trials infrastructure that will remove all barriers and ensure that every American who wishes to participate may do so. Over the past year, we have taken a number of steps to strengthen our clinical trials program, including:

- Conducting a rigorous review of our clinical trials program to determine the steps that we should take to create a more efficient and effective clinical research effort.
- Establishing a new clinical cooperative group with the American College of Surgeons Oncology Group.
- Launching the Rapid Access to Intervention Development program to help move meritorious treatments developed in an academic setting into the clinic.

Informatics and Information Flow. Sharing of information is a critical part of research. To facilitate the best possible information flow among researchers, clinicians, and the public, NCI is working to develop a Cancer Informatics Infrastructure (CII) — a new architecture for the flow of information in our clinical trials program. We have started to take steps toward creating and implementing components of this new system by:

- Developing the Clinical Data Update System and the Adverse Drug Experience Reporting System.
- Launching an initiative to make our clinical trials information more understandable and accessible to the public.

Studying Emerging Trends. NCI monitors emerging trends in cancer incidence, survival, risk factors, and death among populations, as well as factors that influence these measures. Our primary means of measuring the Nation's cancer burden is through our Surveillance, Epidemiology, and End Results (SEER) Program. We are now engaged in expanding our surveillance capabilities by:

- Establishing a Surveillance Implementation group that is developing a post-millennium vision and road map for our surveillance efforts.
- Enhancing the collection of data on such risk factors as diet, smoking, exercise practices, and genetics.

Physicians Data Query (PDQ) a clinical trials database, and has developed the new cancerTrials website, which is designed to assist the public in finding clinical trials information.
see p.81

- Training is the key to developing tomorrow's researchers and clinicians and making sure that those in the field stay abreast of the latest advances. **NCI has developed not only new training grants, such as the Mentored Clinical Oncology Award (K23),** but has revamped its system to create training pathways that support researchers and clinicians throughout their careers.
see p.84

• Enhancing the Breast Cancer Surveillance Consortium's efforts to collect breast cancer data and establishing a Colorectal Cancer Surveillance Health Information System.

Training, Education, and Career Development. NCI is dedicated not only to maintaining, but to augmenting our support for the cancer research field's most valuable resource: our scientists. In the past year, we have a taken number of steps toward enhancing our training efforts, including:

• Planning to increase the amount of awards received by recipients of the National Research Services Awards.

• Establishing the Mentored Clinical Scientist Award (K23) and the Mid-Career Clinical Scientist Award (K24).

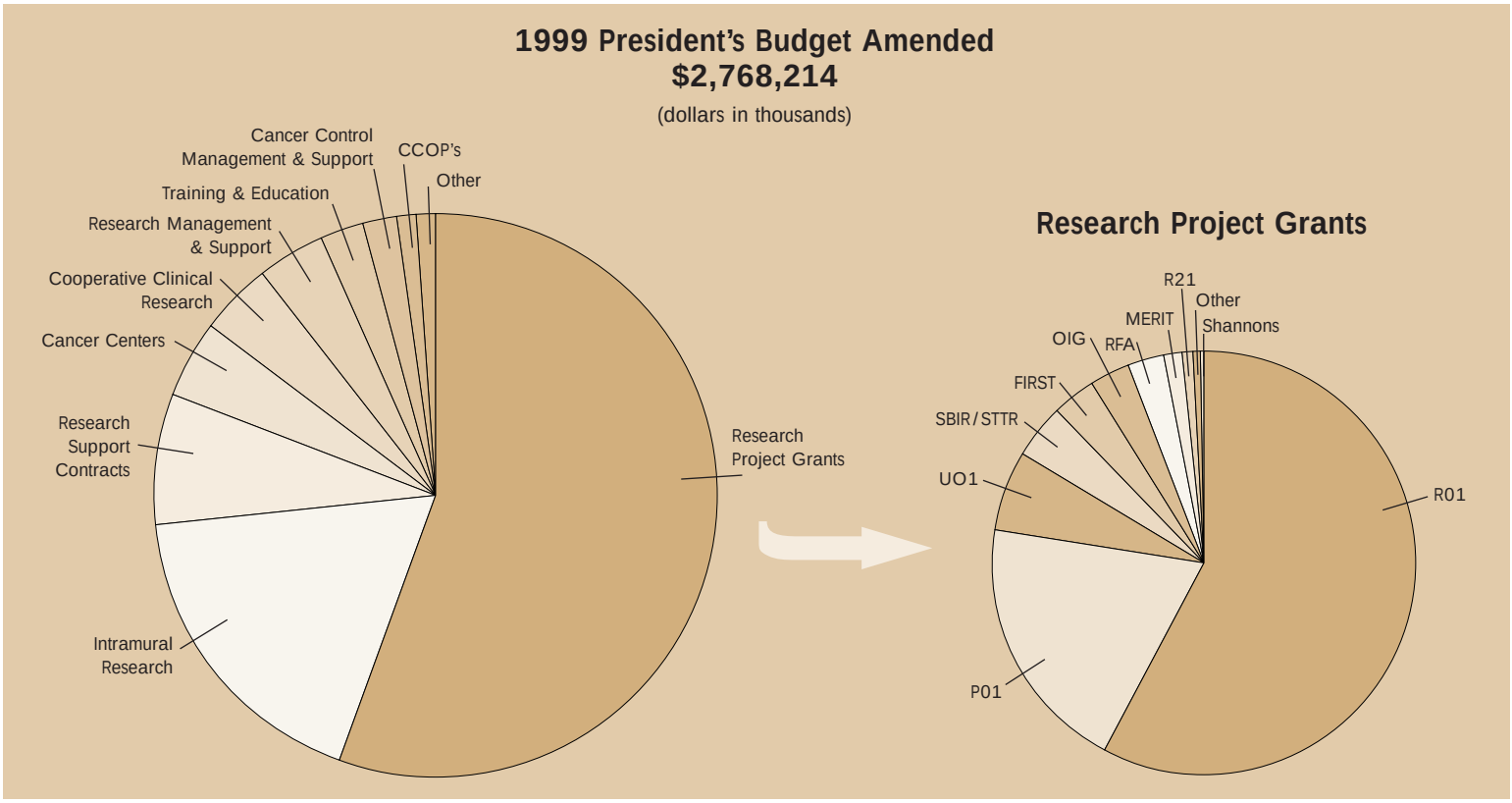
• Increasing the number of mentored training awards (K01) presented to minority, post-doctoral students.

To strengthen our Infrastructure for Discovery that supports all of our research efforts, as well as to continue our progress toward pursuing our Extraordinary Opportunities for Investment, and spanning the gap between discovery and application, the National Cancer Institute requests the following funding:

NATIONAL CANCER INSTITUTE 2000 BYPASS BUDGET REQUEST

2000 Bypass Budget (dollars in thousands)

	1998 Operating Level	1999 President's Budget Amended	Core Request	Core and Investment Request	Core, Investments & Challenge Request
RESEARCH PROJECT GRANTS (RPGs):					
Ongoing	$904,545	$958,915	$1,072,207	$1,072,207	$1,072,207
New (New and Renewal)	305,021	363,031	401,048	504,107	674,891
Small Business Innovation Research	50,978	56,978	58,972	58,972	78,058
SUBTOTAL	**1,260,544**	**1,378,924**	**1,532,227**	**1,635,286**	**1,825,156**
Intramural Research	438,262	443,225	464,700	468,700	491,700
Cancer Centers	170,188	184,515	192,373	192,373	267,173
CLINICAL TRIALS INFRASTRUCTURE:					
Cooperative Clinical Research	92,854	110,960	114,844	121,844	306,844
Community Clinical Oncology Program (CCOPs)	40,692	42,848	45,348	45,348	116,873
SUBTOTAL	**133,546**	**153,808**	**160,192**	**167,192**	**423,717**
Training and Education	86,668	98,570	107,220	123,220	210,025
Research Support Contracts	274,478	320,391	332,005	367,946	409,446
Cancer Control Management and Support	71,929	62,489	65,676	67,676	72,676
Research Management and Support	99,091	104,793	110,461	116,461	132,461
Other	16,593	21,499	25,146	40,646	40,646
TOTAL	**$2,551,299**	**$2,768,214**	**$2,990,000**	**$3,179,500**	**$3,873,000**
Cancer Control included above	*$253,135*	*$277,707*	*$299,499*	*$309,499*	*$386,024*


1999 President's Budget Amended
$2,768,214
(dollars in thousands)
Cancer Control
Management & Support
CCOP's
Other
Training & Education
Research Management
& Support
Cooperative Clinical
Research
Cancer Centers
Research
Support
Contracts
Intramural
Research
Research
Project Grants
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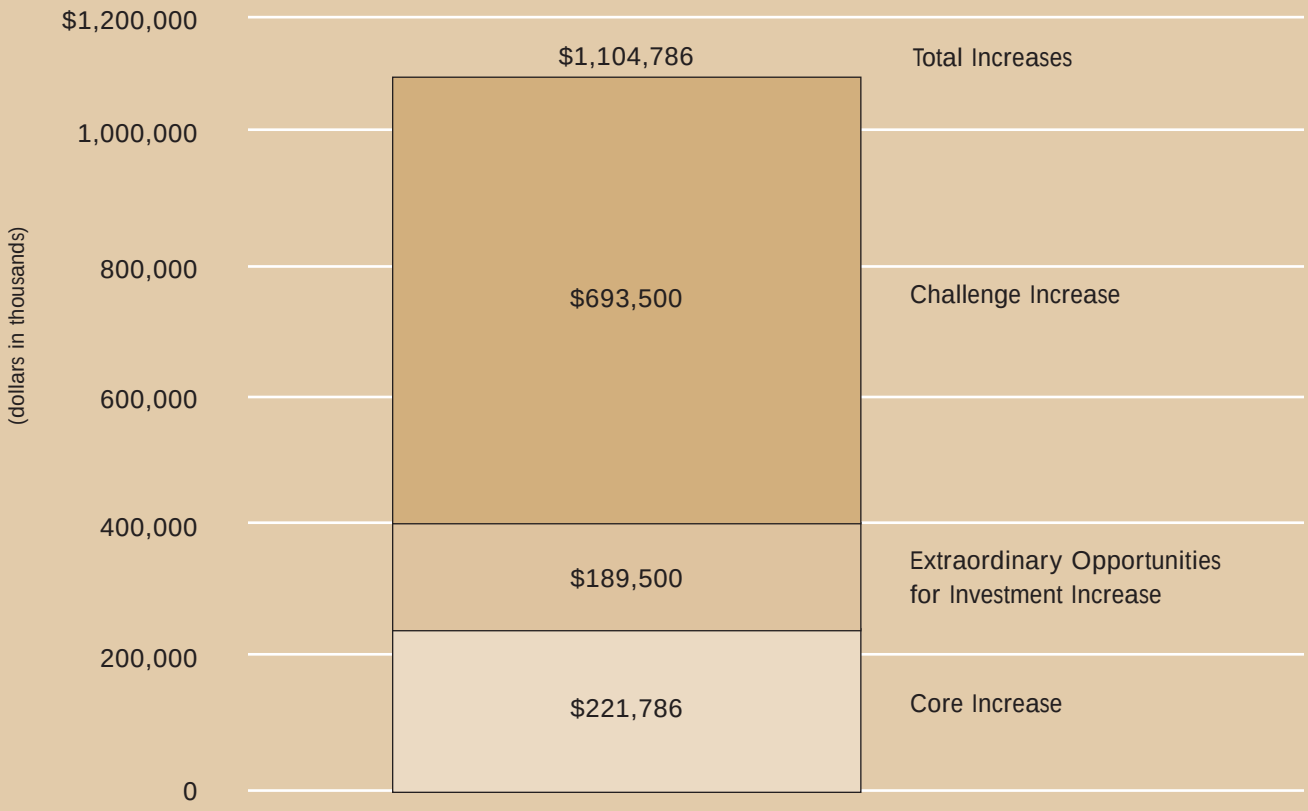
Shannons
MERIT
RFA
OIG
FIRST
SBIR/STTR
UO1
R01
P01


2000 Bypass Budget Request
Increases over the 1999
President's Budget Amended
(dollars in thousands)
$1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
$1,104,786
Total Increases
$693,500
Challenge Increase
$189,500
Extraordinary Opportunities
for Investment Increase
$221,786
Core Increase

NCI's Research Programs

During the past 25 years, we have witnessed remarkable progress against cancer. Perhaps the most tangible evidence of this progress is to be found in the recent declines in cancer incidence and mortality rates.

As long as people continue to suffer from the devastating effects of cancer, however, our work is not done. In our continuing battle against cancer, it is likely that our advances will remain incremental, but our commitment remains unwavering and our hopes high. The basis for this optimism is our ever-growing knowledge of the factors that increase cancer risk and of the processes within the cell that are disrupted in cancer's onset and progression. The revolution in the understanding of the molecular basis of cancer is now enabling us to develop improved tests for early detection, more precise methods for diagnosis, more effective strategies for prevention, and more powerful approaches for treatment.

As we move toward a new century, talented researchers and clinicians across the cancer field are working with great vigor and intense focus to achieve the preeminent goal of cancer research: to prevent and cure cancer.

In pursuit of this goal, NCI conducts three classes of research: laboratory, clinic, and population. In the laboratory, research is pursued on the biology of cancer, the fundamental properties of cancer-causing agents and processes, and the body's defense against and response to cancer. In the clinic, research is carried out on cancer prevention, detection, diagnosis, treatment, and rehabilitation. In the population, research focuses on the causes, risks, predispositions, incidence, and behavioral aspects of cancer. As the diagram illustrates, these three settings influence one another. For example, population-based research on the effects of exposure to a potential cancer-causing agent links to the laboratory where an understanding of the agent's effect on the cell can be explored. Through these linkages, we have identified a sexually transmitted papillomavirus as a primary cause of cervical cancer and subsequently explained why only certain viral subtypes are cancer-causing. We have established the relationship between asbestos and mesotheliomas; between reproductive variables such as late menopause and breast cancer; and between dietary factors and a variety of cancers. Population-based research on cancer-prone families has led to the isolation of specific genes responsible for inherited cancer syndromes. Specific genetic pathways in cells identified in the laboratory then can be used to predict the course of a patient's disease and his or her response to therapy, or to find ways to detect these cancers very early in their development. All three classes of research are supported by our infrastructure for discovery.

NCI's Infrastructure for Discovery

The national cancer research program represents our Nation's commitment to progress against cancer through science. Science cannot thrive — indeed, it cannot even take place — without the resources that support an enterprise of discovery. The engine that drives progress is the creativity, commitment, and hard work of scientists and clinicians whose discoveries and ideas are tested to find ways to prevent, detect, diagnose, and treat cancer and to care for the people who have cancer, have survived it, or are at risk.

In support of the entire community of cancer researchers, NCI has built an infrastructure for discovery composed of support mechanisms, organizations, and networks that link scientists, facilities, and information. It is this infrastructure that NCI's budget supports.

Planning for Progress: New Opportunities and Challenges

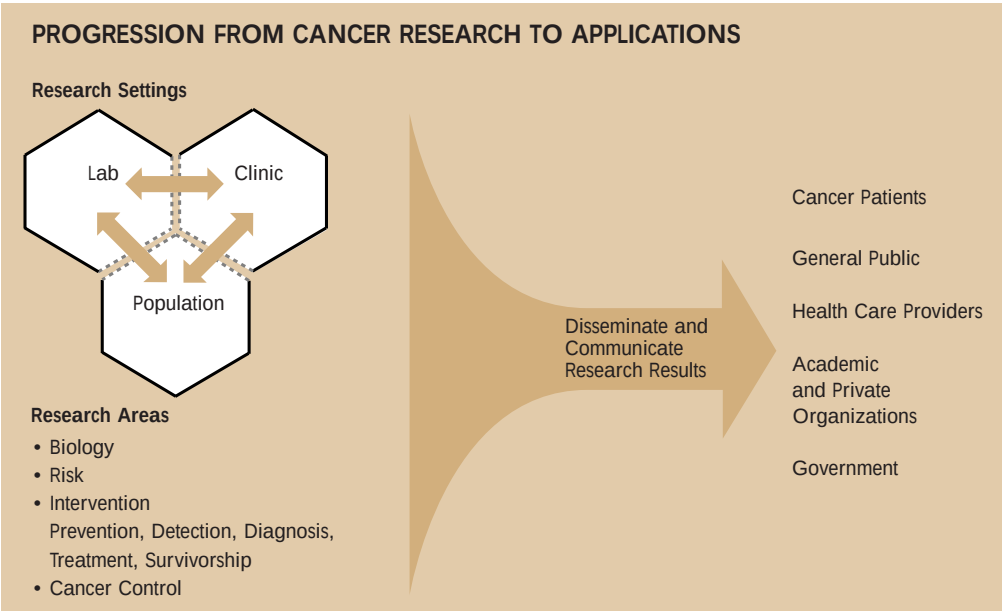
Planning — identifying needs and opportunities, setting priorities, implementing decisions, and making sure that a reliable infrastructure underlies all of our initiatives — is an integral part of all the Institute's activities. In fact, this Bypass Budget serves as the Institute's principal planning document — a sort of road map that points out NCI's priorities, opportunities, and challenges, as well as the ongoing programs through which we address each of these items.

Setting Priorities

Setting NCI's funding priorities is a complex and dynamic process driven by several principles. We recognize that we must support the full range of research activities necessary to confront cancer; therefore, we strive for a "balanced" portfolio of research in behavior, epidemiology, cancer control, cancer prevention, cancer detection, cancer diagnosis, and cancer treatment, as well as survivorship, rehabilitation, and end-of-life issues. This balance must include attention to all of the distinct diseases we collectively refer to as cancer and to all of the various populations that experience these diseases differently.

In addition, if we are to make progress, it is critical that we not only balance these pieces of the cancer research enterprise but also link them through translational research. Translational clinical research is the bridge between the laboratory and new methods of diagnosis, treatment, and prevention and is thus essential to progress against cancer. This research has been responsible for some of the most stunning clinical suc-

The diagram shows a progression from the results of research through dissemination to application. Research results must be communicated to those who ultimately apply these results in health care and disease prevention settings.



cesses of this century, including determining the molecular mechanisms of colon cancer, the engineering of improved AIDS treatment, and the new treatments to reduce the side effects of chemotherapy. Translational research is critical to develop fully the major advances made by basic scientists in areas such as molecular genetics, regulatory proteins, and cellular signaling into new detection technologies, targeted treatments, and prevention strategies.

In setting its priorities and planning for the future, we rely on our diverse constituencies to help us identify new opportunities, gaps, and barriers to progress, and to help us create new programs and improve existing ones.

Revitalizing NCI's Programs: Program Reviews

NCI supports research through a variety of mechanisms, many of which provide funds tailored to specific research processes. As part of an ongoing process of review and revitalization, NCI has instituted a series of external reviews to guide us in strengthening our major research support programs. In the past two years, we have undertaken in-depth reviews of the following programs:

Cancer Centers. The Program Review Group made recommendations regarding the designation, structure, function, and review of Cancer Centers, as well as the distribution and use of Cancer Center funds. In general, their recommendations aim to reward research excellence, provide for stringent quality review, increase flexibility, enhance productivity, streamline administrative responsibilities, and improve communication among Cancer Centers and NCI.

Cancer Control. The Program Review Group recommended that NCI pursue a vigorous effort to seize existing and emerging opportunities in behavioral prevention and cancer control. In addition, they encouraged NCI to facilitate research in basic behavioral science, primary prevention, and cancer screening. They called for research to improve the quality of life of those who still get cancer despite our best efforts. In addition, they emphasized the importance of continued commitment to the surveillance programs.

Clinical Trials. This Review Group made major recommendations regarding review, funding, design, oversight, and administration of the NCI clinical trials system. The recommendations are intended to create a more efficient and effective clinical research effort and to help NCI enhance and maintain a critical endeavor that continually faces new internal and external challenges.

Cancer Prevention. The Cancer Prevention Program Review Group made wide-ranging recommendations concerning research on modifiable risk factors for cancer; the use of animal models in prevention research; research on genetic predisposition for cancer; chemoprevention trials; behavioral research; and the organization and infrastructure of NCI's Division of Cancer Prevention (DCP). Based on this review, the

HOW DO WE SPEND OUR BUDGET ?

- About 73% of our budget supports basic and clinical studies conducted by scientists and clinicians across the Nation through our Extramural Research Program.
- We spend about 16% of our budget on our Intramural Research Program, in which NCI's own scientists conduct important cancer-related research.
- About 4% of our budget is devoted to training, education, and career development of scientists and clinicians at every stage of their career.
- We use about 3% of our budget to communicate the latest information about cancer risk, detection, prevention, treatment, rehabilitation, and control to people with cancer, health professionals, and the public at large.
- About 4% of our budget supports the administration and management of the Institute.

DCP was restructured, as were the Institute's chemoprevention efforts.

In addition, a review of NCI's Developmental Therapeutics Program is nearing completion. The results of these reviews are presented to our major advisory boards; implementation of Program Review Group recommendations, under the direction of the NCI Implementation Groups (see below) is ongoing. Available Program Review reports can be found at http://deainfo.nci.nih.gov/ADVISORY/boards.htm.

Following Through: Implementation Groups

Implementation groups of external scientists and NCI staff work to flesh out and grapple with the design of new initiatives that the Review Groups recommend for critical programs. Ongoing groups include the Clinical Trials, Prevention, Early Detection, and Surveillance Implementation Groups. In addition, NCI has a Tobacco Research Implementation Group that is addressing tobacco research opportunities and our plans to address them across the Institute.

Peer Review

The high caliber of NCI's research is maintained through peer review, a "quality control" process in which ideas for research are reviewed by experts in the field under study. The peer review mechanism helps ensure that NCI uses its resources wisely and funds research that has the potential to make a significant contribution to science. NCI's extramural programs and activities are funded through peer-reviewed grants. Programs funded through contracts also are subject to peer review, as are projects conducted in the intramural research program.

Oversight

To ensure the wise use of resources to meet the goals of the National Cancer Program, NCI actively seeks out expert advice from a variety of advisory bodies from both within and outside the Institute. NCI's primary advisory groups include:

National Cancer Advisory Board. NCI's principal advisory body is the Presidentially-appointed National Cancer Advisory Board. The Board advises the NCI Director on issues related to the entire National Cancer Program and provides a second level of review for grant applications referred to NCI.

Board of Scientific Advisors. With the Board of Scientific Counselors (below), the Board of Scientific Advisors (BSA) represents the scientific community's voice in the science NCI conducts and supports. The BSA, composed of distinguished scientists from outside NCI and representatives from the consumer advocacy community, advises the NCI leadership on the progress and future direction of the Institute's Extramural Research Program. The BSA evaluates Institute-awarded grants, cooperative agreements, and contracts, and reviews ideas for new research solicitations to ensure that a concept is meritorious and consistent with the Institute's programs.

Board of Scientific Counselors. The Board of Scientific Counselors (BSC) advises the Institute leadership on the progress and future direction of NCI's Intramural Research Program. This group of scientific experts from outside NCI evaluates the performance and productivity of NCI staff scientists through periodic site visits to intramural laboratories, and provides evaluation and advice on the course of each division's programs.

NCI Executive Committee. The NCI Executive Committee, which includes the chairs of the BSC and BSA, as well as division directors and other key advisors to the Director, meets weekly to make major policy and operating decisions for the Institute.

Director's Consumer Liaison Group. In 1997, the first all-consumer advocate advisory committee at NCI/NIH was established. The Director's Consumer Liaison Group (DCLG) consists of 15 consumer advocates selected by a national nomination process. This diverse group represents the face of consumer advocacy across the U.S. The three-fold purpose of the DCLG is to:

- Serve as a primary forum for discussing issues and concerns and exchanging viewpoints that are important to the broad development of NCI program and research priorities.

- Help develop and establish processes, mechanisms, and criteria for identifying appropriate consumer

TOBACCO

Tobacco use is the leading preventable cause of death in the United States, but 50 million Americans continue to smoke and/or use smokeless tobacco, despite strong evidence linking cigarette or cigar smoking to lung cancer and linking all forms of tobacco to oral cancers. Another 46 million Americans are former smokers, who will retain a somewhat heightened cancer risk for the rest of their lives. During the past several decades, NCI has been alerting Americans to the dangers of tobacco use and of its addictive nature, and has developed effective interventions to help people quit smoking. To continue and intensify this effort, and to develop methods of further lowering cancer risk for former tobacco users, NCI has gathered a group of intramural and extramural researchers, the Tobacco Research Implementation Group, to prepare and implement a comprehensive tobacco research agenda. The goal is greater coordination of NCI's varied tobacco research efforts from basic research on cellular changes caused by smoking, to behavioral research on ways to keep young people from starting to smoke and help those who smoke stop, to population-based research to help us tailor public health messages. A principal focus of this effort will be to expand our research into the biobehavioral aspects of tobacco use, including the relationship of behavior to biology and the mechanisms of addiction.

In addition to coordinating and expanding our future tobacco research efforts, we also are engaged in many ongoing tobacco research projects. In FY 1997 and FY 1998 we set aside funding aimed at the struggle to prevent tobacco use among children and to help those who are using tobacco products to quit. Pharmacobehavioral research — evaluating new pharmacologic agents and methods of behavior modification — aims to help adults stop using tobacco and identify biological and behavioral factors that influence who benefits most from different treatments. In response to the recent increase in cigar use, NCI has published a monograph, *Cigars: Health Effects and Trends,* which provides a complete review of available information on health risks, especially cancer, and cigar smoking.

advocates to serve on a variety of NCI program and policy committees.

• Establish and maintain strong collaborations between NCI and the cancer advocacy community.

Community Input

Input from the community is very important to NCI. So that we can better understand the needs of cancer patients, those at risk of cancer, and the public at large, NCI has established the *Office of Liaison Activities* (OLA).

Throughout the Nation, hundreds of cancer advocacy and outreach organizations provide education and support to their communities. The OLA is NCI's central point of contact with these national advocacy organizations and, through them, the community-based groups. OLA maintains ongoing communications and information exchange between the national cancer advocacy organizations and NCI, encourages input and feedback from these organizations, and cooperates and collaborates with these groups in areas of mutual interest. The office serves as a catalyst and resource to link advocates with NCI programs, working groups, and advisory committees, and helps integrate consumer advocate representatives throughout NCI. OLA supports the Division of Extramural Activities in expanding representation of consumer advocates on NCI peer review panels and coordinates and supports the DCLG (see above). In addition, OLA builds relationships with professional societies and other Federal agencies, and provides input and perspective to NCI on complex issues relevant to cancer patients and the public.

Extramural Research

Investigator-initiated extramural research — studies proposed and conducted by scientists in laboratories and clinical facilities throughout the country — is the most important component of NCI's research program; nearly two thirds of the Institute's budget is devoted to such research, which is funded under a variety of peer reviewed mechanisms. These different mechanisms focus on single projects undertaken by individual investigators; on program projects that

enable a team of investigators to develop a group of related projects; and on small business and industry-academic collaboration.

NCI's extramural research program, which serves as its link to the greater scientific community, includes the Divisions of Cancer Biology, Cancer Treatment and Diagnosis, Cancer Prevention, and Cancer Control and Population Sciences. An essential component of the extramural research program is NCI program staff. Their scientific expertise in cancer-related fields, combined with their national focus in a given research area, enables them to work effectively with NCI-funded scientists in academia and industry to foster and facilitate research progress. They synthesize the state of the science in important areas, identify priorities for new directions, foster collaborations between scientists, keep abreast of the research program through active communication with investigators, organize scientific meetings to facilitate the interchange of information between investigators, remain accessible to answer the scientists' questions, and secure supplemental funds as deemed meritorious. In addition, program staff act as a resource for researchers by educating them on NCI policies and procedures, by advising scientists new to the NCI system on the preparation of research grant applications, and by reviewing and identifying gaps in the NCI research portfolio that may lead to new areas of research emphasis.

Research Project Grants

The main pool of funds expended by NCI for grants to extramural scientists is known as the Research Project Grant (RPG) pool. NCI offers these funds to foster the creativity of talented scientists and provide them with the freedom to pursue the best ideas that will yield progress against cancer. NCI funds two main types of research project grants: Single Research Project Grants are awarded to institutions on behalf of individual principal investigators, and Program Project Grants are funded to foster collaborations among groups of scientists involved in related research projects. In FY 1999, NCI anticipates expending more than $1.32 billion in support of over 3,900 separate research grants. More than 1,000 of these awards will be new or competing renewal projects.

A NEW PARADIGM FOR COLLABORATIVE RESEARCH

NCI, through its Division of Cancer Biology, is testing new paradigms of collaboration through an innovative pilot known as Activities to Promote Research Collaborations. Through this initiative, NCI-funded laboratories around the country can apply for supplemental resources to hold workshops and/or form consortia to share resources, techniques, and data to enhance their individual (and competing) research programs in areas of mutual scientific interest. In addition, these laboratories are encouraged to collaborate with communities that have not traditionally been involved in cancer research, or to work with individuals in multidisciplinary fields to gain new insights and develop new cancer research questions. For example, a group of investigators representing four laboratories has been working together to gain a comprehensive understanding of a fragile site on chromosome 3p — that is, an area of the chromosome that is prone to breakage — and to determine how this fragile site contributes to a number of epithelial cancers. Through their collaboration, this group has been able to move beyond their original focus on the particular fragile site, and the gene or genes that may exist at that site, to a more global hypothesis about fragile sites and their collective role in the genomic instability that may lead to cancer.

How does cancer research benefit from this support? Collectively, research project grants span the full range of basic, clinical, and population-based studies of cancer etiology, biology, prevention, detection, diagnosis, treatment, and control. These grant awards and the dedicated researchers behind them constitute the largest single categorical expenditure of resources that NCI, through the extramural research community, commits annually to combat cancer. The scientific and medical advances that come from these investments represent the irreplaceable intellectual capital upon which rests the future of cancer research and cancer care.

NCI program staff monitor the progress of each grant through contact with the investigators throughout the year; investigators also submit a report to NCI each year that describes their research progress. Results of projects conducted with NCI funding are communicated to the scientific community and the public primarily through peer reviewed scientific journals, but also through major scientific meetings, workshops, and symposia.

Research Project Grants (RPGs) (dollars in thousands)

	1997 Obligations	1998 Operating Level	1999 President's Budget Amended	2000 Core Budget
Ongoing	$823,615	$904,545	$958,915	$1,072,207
*New	283,450	305,021	363,031	401,048
SUBTOTAL	1,107,065	1,209,566	1,321,946	1,473,255
Small Business Innovation Research	47,156	50,978	56,978	58,972
TOTAL	**$1,154,221**	**$1,260,544**	**$1,378,924**	**$1,532,227**

*Includes both New and Renewal Awards

The Single Research Project Grant and Its Derivatives. The mainstay of the RPG pool is the Single Research Project Grant. This support system has produced many of the most significant research advances in the NCI portfolio. For example, researchers funded through this mechanism first discovered that oncogenes — altered genes in cancer cells that promote the out-of-control cell growth that characterizes cancer — can arise from normal genes; this discovery earned the Nobel Prize for Physiology or Medicine in 1989. This funding mechanism is enabling researchers in the field today to continue their search to identify new oncogenes and explore the function of their normal counterpart genes within the cell. Through this mechanism, NCI also has supported studies leading to the discovery of a potential switch controlling angiogenesis — the process by which cancerous tumors stimulate new blood vessel formation that enables the tumor to grow, invade nearby tissue, and spread to distant sites in the body; and the discovery and development of important drugs such as paclitaxel (Taxol®) and tamoxifen (Nolvadex®); new methods of therapy including conservative surgery techniques for breast and prostate cancers; and adjuvant chemotherapy for all cancers.

Recognizing the key role that individual investigators play in the cancer research enterprise, NCI has, over the past year, shifted its funding priorities to increase significantly the number of new, investigator-initiated Single Project Research Grant applications that receive funding. This shift ensures that a greater number of promising research projects have the support they need to come to fruition. The single-investigator grant payline rose from 15 percent in FY 1995 to an estimated 25 percent in FY 1999.

The Program Project Grant. Like the Single Research Project Grant, the Program Project Grant is an investigator-initiated award. The Program Project Grant, however, is a multi-component award that allows groups of researchers who are pursuing thematically related research projects requiring additional shared resources — such as specialized core research facilities — to be peer reviewed and supported under a single award. This mechanism gives investigators access to a much broader range of projects and common access to patients and tissue samples that would be difficult, if not impossible, to arrange in a single project setting. This approach is especially useful in interdisciplinary and translational research in which basic and clinical projects are combined, fostering synergy between the investigators.

The value of this mechanism is exemplified by a large program project centered in Seattle that has led the way in understanding both basic bone marrow transplant biology and developing its clinical application in high dose chemotherapy regimens for several types of cancer. In 1990, the Nobel Prize for Physiology or Medicine was awarded in recognition of some of the work performed under this award.

Other Grant Mechanisms

NCI also has special mechanisms for innovative exploratory and developmental research activities, to allow seasoned investigators with an outstanding record of research productivity to embark on projects of unusual scientific potential, and to support research and development ideas that are likely to result in the development of a commercial product or service. A more complete listing and description of the grant mechanisms NCI uses can be found at: http://deainfo.nci.nih.gov/flash/awards.htm.

Support for Clinical Research

Clinical research, or research conducted with cancer patients, is one of the cornerstones of the National Cancer Program. Every new treatment we use today, every preventive measure that is widely recommended, and every innovative detection strategy was, at one time, tested in cancer patients or in people at risk for the disease. These true heroes of the fight against cancer have allowed us to amass the body of information we are building upon even today. Even though trials often test the latest therapies, there is no guarantee for success — a patient may be randomly assigned to a control group to receive standard therapy, or may participate in a Phase I or II trial in which it may still be too early in the drug's development to know if it is effective. Nonetheless, trials provide a patient access to cutting edge interventions and provide researchers with information that will ultimately enable us to prevent and effectively treat all cancers.

A strong clinical research infrastructure, including a comprehensive program of clinical trials in treatment, early detection, and prevention, is a vital component of NCI's research program. NCI's Cancer Centers, Cooperative Groups, and Community Clinical

NEW HORIZONS: TECHNOLOGY DEVELOPMENT INITIATIVES

Based on needs identified by the Working Groups for NCI's Extraordinary Opportunities for Cancer Research (see p.38), NCI has initiated two programs focused on harnessing new technologies that will give scientists the tools they need to realize those opportunities.

The *Phased Innovation Award* supports technology research from the evolution of innovative concepts, through feasibility testing, to subsequent full-scale development. It is meant to fund programs with the potential to have an impact on cancer research in the short term. The Phased Innovation Award is unique in that it combines two grants: in the first phase, the researcher receives an R21 (exploratory/developmental) grant for pilot technology research and feasibility testing, while in the second phase, he or she receives an R33 grant — a new mechanism — for full-scale technology development. The researcher submits applications for both grants at the same time, and there is no (or a minimal) funding gap between disbursement of the two grants. The Phased Innovation Award mechanism is currently being used to fund the development of technologies for the molecular analysis of cancer that will support research for the Cancer Genome Anatomy Project (see p.64).

A logical extension of the Phased Innovation Award, the *Unconventional Innovation Program* supports innovations in technology discovery for cancer research applications. Intended to support high-impact, long-range opportunities, this program focuses on developing technologies to support integrated strategies for non-invasive or minimally invasive cancer detection, diagnosis, and treatment approaches, based on the molecular characteristics and physiology of an individual tumor. NCI is currently soliciting ideas on such technologies from the research community to aid in deciding the types of research that will be funded in the first round of awards, and will invest up to $4 million in quality projects in FY 1999.

Oncology Program are where findings from the laboratory are translated into new treatments, diagnostic tools, and preventive interventions, and where these measures are first tested for safety and effectiveness. These programs are fundamentally interrelated: every Cancer Center is a participant in at least one Cooperative Group, and each Cooperative Group is a research base for participants in the Community Clinical Oncology Program. Hundreds of clinical trials are supported through these and other research mechanisms, such as individual research project grants, program project grants, cooperative agreements, and contracts.

Clinical Trials Infrastructure (dollars in thousands)

	1997 Obligations	1998 Operating Level	1999 President's Budget Amended	2000 Core Budget
TREATMENT:				
Clinical Cooperative Research	$88,499	$92,854	$110,960	$114,844
Community Clinical Oncology Program	22,425	23,692	20,998	22,223
SUBTOTAL TREATMENT	110,924	116,546	131,958	137,067
PREVENTION:				
Community Clinical Oncology Program	16,682	17,000	21,850	23,125
TOTAL	**$127,606**	**$133,546**	**$153,808**	**$160,192**

NCI's programs in clinical research have enjoyed many notable successes over the years. NCI has been responsible for the early testing of many important treatments, including paclitaxel (Taxol®) for breast and ovarian cancer and interferon alpha-2b for malignant melanoma. Similarly, NCI will soon begin studies to evaluate the effectiveness of the exciting new drug Herceptin® in breast cancer patients with varying stages of the disease and in combination with other agents. Ongoing studies to test the effectiveness of certain drugs to prevent first occurrences of cancer include the Prostate Cancer Prevention Trial and the Breast Cancer Prevention Trial — which recently demonstrated a 45 percent reduction in breast cancer incidence among high-risk participants who took the drug tamoxifen (Nolvadex®).

Through our clinical research programs, we also have identified successful interventions for symptom management and continuing care of cancer patients, including treatment for mouth sores and hot flashes, both common side effects of chemotherapy. In addition, based on the results of laboratory research, we are now exploring interventions for individuals whose genetic profile places them at increased risk of cancer.

However, our ability to conduct clinical trials is in danger of being compromised by changes in the health care system. In the past, institutions have used surplus revenues from patient care services to supplement government research support. The growth of managed care has all but eliminated those discretionary funds. As a result, institutions can no longer sponsor research activities requiring capital expenditures and cannot support essential training for young investigators. These changes pose a very real danger for the continuation of cancer research and our continued progress against cancer.

To combat these undesirable effects of changes in the health care system, we have begun looking for ways to increase access to clinical trials. One such mechanism is our new Midcareer Investigator Award in Patient-Oriented Research, which is now offering subsidies to clinicians that will allow them protected time to devote to vital patient-oriented research. Further, through agreements with insurers and other government agencies, we are working to ensure that anyone who wants to be treated on a clinical trial can be reimbursed for doing so. For example, the Pediatric Cancer Care Network was established to facilitate the entry of children onto clinical treatment trials. About 95 percent of children up to age 14 who develop cancer are evaluated at a Cooperative Group institution; of these, over 50 percent participate in one or more clinical trials. However, we hope that the establishment of the Network will improve pediatric participa-

THE NATIONAL CANCER INSTITUTE CANCER CENTERS PROGRAM

■ **Comprehensive Cancer Center** ◆ **Clinical Cancer Center** ● **Cancer Center**

ALABAMA
■ University of Alabama at Birmingham
Comprehensive Cancer Center
Birmingham, AL

ARIZONA
■ Arizona Cancer Center
University of Arizona
Tucson, AZ

CALIFORNIA
■ Beckman Research Institute
City of Hope
Duarte, CA
● The Burnham Institute
LaJolla, CA
■ Chao Family Comprehensive
Cancer Center
University of California at Irvine
Orange, CA
■ Jonsson Comprehensive
Cancer Center
University of California at Los Angeles
Los Angeles, CA
■ Norris Comprehensive
Cancer Center
University of Southern California
Los Angeles, CA
● The Salk Institute Cancer
Research Center
LaJolla, CA
◆ University of California at San Diego
Cancer Center
LaJolla, CA

COLORADO
■ University of Colorado
Cancer Center
Denver, CO

CONNECTICUT
■ Yale University Comprehensive
Cancer Center
New Haven, CT

DISTRICT OF COLUMBIA
■ Lombardi Cancer Research Center
Georgetown University Medical Center
Washington, DC

FLORIDA
◆ H. Lee Moffitt Cancer Center and
Research Institute
University of South Florida
Tampa, FL

HAWAII
◆ Cancer Research Center of Hawaii
University of Hawaii at Manoa
Honolulu, HI

ILLINOIS
■ Robert H. Lurie Cancer Center
Northwestern University
Chicago, IL
■ University of Chicago Cancer
Research Center
Chicago, IL

INDIANA
● Purdue University Cancer Center
West Lafayette, IN

MAINE
● The Jackson Laboratory
Bar Harbor, ME

MARYLAND
■ The Johns Hopkins Oncology Center
The Johns Hopkins University
Baltimore, MD

MASSACHUSETTS
■ Dana-Farber Cancer Institute
Boston, MA
● Massachusetts Institute of Technology
Center for Cancer Research
Cambridge, MA

MICHIGAN
■ Barbara Ann Karmanos
Cancer Institute
Wayne State University
Detroit, MI
■ University of Michigan Comprehensive
Cancer Center
Ann Arbor, MI

MINNESOTA
◆ Mayo Cancer Center
Mayo Foundation
Rochester, MN
■ University of Minnesota Cancer Center
Minneapolis, MN

NEBRASKA
● Eppley Cancer Center
University of Nebraska Medical Center
Omaha, NE

NEW HAMPSHIRE
■ Norris Cotton Cancer Center
Dartmouth-Hitchcock Medical Center
Lebanon, NH

NEW JERSEY
◆ The Cancer Institute of New Jersey
Robert Wood Johnson Medical School
New Brunswick, NJ

NEW YORK
■ Albert Einstein College of Medicine
Cancer Research Center
Bronx, NY
● American Health Foundation
New York, NY
● Cold Spring Harbor Laboratory
Cold Spring Harbor, NY
■ Herbert Irving Comprehensive
Cancer Center
Columbia University College
of Physicians and Surgeons
New York, NY
■ Kaplan Cancer Center
New York University
Medical Center
New York, NY
■ Memorial Sloan-Kettering
Cancer Center
New York, NY
■ Roswell Park Cancer Institute
Buffalo, NY
◆ University of Rochester
Cancer Center
Rochester, NY

NORTH CAROLINA
■ Duke Comprehensive Cancer Center
Duke University Medical Center
Durham, NC
■ UNC Lineberger Comprehensive
Cancer Center
University of North Carolina
School of Medicine
Chapel Hill, NC
■ Wake Forest University Comprehensive
Cancer Center
Winston-Salem, NC

OHIO
■ Ohio State University Comprehensive
Cancer Center
Columbus, OH
■ University Hospitals Ireland
Cancer Center
Case Western Reserve University
Cleveland, OH

OREGON
◆ Oregon Cancer Center
Oregon Health Sciences University
Portland, OR

PENNSYLVANIA
■ Fox Chase Cancer Center
Philadelphia, PA
◆ Kimmel Cancer Center
The Thomas Jefferson University
Philadelphia, PA
■ University of Pennsylvania Cancer Center
Philadelphia, PA
■ University of Pittsburgh
Cancer Institute
Pittsburgh, PA
● Wistar Institute Cancer Center
Philadelphia, PA

TENNESSEE
◆ St. Jude Children's Research Hospital
Memphis, TN
◆ Vanderbilt Cancer Center
Vanderbilt University
Nashville, TN

TEXAS
■ San Antonio Cancer Institute
San Antonio, TX
■ The University of Texas M.D.
Anderson Cancer Center
Houston, TX

UTAH
◆ Huntsman Cancer Institute
University of Utah
Salt Lake City, UT

VERMONT
■ Vermont Cancer Center
University of Vermont
Burlington, VT

VIRGINIA
◆ The Cancer Center at the University of
Virginia Health Sciences Center
Charlottesville, VA
◆ Massey Cancer Center
Virginia Commonwealth University
Richmond, VA

WASHINGTON
■ Fred Hutchinson Cancer Research Center
Seattle, WA

WISCONSIN
● McArdle Laboratory for
Cancer Research
University of Wisconsin
Madison, WI
■ University of Wisconsin Comprehensive
Cancer Center
Madison, WI

CLINICAL TRIALS

Clinical trials are research studies conducted to answer specific scientific questions about new ways to prevent, diagnose, detect, and treat cancer. Although most are designed to test new cancer treatments, trials also may look at the psychological impact of cancer or ways to improve a patient's quality of life. In addition, the number of chemoprevention trials has been increasing, because of recent success with large precedent-setting prevention trials, such as the Breast Cancer Prevention Trial.

Before a clinical trial of a promising new treatment or chemopreventive agent can be launched, the agent must undergo rigorous laboratory testing to prove that it may be beneficial to patients and will be safe to use during testing. Then researchers design a trial in an effort to answer a specific scientific question. The researchers then establish strict entry criteria to help identify patients who are best suited for the trial. Only then can the researchers recruit volunteers to participate. Trials are generally conducted in three phases:

- ***Phase I*** — These are small trials designed to tell researchers how best to administer the new intervention and, in studies of new agents, the optimal dose of the drug to give to achieve an anti-cancer effect while minimizing side effects.
- ***Phase II*** — Using a small number of people, these studies determine if the treatment, delivered at the optimum dose, destroys or prevents cancer and what types of cancer it works best against.
- ***Phase III*** — Once a therapy has been proven to have an anti-cancer effect and be safe, it then moves to a Phase III trial to compare the effectiveness of the new therapy with a standard therapy. Phase III trials are often large and may include hundreds or thousands of people from across the country.

As each phase of testing is completed, the data collected are analyzed and the results published. Based on this analysis, the researchers determine whether the agent is showing enough of a benefit to continue testing. Once a therapy has successfully completed these three phases of testing, a New Drug Application is submitted to the U.S. Food and Drug Administration. The testing and approval process can take many years; however, the approval process can sometimes be accelerated, particularly if the agent is beneficial for patients with a form of cancer that has few treatment or prevention options. Occasionally, additional trials (called ***Phase IV*** trials) are conducted after the approval of the drug to provide longer-term safety data or to collect new types of information, such as quality-of-life assessments.

Ensuring Diversity in Clinical Trial Participation

Ensuring participation in clinical research, particularly among women and members of special population groups, is a high priority for the Institute; several programs help us ensure that all populations are well-represented. The Minority-Based Community Clinical Oncology Program, begun in 1990, has been successful in accruing minority cancer patients to trials and allows for studies in minority populations that may lead to better understandings about the dynamics of patient accrual. In addition, two new grant programs are supporting research on ways to draw more women and minority participants into prevention and screening studies. The Institute also has funded a number of conferences aimed at sharing current information and strategies to increase and maintain its good record of minority accrual to clinical trials.

As a result of our efforts, analysis of accrual patterns in Cooperative Group cancer treatment trials has shown that women and ethnic/racial minorities are proportionally represented in NCI cancer treatment trials. Nearly 20 percent of the over 20,000 patients entering treatment clinical trials every year are from an ethnic/racial minority group.

Advancing Cancer Treatment Through Clinical Trials

Conducting treatment clinical trials is a critical step in establishing the best possible means of treating a specific cancer. Clinical trials allow us to assess the ability of new treatments to increase patient survival and to improve quality of life. During the past year, NCI sponsored hundreds of clinical trials, many of which produced promising findings. These trials include:

Breast Cancer

Treating patients whose breast cancer has spread to their lymph nodes often involves using a combination of chemotherapy drugs — doxorubicin and cyclophosphamide — following surgery. Researchers are now conducting a study to determine whether increasing doses of doxorubicin and adding, in some patients, the drug paclitaxel (Taxol®) improves the women's survival. In an early finding, recurrence of breast cancer was reduced by 22 percent, and survival increased by 26 percent, among the women who took paclitaxel. However, increasing the amount of doxorubicin did not appear to improve outcome. Although it is still early in the trial's course, these results show that the addition of paclitaxel to standard therapy could make a significant difference in survival.

Among women whose cancer has not spread to the lymph nodes, can tumor characteristics such as size and presence of hormone receptors, along with newer measures such as tumor growth rate, be used to distinguish women who need aggressive treatment for their cancer from those who do not? A recent trial separated participants into three groups — high-risk, low-risk and uncertain-risk. High-risk patients were identified as having tumors larger than 2 cm and/or no hormone receptors, while low-risk patients had tumors too small to perform hormone receptor measurements. Those with uncertain risk had tumors less than 2 cm with hormone receptors. Tumors in women of uncertain risk were also analyzed to determine growth rate; patients with fast growing tumors were then placed in the high-risk group and those with slow growing tumors were placed in the low-risk group. All women at low risk were followed carefully after initial treatment (surgery, in some cases with radiation). All women at high risk were randomly assigned to receive one of two adjuvant chemotherapy combinations, cyclophosphamide, adriamycin, and 5-fluorouracil (CAF) or cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). After receiving adjuvant chemotherapy, the high-risk women were randomly assigned to receive tamoxifen for five years or no further therapy.

Researchers made three important findings:

- After five years, women treated with CAF had a slightly better survival rate, but CAF's side effects were worse than those of CMF.
- Taking tamoxifen resulted in a significant benefit for women whose tumors had hormone receptors, but did not help those whose tumors did not have hormone receptors.
- Most importantly, low-risk women who received no further treatment following surgery had an excellent five-year survival rate of 96 percent, indicating that small, node-negative, slow-growing tumors are unlikely to require additional therapy.

Neuroblastoma

We have made significant progress in the treatment of children with high-risk neuroblastoma. In a landmark clinical trial, researchers found that using autologous bone marrow transplantation (ABMT) versus intensive conventional chemotherapy improved the children's three-year, event-free survival from 18 percent to 34 percent. (*Event-free* indicates that the patients experienced no tumor recurrence, and none died from other causes.) The researchers also found that 47 percent of the children who received 13-cis-retinoic acid, a drug that arrests the growth of neuroblastoma cells, versus 25 percent of the children who did not receive the drug were event-free after three years. 13-cis-retinoic acid is a differentiating agent, or a drug which forces cancer cells to behave more like normally programmed cells; these important results mark the first time a differentiating agent has been shown to improve outcome for children with solid tumors.

THE SPECIAL ROLE OF SPORES

Specialized Programs of Research Excellence (SPOREs) focus on research that is designed to convert novel ideas with the potential to reduce cancer incidence and mortality, improve survival, and improve quality of life into interventions that can help people with cancer or people at risk. For example, recent findings from the SPORE program include the identification of several tumor suppressor gene mutations that lead to pancreatic cancer, as well as the first human gene therapy for advanced prostate cancer.

NCI-designated Cancer Centers and other research institutions are eligible to compete for SPORE awards. In 1997, NCI funded the following SPOREs*:

Breast Cancer SPOREs
- Duke University Medical Center
  Durham, NC
- Lombardi Cancer Research Center
  Washington, DC
- Sloan-Kettering Institute for Cancer Research
  New York, NY
- University of California at San Francisco
  San Francisco, CA
- UNC Lineberger Cancer Center
  Chapel Hill, NC
- University of Texas Health Science Center
  at San Antonio
  San Antonio, TX

Prostate Cancer SPOREs
- Baylor College of Medicine
  Houston, TX
- The Johns Hopkins Hospital
  Baltimore, MD
- University of Michigan Comprehensive
  Cancer Center
  Ann Arbor, MI

Lung Cancer SPOREs
- The Johns Hopkins University
  Baltimore, MD
- University of Colorado Cancer Center
  Denver, CO
- University of Texas Southwestern Medical Center
  Dallas, TX

Gastrointestinal Cancer SPOREs
- University of Nebraska Medical Center
  Omaha, NE
- The Johns Hopkins University School of Medicine
  Baltimore, MD

**At least one Ovarian Cancer SPORE will be funded in the coming year.*

tion even more. This network, a cooperative agreement between the Children's Cancer Group, the Pediatric Oncology Group, and the Blue Cross/Blue Shield System (BC/BS) nationwide, will ensure that children of BC/BS subscribers receive care at designated centers of cancer care excellence and will promote the enrollment of children in Cooperative Group clinical trials.

Cancer Centers

Fifty-eight research-oriented institutions throughout the Nation have been designated NCI-supported Cancer Centers in recognition of their scientific excellence. The Centers are key partners in NCI's efforts to speed the process of discovery and bring the benefits of cancer research directly to the public. Located throughout the country, each Cancer Center is a hub of cutting-edge research, highest quality cancer care, and outreach and education of health care professionals and the general public alike.

When an institution meets the rigorous competitive standards to become an NCI Cancer Center, it is awarded a Cancer Center Support Grant. These funds enable the institution to coordinate multidisciplinary approaches to research questions, to gain access to the most advanced research technologies, and to take rapid advantage of new research opportunities. Support for the Cancer Centers helps assure a close association between state-of-the-art research and state-of-the-art care activities within the institution. It also allows

Cancer Centers (dollars in thousands)

	1997 Obligations	1998 Operating Level	1999 President's Budget Amended	2000 Core Budget
Basic	$16,333	$20,846	$24,145	$24,990
Clinical / Comprehensive	115,615	118,127	129,565	135,100
SUBTOTAL CORE GRANTS	131,948	138,937	153,710	160,090
SPOREs (P50)	28,765	31,215	30,805	32,283
TOTAL	**$160,713**	**$170,188**	**$184,515**	**$192,373**

each Center to develop key collaborations with industrial, community, and state health organizations, and link the research capabilities and expertise of scientists within the institution to problems of cancer incidence and mortality in their communities and regions.

In the past year, NCI's Cancer Centers Program added two Centers to its roster, bringing the total number to 58. In addition, the number of Centers recognized as NCI-designated Comprehensive Cancer Centers has increased from 31 to 35. To be chosen as a Comprehensive Cancer Center, a Center must demonstrate both significant scientific strength in basic, clinical, and population studies and strong interdisciplinary collaboration. Comprehensive Centers also must have in place effective cancer information, education, and outreach activities for the regions and communities they serve.

Traditionally, Cancer Centers have had broad scientific bases, and most have been developed within a single institution. Recent changes in the program, however, are enabling the planning of new consortia of institutions, often linking free-standing clinical and academic centers with community hospitals, forming networks with tremendous research strength and the ability to deliver quality care in a managed care environment. In addition, more focused scientific concepts are being developed for Cancer Centers. For example, some Centers are focusing on population sciences and others are concentrating on translational research opportunities within a specific scientific discipline, such as immunology. Overall, such changes in the Cancer Centers program promise to increase the scientific versatility, translational research capabilities, and geographic distribution of NCI-supported Cancer Centers.

Cooperative Group Clinical Trials Program

The sheer number of different types of cancers and the biological complexity of individual cancers make the process of efficiently identifying and evaluating new anti-cancer or new treatment strategies particularly challenging. To test potential treatment advances in patients more rapidly, NCI maintains the Cooperative Group program, a national network consisting of a number of consortia (cooperative groups) that seek to define the key unanswered questions in cancer and then conduct clinical trials to answer them. This kind of cooperation makes it possible to centralize administration and data collection for trials taking place at a large number of sites all over the country. Current Cooperative Groups differ in structure and research organization, but they share the common purpose of developing and conducting large-scale trials in multi-institutional settings. For example, the National Wilms' Tumor Study Group concentrates on treatment of this single cancer; in contrast, the Radiation Therapy Oncology Group explores the use and effectiveness of radiation therapy

SPOTLIGHT ON RESEARCH

Monoclonal Antibodies

The first monoclonal antibody for the treatment of cancer, C2B8 (Rituxan®), has been approved for the treatment of B-cell non-Hodgkin's lymphoma. C2B8 works by attaching to a specific protein, or antigen, present on the surface of a cancerous B-cell. Once the monoclonal antibody attaches, it triggers the body's immune system, causing a response that leads to destruction of the cancerous cell. NCI is now collaborating with a pharmaceutical company to test C2B8 for use in older patients with non-Hodgkin's lymphoma and for the treatment of patients with chronic myelocytic leukemia and other types of lymphomas. Similarly, NCI is conducting clinical trials with Herceptin®, a HER2/neu monoclonal antibody that targets breast cancer cells having a protein on their surface called HER2. Currently, Herceptin® is being tested in Phase III trials for the treatment of women whose breast cancers have not responded to other treatment. In addition, Phase I trials are being launched to see if Herceptin® is effective against other solid tumors, and a Phase II trial is underway for patients with ovarian and peritoneal cancers.

IMPORTANT FACTS ABOUT:

Community Clinical Oncology Programs
The Community Clinical Oncology Program includes...

- 48 central offices in 30 states
- 330 participating hospitals
- 2,300 participating physicians

Each year, the Program enters...

- 4,000 patients into cancer treatment clinical trials
- 4,000 patients into cancer prevention and control clinical trials

An additional seven minority-based CCOPs increase the participation of minority individuals in clinical trials research. Each year over 900 patients enter clinical trial through these specialized CCOPs. These programs are located in six states and Puerto Rico and bring an additional 33 hospitals and 250 physicians into the clinical trials network.

NCI's Cooperative Groups

- The Cooperative Group program conducts and promotes clinical trials in cancer treatment, prevention, and early detection, and explores issues concerning quality of life and rehabilitation during and after treatment for cancer.
- There are currently 12 Cooperative Groups. Each year, 1,700 institutions throughout the United States, Canada, Europe, and Australia, and more than 6,000 investigators in these institutions, participate in Cooperative Group studies.
- Approximately 20,000 new patients participate in Cooperative Group clinical trials each year, principally in large Phase III trials that help establish the state of the art for cancer therapy. (See p.24 for more information on the phases of clinical trials.)
- To learn more about the Cooperative Group program, visit the Cooperative Group Web site at **http://ctep.info.nih.gov/CoopGroup/Coop_Group_Prog.html**

for many types of cancer, and the four pediatric Cooperative Groups deal with the entire range of cancers that afflict children. The leaders of the four pediatric Groups have agreed to coalesce their activities into a single structure, in order to more effectively and efficiently identify new treatments for children with cancer. The unification process, which is beginning in 1998, should be completed within approximately four years.

Cooperative Groups frequently work together to conduct large-scale clinical trials, particularly when the cancer in question is so rare that one group working alone would be unable to accrue enough patients to conduct a meaningful study. For example, six Cooperative Groups worked together on the landmark study establishing that all-trans retinoic acid (ATRA) significantly improves disease-free survival time for patients with acute promyelocytic leukemia. ATRA is now a standard component of therapy for this rare disease. Cooperative Groups regularly collaborate on clinical trials for solid tumors in children, breast cancer, colorectal cancer, lung cancer, and cancers of the head and neck.

Many new anti-cancer drugs are tested in patients for the first time under NCI Investigational New Drug (IND) sponsorships through the Cooperative Group program. Close to 200 investigational agents or treatment strategies, ranging from new chemotherapy drugs and cancer vaccines to agents that prevent tumor blood vessel development (angiogenesis), are currently being studied under NCI INDs.

A new agreement between the U.S. Office for Protection from Research Risks and the European Organization for Research and Treatment of Cancer (EORTC) promises to improve the ability of NCI's 12 Cooperative Groups to collaborate with the EORTC and other international cancer research groups. The agreement, which was created to strengthen the protection of patients in international clinical trials, will help avoid duplication of research efforts here and abroad, ease the way for large-scale trials, improve the recruitment of patients into trials for rare cancers, and ultimately, speed the transfer of laboratory findings to clinical practice.

Community Clinical Oncology Program (CCOP)
The Community Clinical Oncology Program is a network that provides the infrastructure to link community cancer specialists and primary care physicians with clinical Cooperative Groups and Cancer Centers. In addition, CCOPs support scientific development and the implementation of ongoing cancer treatment, prevention, and control clinical trials among community Cooperative Group members and Cancer Centers. This network enables individuals to participate in state-of-the-art clinical research trials at community hospitals without the added burden of traveling to a distant site. By increasing the number of patients and physicians who can participate in clinical trials, the program helps in the transfer of the latest research findings to the community.

Intramural Research

The NCI Intramural Research Program (IRP), which consists of the Divisions of Basic Sciences, Clinical Sciences, and Cancer Epidemiology and Genetics, is dedicated to the comprehensive understanding of cancer. IRP scientists, research fellows, and visiting scientists from around the world conduct basic, clinical, and population-based studies. They also collaborate with national and international investigators in academia and in the biotechnology and pharmaceutical industries to help speed the application of new knowledge to the development of products that will benefit human health.

Within the Intramural Research Program, the Institute sets a standard of scientific excellence and works to establish a stimulating environment in which young people receive mentorship, training, and inspiration and where scientists at all stages of their careers are encouraged to be creative and strive for critically important knowledge. The IRP has long served as a training locus for cancer researchers, and many leading scientists across the country and in other nations have been trained in its clinics and laboratories. It continues to be an important resource for training the next generation of men and women who will continue the quest for knowledge that we will use to prevent, control, and cure cancer.

The clinical research program of the IRP is housed principally in the NIH Warren G. Magnuson Clinical Center (http://www.cc.nih.gov) on the NIH campus. This component of the intramural program provides the opportunity for patients around the country to be treated through ground-breaking research protocols. The Clinical Center is a unique environment in which investigators throughout the NIH community develop and test novel therapies derived from our growing body of knowledge; this environment provides the rich opportunity for new information to be quickly transferred from the laboratory to the patient and back again to the laboratory for additional analysis.

Intramural Research (dollars in thousands)

	1997 Obligations	1998 Operating Level	1999 President's Budget Amended	2000 Core Budget
Basic	$127,176	$131,061	$137,400	$139,410
Clinical	96,510	103,651	101,942	111,528
Epidemiology & Genetics	35,470	42,936	39,890	46,470
NIH Central Services	153,361	160,614	163,993	167,292
TOTAL	**$412,517**	**$438,262**	**$443,225**	**$464,700**

Training, Education, and Career Development

In the past decade, we have made stunning advances in our understanding of cancer at the genetic and molecular levels. Today, we are poised to use this knowledge to develop new prevention, screening, diagnostic, and treatment interventions. But without a national cadre of scientists and physicians who are specially trained in cancer research, the Nation's scientific and medical workforce will be unable to bring new discoveries to the communities and clinics where they can benefit cancer patients and those who are at risk for developing the disease.

To address these challenges, NCI is implementing the first stages of a new strategic plan for training and

career development of basic, clinical, and population scientists. These new strategies will focus on attracting the best young scientists into cancer research and on providing stability and protected time for those disciplines critical to the translational research enterprise. NCI's strategic plan focuses on four broad objectives in the areas of training, career development, and cancer education:

• Maintain the critical mass of independent scientists studying cancer at its most fundamental levels, thereby enabling discoveries in genetics and molecular biology that will serve as the foundation for early detection, prevention, and treatment advances against cancer.

• Encourage a greater proportion of well-trained basic scientists to expand their interests to include human biology and human disease, establishing the foundation for more effective collaborations among basic, clinical, and population scientists.

Training and Education (dollars in thousands)

	1997 Obligations	1998 Operating Level	1999 President's Budget Amended	2000 Core Budget
National Research Service Awards	$44,559	$47,134	$54,619	$57,031
Research Career Program	19,661	22,861	27,236	32,289
Cancer Education Program	12,085	13,885	13,692	14,771
Minority Biomedical Research Support	2,588	2,788	3,023	3,129
TOTAL	**$78,893**	**$86,668**	**$98,570**	**$107,220**

• Attract more young physicians and public health specialists into cancer research, and continue programs that will develop a larger contingent of physicians and public health specialists in the biostatistical, epidemiological, behavioral, and other prevention and control sciences.

• Use education grants to improve medical and public health curricula and to improve community education and information dissemination programs. A critical concern in public education includes identifying how we can encourage health care professionals and the lay public to make the most effective use of current knowledge.

In pursuit of these objectives, NCI is following a number of new training and career development strategies that will enable investigators to stabilize and sustain productive research careers, and that offer greater opportunities for investigators to engage in translational research.

• Provide a continuum of career development opportunities that will sustain the careers of medical doctors in both basic and clinical research. NCI's training programs encompass support for the earliest stages of an investigator's career, for the transition support of young medical scientists starting their first independent research programs, and for protected time to enable established investigators to focus both on their own research and the mentoring of young scientists.

— *For young investigators*, the NCI Scholars Program provides outstanding young investigators with the resources to design and pursue their first independent research program within NCI's intramural environment and to facilitate their transition to an extramural environment. In addition, the Howard Temin Award has been developed to foster the careers of outstanding junior basic, clinical, and behavioral scientists who are committed to developing research programs highly relevant to the understanding of human biology and human disease as it relates to the etiology, pathogenesis, prevention, diagnosis, and treatment of cancer.

— *For more experienced investigators,* the Mentored Patient-Oriented Research Career Development Award supports the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research, while the Midcareer Investigator Award in Patient-Oriented Research provides support for clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for beginning clinical investigators. Further, NCI is creating a new "transition" award for basic and clinical scientists, which we hope to employ within the next year.

• Increase the number of prevention, control, and population scientists. A critical mass of scientists in these fields is essential to the development of early detection and prevention strategies. NCI is expanding the use of special institutional training grants for training individuals at the undergraduate and graduate levels, employing new career programs for young postdoctoral "mentored" scientists, establishing new "transition" support opportunities for scientists initiating their first independent research programs, and providing protected time for senior investigators.

• Increase the participation of underrepresented minorities in cancer research. NCI is establishing the Continuing Umbrella of Research Experience for Underrepresented Minorities Program (CURE Program). The CURE Program will enable NCI to identify highly talented young individuals as early as high school, proactively move them into the best graduate and postdoctoral training environments, and then provide transition and protected time opportunities while they are establishing their first independent research programs. Ongoing NCI training programs support minority students in the pre- and postdoctoral phases of development, with awards made through the National Research Service Awards, career development awards, supplements to institutional awards, and cancer education grants. The Comprehensive Minority Biomedical Program also supports minority biomedical career development through several mechanisms, including recently developed minority medical oncology awards intended to encourage newly trained clinicians to acquire clinical research experience in oncology. A complete list of the Institute's extramural training programs can be found at: http://deainfo.nci.nih.gov/flash/awards.htm#TP.

NCI's intramural research divisions also have begun to develop their own training programs. Examples include the Clinical Intramural Research Award, developed by the Division of Clinical Sciences to support innovative and collaborative clinical research projects that emphasize novel approaches or promising new outcomes to current research; and the Cancer Genetics and Epidemiology Fellowship Program, created by the Division of Cancer Epidemiology and Genetics, which provides interdisciplinary training in clinical, molecular, and quantitative genetics, and genetic epidemiology.

Resources for training are shrinking at many institutions, but NCI is committed to supporting research training in the many disciplines that can contribute to understanding and ultimately solving cancer's mysteries. Strengthening the skills of basic, clinical, behavioral, and population scientists is an essential underpinning of our efforts to improve public health by reducing the burden of cancer.

Research Support Contracts

The Institute uses contracts to provide support for research, information dissemination, and management. Contracts principally support program development activities in which NCI defines the area of work, provides guidelines as to how the work will be accomplished, and establishes specific deliverables. The programs that employ contracts are broad and diverse, with a vital role in laboratory, clinical, and population-based research, NCI's management infrastructure, and information dissemination to both the public and the scientific community.

The use of contracts is exemplified in the drug development program, where a range of services are acquired to support drug screening, synthesis, acquisition, preclinical testing, pharmacology, toxicology, and drug formulation activities necessary to produce a new drug. With this support, many agents are being developed clinically as a result of active NCI cooperation with biotechnology and pharmaceutical companies, accelerating the clinical testing of scientific advances emerging from these sources.

Research Support Contracts (dollars in thousands)

	1997 Obligations	1998 Operating Level	1999 President's Budget Amended	2000 Core Budget
Cancer Biology	$85,463	$79,599	$92,913	$96,281
Cancer Risk	41,258	38,427	41,651	43,161
Cancer Interventions	117,880	109,791	124,953	129,482
Cancer Control Contracts	50,099	46,661	60,874	63,081
TOTAL	**$294,700**	**$274,478**	**$320,391**	**$332,005**

PEOPLE'S STORY

UNDERSTANDING PROSTATE CANCER

My prostate cancer was diagnosed last year. I've been treated, and I'm optimistic that I'll be okay now. But choosing my treatment was hard, because no one could tell me for sure if I had the kind of tumor that grows slowly, or the kind that moves fast.

It has long been recognized that most prostate cancers progress quite slowly — so slowly, in fact, that some tumors confined to the prostate may not even require treatment. But a subset of prostate tumors are aggressive, causing many of the deaths from this disease. As a result of prostate specific antigen (PSA) screening for prostate cancer, more men are now being diagnosed at earlier stages of disease. Since prostate cancer treatment can seriously affect sexual, urinary, and bowel functions, it is critical to be able to distinguish between tumors that are potentially life altering or life threatening, and those that are not.

Identifying more refined indicators of prostate cancer prognosis is a high priority for NCI research. Currently, prostate cancer is evaluated based on serum PSA level and measures of tumor stage and grade. But researchers are now studying a broad array of markers to find those that will tell which tumors have undergone the full set of genetic and biochemical changes that lead to metastasis, and whether cancer cells have already escaped from tumors that appear to be localized. Several of these markers are showing promise, and may also help predict a man's response to treatment. Having this more precise profile of individual prostate tumors will be essential to enable men to choose the treatment with the best chance of cure and the fewest possible side effects.

I'll continue getting regular check-ups, of course, to watch for any signs of recurrence. My doctor says that for some reason, when prostate cancer comes back, it tends to show up in the bones.

Prostate cancer is one of several cancers that typically spread to the bones, causing bone degeneration and pain. Researchers are aggressively pursuing several leads to determine why this is so. One hypothesis is that bone provides a favorable growth environment for prostate cancer cells, which randomly "seed" the bone marrow from the bloodstream. Another theory is that prostate cancer cells may adhere more readily to the bone matrix, specifically to bone marrow endothelial cells, than to other types of tissue. There is also convincing evidence that prostate cancer cells may reach the spine through a connection between veins surrounding the prostate and blood vessels surrounding the vertebrae.

Research in this area is accelerating. As the mechanisms underlying bone metastasis in prostate cancer are better understood, we will be poised to develop new ways to prevent it, and to effectively treat men whose cancer has advanced.

My prostate cancer was diagnosed last year. I've been treated, and I'm optimistic that I'll be okay now.

Cancer Control

"Cancer control" is a broad term that encompasses basic and applied research in the behavioral, social, and population sciences aimed at creating or enhancing interventions that, by themselves or in combination with biomedical approaches, reduce cancer risk, incidence, morbidity, and mortality. For example, a cancer control study might investigate the use of a medical intervention, such as a nicotine patch, in combination with a behavioral intervention, such as a tool to motivate people to reduce their risk of cancer by adopting a healthier diet. Interventions may be directed at patients, physicians, or other health care providers. Cancer control research seeks to improve interventions across the human lifespan and over the entire cancer continuum, and to move research findings into clinical and public health practice. The foundation of cancer control research is epidemiology, and surveillance and outcomes research are the fundamental mechanisms for assessing progress.

NCI maintains a firm commitment to cancer control research. In 1997, the former Division of Cancer Prevention and Control was split into two new divisions, the Division of Cancer Control and Population Sciences (DCCPS) and the Division of Cancer Prevention (DCP). The DCP will bring added visibility, prominence, and strength to NCI's prevention programs, while the DCCPS will be the new focus for NCI-sponsored research programs aimed at studies in populations, behavior, surveillance, special populations, outcomes, and other aspects of cancer control.

DCCPS's wide-ranging research programs include:

• Research in epidemiology and genetics, including interactions of genetic and metabolic factors with lifestyle, social and behavioral factors, diet and nutrition, and hormones and medications; special populations with different patterns of cancer risk; and the prevalence of certain cancer-promoting genes, their associated metabolic markers, and our ability to predict cancer risk based on the presence of these genes and markers.

• The Nurses' Health Study and the Health Professionals' Follow-up Study, large-scale projects based at Harvard University that assess diet and lifestyle factors among health care professionals and how those factors play into the etiology of disease.

• The Cancer Genetics Network, which will support the development and maintenance of a nationwide system of centers that will provide information on and perform genetic testing, and, by registering potential study subjects, provide a platform from which research on the genetic determinants of cancer, counseling strategies, behavioral interventions, and other studies can be mounted.

SPOTLIGHT ON RESEARCH

Cancer Pain

Studies show that at least a third of all cancer patients undergoing treatment, and fully two thirds of people with advanced cancer, experience significant pain. Relief is possible for as many as 95 percent of patients, but pain is frequently undertreated, particularly among the elderly, the less educated, and the economically disadvantaged.

NCI's portfolio of pain research is wide-ranging. An NCI-supported study of resiniferatoxin, an anti-pain substance isolated from a cactus-like plant, will give us important information about how this agent works, and may lead to the development of new pain relief drugs. A study of the side effects of morphine and hydromorphone, the two most commonly prescribed opioids for cancer patients, will provide valuable information to physicians, who are often reluctant to prescribe these drugs. NCI-supported clinical trials of a variety of pain-relieving drugs will help us identify the treatments that are most effective. Studies of behavioral interventions such as distraction, relaxation, and imagery may offer care providers non-drug "tools" to help their patients handle pain. In addition, a variety of research projects are evaluating new tools to help patients and health care professionals assess pain, including new "coaching" techniques to facilitate discussion of pain between cancer patients and their caregivers.

• Tailored communications research, in which investigators study how best to individualize and deliver information to a person based on his or her needs. NCI-funded investigators have shown that tailored programs, which can be delivered in many formats — such as telephone, interactive kiosk, or printed materials — are more effective than standard programs in helping people quit smoking, in encouraging women to get mammograms, and in encouraging increased fruit and vegetable intake. Research is continuing to refine our understanding of how to improve tailored communications to enhance both decision making and behavior changes.

Cancer Control* (dollars in thousands)

	1997 Obligations	1998 Operating Level	1999 President's Budget Amended	2000 Core Budget
Grants	$70,013	$67,851	$90,765	$104,614
Contracts	110,420	113,355	124,453	129,209
Cancer Control Management & Support	51,485	71,929	62,489	65,676
TOTAL	**$231,918**	**$253,135**	**$277,707**	**$299,499**

*Cancer Control grant and contract funds are distributed among appropriate extramural mechanisms.

• Research aimed at preventing tobacco use among children and teenagers. NCI has teamed up with the National Institutes of Child Health and Human Development, Drug Abuse, Dental Research, Mental Health, and Nursing Research to fund innovative projects that have clear implications for the immediate and significant reduction of tobacco use by children and youth.

• New theoretical models for studies of human behavior and behavior change that will help us yield more insights from behavioral studies. Behavioral components are critical to all DCCPS research. Yet NCI recognizes the need for improved theoretical models in this area and will address the need through a program targeting the creation of new models.

NCI also is conducting research to determine how best to integrate effective prevention and early detection strategies and how to improve the efficacy of cancer-related health services in the managed care environment. For example, NCI funds the Cancer Research Network, a consortium of 10 non-profit HMOs covering nine million subscribers. Through the Cancer Research Network, the participating members will establish an ongoing research infrastructure and data resources, enabling them to collaborate with affiliated academic medical centers and NCI on critical cancer control research in defined populations. Currently, three major studies are planned: an evaluation of the smoking cessation programs developed by participating HMOs; a study designed to assess the reasons why some invasive breast and cervical cancers "slip by" our best screening methods; and a study of women at high risk for breast cancer to examine whether an intensive screening program in women under 50 has a significant impact on later breast cancer risk, and if prophylactic mastectomy prevents breast cancer in this population.

Cancer surveillance, or tracking and analyzing trends in cancer incidence, mortality, and survival rates, is a critical component of cancer control. The keystone of NCI's surveillance efforts is the Surveillance, Epidemiology, and End Results (SEER) program, which monitors the Nation's cancer burden and provides the basis for assessing individual, organizational, and societal factors that can reduce cancer rates. Through its comprehensive database, the SEER program monitors annual cancer incidence trends to identify unusual changes in specific forms of cancer occurring in population subgroups defined by geographic, demographic, and social characteristics (i.e., "cancer clusters"). SEER also tracks changes over time in the extent of disease at diagnosis, trends in therapy, and associated changes in patient survival. By calculating and reporting regularly on cancer incidence and death rates in the United States, SEER also gives us a yardstick by which to measure our progress — the program reminds us how far we have come, and how far we have yet to go.

NCI'S INFORMATION SERVICES

Many people — cancer patients, health professionals, and the general public — benefit from the NCI's array of information services. Using everything from basic printed materials to sophisticated Internet technology, NCI provides millions of people each year with the complete, trustworthy information they need to make decisions about cancer prevention, detection, treatment, and follow-up care. NCI's services include:

- ***The Cancer Information Service (CIS).*** This nationwide cancer information and referral service, available in all 50 states and Puerto Rico, receives more than 2,000 calls each day. By calling a single, toll-free number, 1-800-4-CANCER (1-800-422-6237), cancer patients, their loved ones, people at risk for cancer, and physicians can receive information about finding the best treatment, including ongoing clinical trials; learn about strategies for dealing with short-term or late effects of cancer treatment; or learn how to initiate health-promoting behaviors. Every call is kept confidential, and trained CIS staff answer questions in English or Spanish.

- ***PDQ Database.*** The PDQ (Physician Data Query) database contains the most current information on cancer prevention, screening, treatment, and supportive care, as well as active research studies and directories of physicians, genetic counselors, organizations involved in cancer care. Information summaries in PDQ are available in technical and nontechnical language and in English and Spanish. PDQ is updated monthly and is reviewed by cancer experts. Most PDQ information is available on the CancerNet™ web site (see below); selected information is available via fax from the NCI's CancerFax® service (301-402-5874).

- ***NCI's Internet Services.*** Patients and health professionals with access to the Internet may search for information about cancer on:

  — the NCI's web site **http://www.nci.nih.gov**

  — the CancerNet™ web site **http://cancernet.nci.nih.gov** or

  — cancerTrials, a new clinical trials resource, **http://cancertrials.nci.nih.gov,** that provides information about ongoing prevention, detection, diagnosis, and treatment clinical trials — including links to databases of ongoing studies — as well as general information about clinical trials.

- ***CancerLit.*** This bibliographic database contains over 1.3 million records on cancer literature from 1963 to the present. It is updated monthly and can be searched from the CancerNet™ web site.

- ***Print Publications.*** NCI produces nearly 600 publications and audiovisual materials in Spanish and English. Designed for Americans of many cultures and literacy levels, these materials address a vast range of cancer-related topics — from coping with the emotional burden of cancer, to lowering the fat content of traditional ethnic foods, to understanding clinical trials.

- ***NIH-wide Clinical Trials Database.*** NCI is participating in the creation of an NIH-wide database of information about federally and privately funded clinical trials regarding serious or life-threatening diseases and conditions as mandated by the FDA Modernization Act of 1997. NCI staff members served on the initial steering committee and now are serving on the NIH-wide committee that will develop and implement the database and other information dissemination components. NCI and other Institutes that have extensive experience with the creation and maintenance of clinical trials databases will provide valuable insight for the NIH-wide effort. In addition, NCI may be called upon to act as a service center to aide other Institutes in adding clinical trials information to the database.

Another critical component of the DCCPS is its Epidemiology and Genetics Program, which plans, develops, and manages a comprehensive program of grant-supported, population-based research that is designed to increase our understanding of the causes and prevention of cancer. Among the program's most recent initiatives are the Cancer Genetics Network and the Cooperative Family Registries for Breast and Colon Cancer Studies, both of which will speed important investigations on cancer susceptibility and prevention. The program also supports the International Consortium on Prostate Cancer Genetics in order to facilitate discovery of the underlying genetics of this cancer. In addition, DCCPS sponsors workshops and other activities to synthesize findings from studies of modifiable risk factors for cancer and to help set priorities for individual and community-based interventions and public health policy.

AIDS Research

Malignancies complicate more than 30 percent of AIDS cases and contribute a great deal to AIDS morbidity and mortality; many areas of fundamental biology developed in NCI programs, including virology, immunology, and cell and molecular biology, are directly applicable to understanding HIV and AIDS. Today, research into the fundamental biology of HIV and AIDS, AIDS treatment, and particularly AIDS-related malignancies takes place throughout all programmatic mechanisms of NCI.

NCI's Intramural Research Program has been an important, internationally recognized center for research in HIV and AIDS, producing important discoveries about HIV, pediatric and adult AIDS, AIDS malignancies, and AIDS therapeutics.

NCI's ongoing programs in AIDS research include:

• The HIV Drug Resistance Program, an NCI-led effort based at NCI's Frederick Cancer Research and Development Center. This program integrates existing and newly formed groups of investigators from numerous disciplines to discover ways to overcome the tendency of the human immunodeficiency virus to mutate in ways that render it impervious to treatment.

• The NIH Vaccine Research Center, a joint project with the National Institute of Allergy and Infectious Diseases. The goal of the Center, formed in 1997, is to stimulate multidisciplinary research in basic and clinical immunology and virology, leading to the design and development of a viable HIV vaccine.

• An AIDS Malignancy Consortium that brings together researchers, clinicians, and relevant support facilities at 13 institutions throughout the country to foster interdisciplinary research on AIDS-associated malignancies and translate laboratory discoveries into new clinical interventions.

• An AIDS malignancy tissue bank that provides resources for testing hypotheses about the development, progression, and response to therapy of these cancers.

• AIDS malignancy initiatives in NCI's clinical trials programs.

• A clinical scientist training program in AIDS oncology.

• An AIDS Oncology Resource Handbook that provides information on the current scope of NCI's activities in AIDS malignancies research.

• An AIDS Malignancy Working Group.

• The Second National AIDS Malignancy Conference, held in April 1998 to discuss progress and stimulate research across diverse disciplines; the next meeting will be held in May 1999.

NCI's research programs have been at the forefront of progress against AIDS since the epidemic was first identified. NCI, in coordination with all of the other NIH Institutes and the NIH Office of AIDS Research, continues its commitment to meeting the challenge of AIDS and is working to ensure integration of NCI-supported AIDS and AIDS-related research with national AIDS strategies.

Research Management and Support

Research Management and Support includes activities essential to sustain, guide, and monitor both the extramural and intramural activities of NCI. These activities include overall scientific program direction and administration by the Office of the Director, with assistance from grant and contract science managers, finance, human resources, legislation, science program direction and assessment, and technology transfer staff. The review and oversight activities of the National Cancer Advisory Board and President's Cancer Panel are also included. This part of the budget also supports a share of central NIH facilities and operations, and extramural program staff salaries (intramural staff salaries are included under the intramural research budget, as is intramural facilities maintenance).

Research Management & Support (dollars in thousands)

	1997 Obligations	1998 Operating Level	1999 President's Budget Amended	2000 Core Budget
Research Management & Support	$100,788	$99,091	$104,793	$110,461

Other Research Support

This area includes activities such as conference grants, resource-related research project grants, scientific evaluation, and construction grants and contracts. Conference grants support meetings, conferences, and workshops relevant to promoting the goals of NCI. Resource-related research project grants support research projects aimed at improving the capability of resources to serve biomedical research. Scientific evaluation awards are the vehicle that supports the scientific review of grant and contract proposals. The grant reviews are conducted by either the NIH Center for Scientific Review or NCI, depending on the granting mechanism. Construction funds provide partial support for the modernization or development of cancer research facilities at institutions located throughout the Nation. Additionally, limited construction funds are provided for repair and development at the Frederick Cancer Research and Development Center.

Other Research Support (dollars in thousands)

	1997 Obligations	1998 Operating Level	1999 President's Budget Amended	2000 Core Budget
Scientific Evaluation (U09)	$3,528	$3,528	$3,669	$3,797
Resource Grants (U24)	668	9,167	13,870	15,355
Construction	3,000	3,000	3,000	5,000
Conference Grants (R13)	922	898	960	994
TOTAL	**$8,118**	**$16,593**	**$21,499**	**$25,146**

Extraordinary Opportunities for Investment

Vision, creativity, planning, meticulous and methodical work, and an occasional stroke of luck — all are needed to achieve progress in cancer research. Most critical, however, is recognizing and acting on promising research opportunities at key points in time. Our world-renowned research program and the scientific process of discovery have enabled us to unravel many of cancer's mysteries, advancing significantly our understanding of cancer and, how to prevent, detect, diagnose, and treat the disease. Our discoveries also have taught us what we could not know when our quest to conquer cancer began — that cancer is not a single disease, but dozens of distinct and highly complex disorders. Despite all our progress, we know there remains much to learn and much to do to lift the burden of cancer. As we continue our work against cancer, we ask ourselves, "What more must we do to vanquish these diseases?"

We must do three things:

• We must continue to support the vital research that has brought us this far.

• We must recognize extraordinary new opportunities for further progress and invest in them. Although research often is driven by need, our history has taught that we must be prepared to seize research opportunities in order to best meet those needs.

• We must build bridges between all components of the cancer research enterprise — among all areas of research, between research and clinical practice, between research and industry, and between the cancer research field and the American people. These bridges will ensure that we close the gap between scientific discovery and cancer care.

In 1996, we began a systematic examination of the cancer research field to identify areas of discovery with exceptional promise for achieving pivotal advances — in our knowledge about cancer, and in benefits for patients and those at risk for cancer. Four frontiers of discovery emerged, together possessing the potential to provide profound insights into how cancer develops and paving the way for new and improved techniques to prevent, detect, diagnose, and treat the disease. These "Extraordinary Opportunities" for immediate investment in cancer research are:

- **Cancer Genetics**
- **Preclinical Models of Cancer**
- **Imaging Technologies**
- **Defining the Signatures of Cancer Cells: Detection and Diagnosis**

Each of these diverse scientific frontiers is ripe with possibilities for taking us to a new era in cancer prevention and cancer care. During the past two years, NCI has pursued important activities in each area through our extramural and intramural research programs. But to truly realize the enormous potential these opportunities offer, we need a more focused effort and an infusion of funds. The resources required are not trivial, but investing now will yield tremendous future benefits in new and better prevention, detection, diagnosis, and treatment techniques for people with cancer and those at risk.

SELECTING EXTRAORDINARY OPPORTUNITIES

What makes an "extraordinary opportunity" different from the many other important areas of research supported by the NCI? To be selected as an extraordinary opportunity, a research initiative must:

- Respond to important recent developments in knowledge and technology;
- Offer approaches to cancer research that go beyond the size, scope, and funding of our current research activities;
- Be able to be implemented with specific, defined investments;
- Be able to be described in terms of achievable milestones, with clear consequences for not investing; and
- Promise advances that are needed for making progress against all cancers.

We identified our four current areas for investment through a simple process. In discussing the state of cancer research with scientists, educators, advocates, and community leaders, we asked them and ourselves the difficult question, "What must we do to succeed?" We found that our most serious deficits have been primarily in failing to pursue promising leads fully. We also identified areas in which we have gathered a critical mass of knowledge, thereby providing the foundation for significant new initiatives that could render remarkable new insights and discoveries.

During a six-month period, 60 different proposals for new opportunities were put forward. Related meritorious ideas from these proposals were blended together to create the list of four opportunities.

To fully exploit the exceptional potential of the four current investment areas, we have established the NCI Director's Working Groups — ad hoc, scientific "think tanks" composed of leaders in laboratory, clinical, and population-based research, members of professional organizations, and consumer and patient advocates — to help us plan and implement activities in pursuit of our goals and objectives. Working Groups in each area met several times in 1997 and 1998. Their recommendations have already resulted in exciting new initiatives, such as the Cancer Genetics Network and the Cancer Genome Anatomy Project. Their deliberations may also result in new extramural grant or contract awards; collaborative efforts with other Institutes, government agencies, or the private sector; and new or expanded scientific programs within the divisions at NCI.

New Opportunities

We fully expect that investment in our current "extraordinary" opportunities will produce the future standards of practice, and new opportunities will emerge as scientific discoveries continue to occur. Therefore, with the selection of the current investment opportunities in 1996, we initiated a three-year cycle for revisiting and recasting these investment opportunities and identifying emerging ones. As we approach the end of the first cycle, NCI is actively seeking research opportunities that meet the criteria described earlier in this section. We invite all within the cancer community — scientists, clinicians, advocates, constituents, and NCI staff — to suggest new opportunities for consideration.

OPPORTUNITY 1

CANCER GENETICS

The Opportunity

Recent discoveries have brought us to an exciting new frontier in cancer research. Over the past 20 years, we have made important progress toward identifying and understanding the basic processes in the cell that become disrupted in cancer. We now know that cells in a tumor descend from a common cell that, at one point, became transformed through the accumulation of mutations in specific types of genes. These accumulated mutations give growth and survival advantages to the tumor cell and allow it to multiply without regard to the body's normal mechanisms for controlling growth. Invading and destroying normal tissue structures, the altered cells escape the body's normal defenses and eventually threaten the life of the individual in whom they live.

The most direct and ultimately the most effective approach to preventing, detecting, diagnosing, and treating cancer is to identify the genes involved in cancer development. Such knowledge is providing important insights into the origins of cancer — insights that are laying the foundation for developing new methods for early detection, and pointing to new targets for prevention and treatment. The number of different genes that can be mutated and contribute to the many types of cancer is large — most likely in the hundreds. Though large, these numbers are not unmanageable.

Finding Cancer Genes

We have long recognized that cancer may "run in families." About five percent of all cancers in the United States occur in individuals who have inherited a mutation that predisposes them to cancer. Several million Americans are estimated to carry such inherited predispositions. These genes, passed from one generation to the next, influence the chance of developing a tumor. Advances in our knowledge of human genetics have provided an important new opportunity to identify cancer genes through studies of cancer-prone families. In the past several years, more than 20 inherited cancer-predisposing genes have been discovered through family studies. This approach provides scientists with the molecular signposts that identify where to look for these "cancer genes."

Moreover, scientists have learned that the same genes that predispose members of cancer-prone families to disease quite often also contribute to the development of cancers in individuals with no family history of

OBJECTIVES

- Expand and integrate basic, clinical, and epidemiologic research, facilities, and training in cancer genetics to identify and characterize genes responsible for inherited predisposition to cancer.
- Develop the informatics needed to collect, store, analyze, and integrate the resulting molecular, epidemiologic, and clinical data.
- Develop diagnostic tests for alterations in these genes.
- Provide the infrastructure to establish effective interventions in individuals with inherited predispositions to cancer.
- Establish approaches to study the interaction between genes and individual genetic variations and the environment to understand cancer risk.
- Provide training in genetic counseling and in cancer genetics for health professionals and educate the public and high-risk persons about cancer genetics.

cancer. We now realize that there are not two different sets of cancer genes, one group for inherited predisposition and one for sporadic (noninherited) tumor development. The mutations that result in inherited predisposition are a subset of the ones that spur most human tumor development. Therefore, using the rare predisposition genes to learn more about the more common sporadic cases of cancer is a highly promising research strategy, and our cancer genetics initiative is designed to take full advantage of this knowledge.

Genes and the Environment

It is also true, however, that most diseases and traits do not follow simple patterns of inheritance. Because a variety of factors may influence a gene's effect, having a genetic mutation does not necessarily mean a person will get cancer. Identifying the factors that determine when a particular genetic mutation will lead to cancer and when it will not is a crucial part of our intensified efforts in cancer genetics research. We now know that cancer risk can be modified, even in individuals who carry cancer-predisposing genes. Discovering the genetic and environmental factors that influence cancer development in high-risk individuals will provide valuable insights about cancer development in the general population. These studies will require the participation of thousands of individuals.

Many lifestyle and environmental carcinogens have been identified by investigating cancer in populations (epidemiology); this knowledge has led to new approaches for reducing cancer risk. But there is still much to learn about the causes of cancer, particularly why one person with the same cancer-causing exposure (such as smoking) develops cancer, while another does not. Individuals' genetic make-up also can affect their risk for developing cancer in ways more subtle than those seen in familial cancer syndromes. Variations in how each of us controls and responds to hormone levels in our bodies; our diet; exposure to carcinogens, sun, and infectious agents; and many other factors are likely to influence our chance of developing cancer and to reveal the environmental factors that contribute to cancer's onset. Observation of these factors has led to a new field of research called molecular epidemiology. A critical part of our initiatives in cancer genetics will be aimed at identifying how these genetic variations interact with environmental exposures to cause the development of cancer.

Further, mounting evidence indicates that mutation patterns detected in certain tumors may be distinct enough to provide a molecular "fingerprint" that is traceable to specific environmental agents. In large, population-based studies now underway, researchers are exploring how genetic factors and environmental exposures, including those related to lifestyle and diet, interact to influence cancer risk. Using minute quantities of DNA in cells obtained from a simple mouth rinse, blood, or tissue, it is possible to detect gene mutations whose patterns, functions, or effects may point the way to environmental, nutritional, hormonal, and other factors that contribute to cancer. As more information about human genes becomes available, there will be striking opportunities to test the importance of newly discovered genes for both their relation to cancer susceptibility, and clues to environmental carcinogens.

Our Responsibilities in Genetic Research

The opportunities afforded by advances in cancer genetics also raise enormous challenges. What clinical, medical, psychosocial, legal, ethical, and surveillance issues arise from being able to determine inherited risk for cancer? What are the psychological, social, and family consequences? The cancer genetics investment initiative also must ensure that individuals are helped, not harmed, by personal genetic knowledge.

Therefore, we must ensure that effective and helpful genetic counseling is readily available, and we must protect the confidentiality of personal genetic information. Our plan to extend our knowledge and use of cancer genetics addresses scientific discovery, clinical research, medical application, and social responsibility.

The Goals

1. Identify every major human gene that predisposes people to cancer.
2. Begin to identify genetic variations that affect cancer risk, often in concert with environmental factors.
3. Begin to apply these discoveries through clinical practice to help patients at risk.
4. Identify and address psychosocial, ethical, and legal issues associated with inherited cancer susceptibility.

PEOPLE'S STORY

DETECTING MELANOMA

As a kid, I was outside all summer. I got sunburned every year. Later, I tanned because I thought it looked healthy — and sexy. Who knew anything about melanoma?

The incidence of malignant melanoma in the U.S. is increasing, due largely to the sun exposure patterns of populations now reaching older ages. By the turn of the century, the lifetime risk of malignant melanoma in this country is expected to reach one in 75.

Because of my coloring and sunburn history, my doctor taught me to check regularly for lesions that could be trouble.

NCI actively supports melanoma prevention efforts, providing information to physicians and the public on how to recognize suspicious moles — those with irregular borders or coloring, large size, or obvious change, or moles that itch or bleed — and how to conduct a self-examination.

At first I resisted doing the self-examinations. I felt like I was being a hypochondriac. But one day I saw a mole on my back that definitely looked different than before. It turned out to be an early melanoma. I had surgery to remove the mole and some tissue around it. I didn't need any other treatment.

Surgery alone can cure many patients whose melanoma is not advanced. The chance for cure is best if the tumor is thin — meaning it has not penetrated deeply into the surrounding tissue. Fortunately, the percentage of patients with a thin lesion at the time of diagnosis has increased over the past 20 years. This improvement has resulted from greater public awareness of melanoma in recent years and more vigilant self-surveillance by individuals who know that having sunburns in childhood, fair skin, and more than an average number of moles all increase melanoma risk.

Could my melanoma come back? I know it could, but I understand there are new treatments right on the horizon.

Studies are underway to find new drugs and drug combinations that can kill melanoma cells throughout the body more effectively than the current standard treatment. Drugs to enhance the immune system, both alone and in combination with cell-killing chemotherapy drugs, are also being studied in high risk patients. One such therapy, high-dose interferon alpha-2a, has now been approved for post-surgical therapy in high risk melanoma patients.

In addition, several melanoma vaccines are under development. Their goal is to stimulate an immune system attack on the melanoma cells by teaching the immune system to recognize certain molecules on the surface of the tumor cells. A recent study has shown that it is possible to induce a vigorous immune response even in patients with many melanoma tumors.

Research is also progressing to assess the risk of metastasis, especially in melanoma patients with thicker lesions. Several techniques are now available to detect microscopic metastases and identify melanoma patients

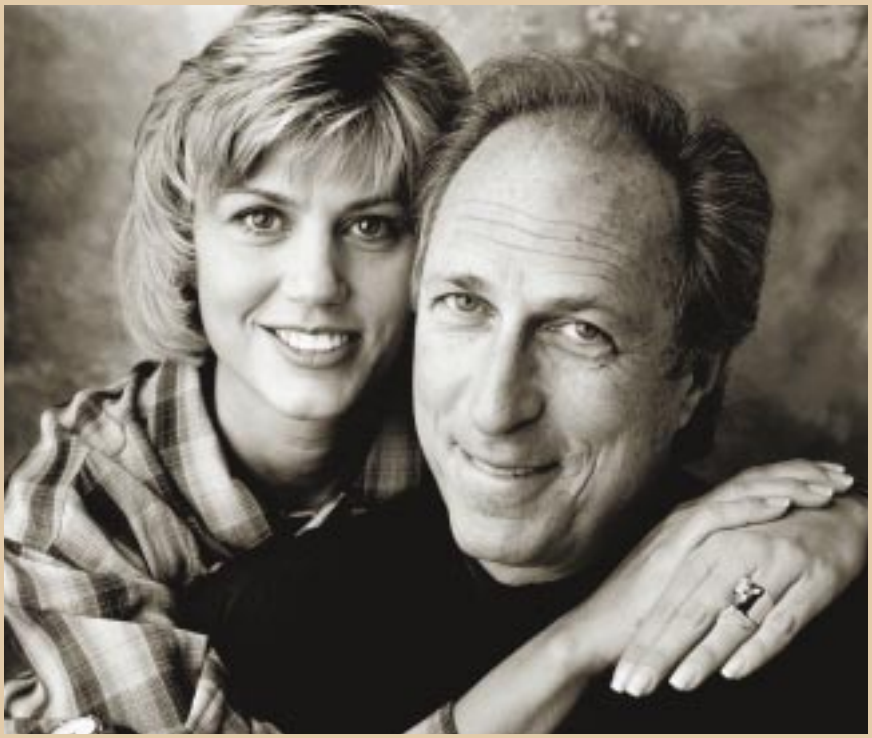
who would benefit from systemic therapy. Since 1994, two hereditary melanoma genes (*CDKN2* and *CDK4*) have been identified in a small proportion of families, and are expected, in the future, to help predict individual melanoma risk in families with a history of the disease. They may also help us understand melanoma that occurs in people with no such family history.

I understand now that I unknowingly increased my risk for melanoma. You can bet I always use sunscreen now, but I asked my doctor — is there anything else I can do?

This is an important question, since once someone has had melanoma they are at an eightfold increased risk of developing melanoma again. So, it is important to:

- avoid sunburn (in addition to using sunscreen),
- perform self-exams monthly,
- get routine exams from one's health care provider every six months to one year, and
- urge close relatives to be examined for melanoma, since one in 10 melanoma patients has a family history.

An NCI-sponsored review of recent research indicates that sunscreens alone are not sufficient to guard against malignant melanoma. Wearing protective clothing like long-sleeved shirts and hats and avoiding the midday sun also are important parts of a safe-sun strategy.



Because of my coloring and sunburn history, my doctor taught me to check regularly for lesions that could be trouble.

The Plan

To capitalize on the unprecedented opportunities and meet the challenges of the cancer genetics era, support is needed for new activities in the following areas.

• We need to support the identification of high-risk families and the multidisciplinary research infrastructure required to identify and characterize cancer predisposition genes.

• We must make available to clinical researchers the technology and resources they require to detect gene alterations and ensure that these alterations can be reliably and effectively measured.

• We must increase resources significantly, including appropriate study populations and biospecimen collections, for clinical and epidemiological research to answer key questions about inherited mutations in cancer susceptibility genes. For example, what is the cancer risk for individuals who inherit different mutated forms of a particular cancer gene? Are there effective surveillance and detection strategies to monitor for early signs of cancer? By integrating clinical, laboratory, and population-based applications, it will be possible to develop more precise and effective strategies designed to prevent cancer, improve care, and address the ethical and psychosocial issues related to genetic testing.

• We need to support training and the development of educational programs aimed at the public, people at high risk for cancer, health care providers, and payers to help them understand the enormous importance of genetics in oncology. A survey of primary care physicians found that most are not prepared to incorporate genetic information into their practice. As the volume and impact of genetic information increase, a medical work force with expertise in genetics and counseling is required, and this must be achieved quickly.

• We need to develop informatics systems to collect, store, analyze, and integrate molecular data with epidemiologic and clinical data. Several parts of the cancer genetics initiative will involve generating and analyzing massive amounts of data about dozens of genes and hundreds of possible alterations in each gene. Data on these gene alterations must be correlated with disease outcomes. These complex activities cannot be accomplished without a dynamic and accessible informatics infrastructure that allows a new level of exchange across scientific disciplines. It is also of the utmost importance to design a secure system that protects the confidentiality of all collected data.

• We must combine new techniques in molecular genetics with powerful statistical and epidemiologic approaches to investigate gene-environment interactions and their influence on cancer risk. By correlating our growing knowledge of the biological mechanisms that allow individuals to respond to the environment with detailed knowledge of genetic variation among individuals, we can begin to identify those individuals who are constitutionally susceptible to particular environmental exposures. This can help to identify people at high risk who may benefit from special interventions.

Together, these areas of the cancer genetics initiative provide a unique opportunity to attack the cancer problem at its core with speed, coordinated effort, and insight. With a national effort in this area, opportunities for key scientific advances will be gained, cancer care advances will be made more rapidly, and difficult psychosocial and societal issues will receive the timely attention they require.

Progress in Pursuit of Our Goals

Having established cancer genetics as an area of extraordinary opportunity, the NCI began intensive efforts to put in place a number of investigations and programs to help us achieve the goals we established for this initiative. As the first step in planning a coordinated national cancer genetics program, the Institute convened the Cancer Genetics Working Group to discuss research opportunities and barriers to scientific progress. This group is continuing its discussions and we expect several recommendations in the coming year.

Many of the programs in cancer genetics, both planned and underway, are large and challenging undertakings. These programs will generate crucial knowledge about genetic factors affecting cancer risk and onset. In addition, as is often true in science, many will reveal fundamental insights and provide innovative tools that will be useful to other areas of study.

In the past year, NCI launched many exciting genetics projects and fostered advancement in several already underway. The following paragraphs describe some of our activities and recent, important progress.

• As a result of the Working Group recommendations, we launched the Cancer Genetics Network — a new initiative to link participating centers that counsel, test, and monitor individuals for cancer susceptibility. Its multi-center and interdisciplinary collaborative structure will enable the participating centers to identify potential study participants and access research resources, information, and expertise beyond the scope of any single institution. It also will be a major resource for collaborative investigations exploring the genetic basis of cancer susceptibility, mechanisms to integrate this new knowledge into medical practice, and means to address the psychosocial, ethical, and legal issues associated with inherited susceptibility to cancer. Finally, the Network will support the development of critically needed educational resources. The Network ultimately will help to answer such important questions as: Does preventive surgery reduce mortality for people who carry altered cancer susceptibility genes? Which environmental exposures interact with predisposing genes to cause cancer? How can we and should we address the ethical and psychosocial issues related to cancer gene mutations? This initiative will complement existing NIH-supported programs, increasing access of individuals at risk for hereditary cancers to counseling and genetic testing within a research setting. It also will enable NCI to rapidly launch critically needed studies in this area. NCI has awarded grants to eight medical research institutions to establish the Network itself; three additional institutions have been awarded funding to develop the supporting informatics and information technology infrastructure.

• Responding to an important need in the research community, NCI has established cooperative family registries for colon cancer and breast/ovarian cancer studies, providing researchers with biological and data resources needed to explore key questions about inherited mutations in cancer susceptibility genes. These resources, which are critical to population-based genetic studies, can be extremely costly and time-consuming for scientists to generate and maintain. Having a central and accessible repository for this information will provide considerable help to scientists as they study the etiology of these cancers. As part of these registries, NCI collects family history information, epidemiologic and clinical data, and biological specimens from individuals with a family history of breast/ovarian or colon cancers. The registry also provides follow-up epidemiologic data, data on recurrence, and new morbidity, and mortality in the participating families. The Institute has established an informatics center to provide support services to effectively share the registries' resources with the research community while protecting the confidentiality of the participants.

• NCI has been involved in the formation and support of an International Consortium on Prostate Cancer Genetics. Investigators participating in this international cooperative group share the goal of more fully defining the genetic basis of prostate cancer, pooling their resources and talents, and adopting coordinated means to translate new findings into ways to benefit affected individuals and families. This initiative will be particularly important to the effort to unravel the complete interaction of genetic and environmental factors contributing to prostate cancer risk. NCI has provided special support to several investigators in this program to expedite the identification and study of genetic susceptibility to prostate cancer among African-Americans.

• Many types of cancer are complex genetic diseases, that is, they result not from changes in a single gene but from the combined, small effects of many genes and the interaction of these genes with environmental, hormonal, and other factors. An important step toward identifying every major gene involved in cancer is detecting polymorphisms variations in a gene's

RECENTLY CLONED FAMILIAL CANCER GENES

Genetic Condition	Main Cancers	Gene	Chromosome Location	Year of Discovery
Hereditary multiple exostoses 2	Chondrosarcoma	EXT2	11p12	1996
Hereditary Melanoma 2	Melanoma	CDK4	12q14	1996
Basal Cell Nevus Syndrome	Skin Cancer Childhood Brain Cancer	PTCH	9q22.3	1996
Tuberous sclerosis 1	Renal Cancer/Brain Tumor	TSC1	9q34	1996
Hereditary papillary renal carcinoma	Renal Cancer	MET	7q31	1997
Hereditary non-polyposis Colon Cancer 5	Colon Cancer Endometrial Cancer Stomach Cancer	hMSH6/ GTBP	2p16	1997
Multiple endocrine neoplasia 1	Endocrine Tumors Carcinoids	MEN1	11q13	1997
Cowden disease	Breast Cancer Thyroid Cancer	PTEN	10q23.3	1997
Familial gastric cancer	Gastric Cancer	CDH1	16q22.1	1998
Hereditary non-polyposis Colon Cancer 6	Colon Cancer	TGFBR2	3p22	1998
Peutz-Jeghers Syndrome	Gastrointestinal Cancers Breast and other Cancers	LKB1/ STK11	19p13	1998
Juvenile polyposis	Colon Cancer	SMAD4/ DPC4	18q21.1	1998
Familial gastrointestinal stromal tumors (GIST)	GIST	KIT	4q12	1998

HUMAN CANCER MODIFIER/SUSCEPTIBILITY GENES

Cancer Site	Gene Family	Gene	Chromosome Location	Year of Discovery
Bladder	N-acetyltransferase	NAT2	8p22	1980
Lung	Glutathione s-transferase	GSTM1	1p13.3	1986
Lung	Cytochrome P450	CYP1A1	15p22-15q24	1990
Lung	Cytochrome P450	CYP2E1	10q24.3-10qter	1991
Lung	NAD(P)H:quinone oxidoreductase	NQ01	16q22.2	1995
Prostate	Androgen receptor	SRD5A2	2p23	1995
Colon	Methylenetetrahydrofolate reductase	MTHFR	1p36.3	1996
Breast	Catechol-O-methyltransferase	COMT	22q11.21- 22q11.23	1997
Prostate	Vitamin D receptor	VDR	12q12-12q14	1997

sequence for cancer-associated genes. A polymorphism can have functional significance in the body if it gives rise to a protein variant or it influences the expression of a particular gene. NCI has established the Genetic Annotation Initiative, part of the Cancer Genome Anatomy Project, to develop systematically a comprehensive notation of variations in the DNA sequences of each cancer-related gene. This systematic survey will be conducted in diverse populations of different geographic and ethnic origins.

The information generated through this initiative will enable scientists to map cancer-related genes more precisely, an important step toward cloning a gene, and in turn, toward identifying the protein that the gene encodes. It also will provide a greater understanding of how such variations may influence an individual's susceptibility to cancer. By applying multiple strategies for identifying genetic variants, this initiative also will enable scientists to evaluate the best technology to use in this pursuit. NCI's Strategic Technologies Office, Laboratory of Genetic Diversity, and Laboratory of Population Genetics are working together to identify and evaluate technologies for this program.

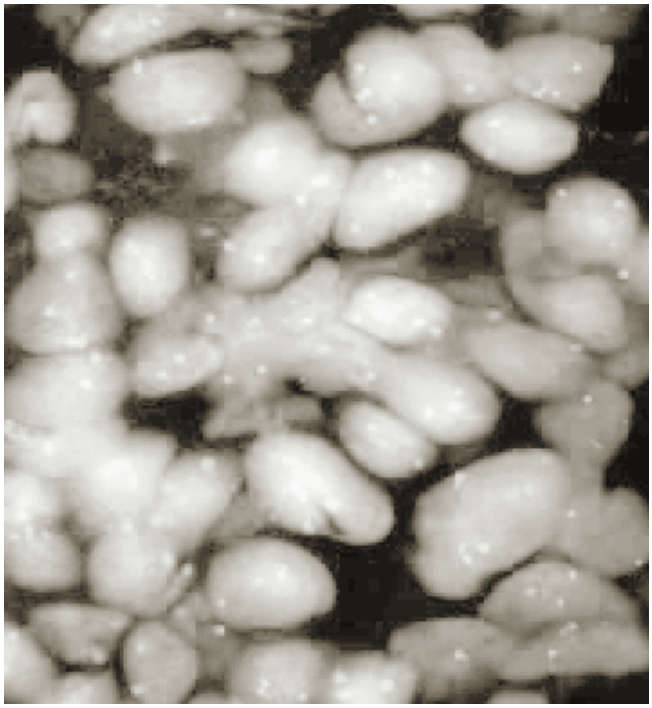


Photo Courtesy of K. Chin, S. Lockett, and J.W. Gray

Scientists use the versatile tool, fluorescence in situ hybridization (FISH), to examine DNA and identify the number of copies of specific genes in human breast cancer.

• A common type of DNA sequence variation in humans, known as single nucleotide polymorphisms (SNPs), is proving to be a powerful new tool for genetic analysis. SNPs can be used as genetic markers in gene mapping studies and also can be used to understand differences in vulnerability to a disease — such as cancer — among individuals in a population. NCI is joining a NIH-initiative to support the development of effective and cost-efficient technologies to develop a high-density map of these slight-but-telling differences in DNA and to identify the variations that are associated with cancer development.

• In addition to the Genetic Annotation Initiative, NCI is pursuing a number of other projects to identify genes involved in cancer development. For example, we plan to support studies to generate and use bacterial artificial chromosome (BAC) clones — a standardized set of gene mapping tools valuable to mapping studies because they contain large inserts of human DNA — as fluorescent probes to identify cancer chromosomal aberrations. NCI's decision to pursue these studies was based on the recommendations developed in a recent workshop attended by research experts from universities and industry throughout the country. BAC clones provide an exciting opportunity to identify the location of cancer genes throughout the human genome. In addition, identifying recurring chromosomal abnormalities can be useful to the clinician, enabling the diagnosis, classification, and treatment selection for a particular tumor. With the explosion of information now available on chromosome aberrations, there is a great need for a public database that compiles this information. NCI plans to support the development of a database of chromosomal abnormalities in cancer that integrates existing databases with clinical data from NCI-supported cooperative groups and Cancer Centers. This database will significantly help research efforts to identify cancer genes and greatly enhance the interaction between clinical and basic researchers.

• NCI has put into place funding for studies to further explore how the interplay of genetic, environmental, and lifestyle factors may increase the risk for cancer. The Institute is encouraging

MODIFYING BREAST CANCER RISK: AN INTERVIEW

You counsel women with genetic alterations that raise their risk of breast cancer. Naturally, women are very upset to learn they have an altered gene, especially if there's already a family history of the disease. But what do we really know about risk factors for breast cancer?

Our understanding of breast cancer risk factors continues to improve. For example, we have discovered that certain alterations in the *BRCA1* or *BRCA2* genes — gene changes that occur somewhat more often in families at high-risk for breast cancer — confer an increased risk for breast cancer, although this risk is less than originally thought. In addition to these gene alterations, factors that indicate higher than average breast cancer risk include:

- A personal history of breast or ovarian cancer
- Having a mother, sister, or daughter with the disease
- Having two or more close relatives (including first cousins) with breast or ovarian cancer histories
- A diagnosis of premalignant breast disease
- A history of two or more breast biopsies.

Are there other factors that raise breast cancer risk?

Other factors believed to influence risk are: more than 75 percent dense breast tissue as indicated by a mammogram, early age at menarche, first birth after age 30, and late menopause. These last three factors affect a woman's lifetime exposure to estrogen, which promotes normal breast cell growth and development throughout life and can promote breast tumor growth in women who may be predisposed due to genetic or environmental reasons. In addition, women must remember that their breast cancer risk increases as they age.

Does this mean women with these risk factors are certain to get breast cancer?

Importantly, having one or more risk factors does not mean a woman is certain — or even likely — to develop breast cancer. Among women with a strong family history but no other risk factors, three-fourths will not develop the disease. At the same time, not having known risk factors does not guarantee freedom from breast cancer. Most women who develop breast cancer do not fall into a known high risk category.

What can a woman do to minimize her risk of breast cancer?

Although many breast cancer risk factors cannot be changed, research indicates that women can choose behaviors that may modify their impact. It is becoming clear that weight gain after menopause raises breast cancer risk. A recent study of Asian American women found that weight gain in the decade immediately preceding breast cancer diagnosis most predicted breast cancer risk. Recent weight loss reduced risk in all age groups compared with women whose weight did not change. Similarly, an NCI study of 95,000 nurses found that gaining weight raised breast cancer risk in the group of postmenopausal women not taking estrogen supplements. Estrogen levels are higher in heavier women because estrogen is made by fat cells as well as the ovaries.

Can diet affect a woman's risk?

Questions remain as to whether specific dietary elements may raise or lower breast cancer risk. For example, research on the role of dietary fats now suggests that monounsaturated fats (found in olive, nut, and canola oils) do not increase breast cancer risk substantially, while polyunsaturated fats (in seafood,

soybean, corn, safflower, and sunflower oils) may raise risk. There is controversy about whether or not saturated fats in meat and dairy products, known to contribute to heart disease, raise breast cancer risk in post-menopausal women. Weight gain as an adult does raise this risk.

Another element of diet — alcohol — has been shown to raise breast cancer risk among women with higher levels of regular consumption. This may be due to the fact that alcohol raises estrogen levels. But some scientists think that one drink per day may provide substantial protection against heart disease, the cause of far more deaths in women each year than breast cancer, with only a very small added breast cancer risk.

Are there any medical interventions to prevent breast cancer?

New findings indicate that the anti-estrogen drug tamoxifen can prevent breast cancer in high-risk women. However, since tamoxifen can have serious side effects, the decision to take it must be made by each woman in consultation with her doctor. More study is needed to assess tamoxifen's preventive value for other groups of women.

Although many breast cancer risk factors cannot be changed, research indicates that women can choose behaviors that may modify their impact.

Is screening important?

Mammography does not prevent breast cancer, but it is an important tool for minimizing the risk of dying from the disease. Although early detection of breast cancer by mammography does not assure that a woman's life will be saved, the five year survival rate of women with localized disease is now 97 percent. Because current mammography still may miss up to 25 percent of breast tumors in women in their forties, compared to about 10 percent of women older than age 50, researchers are working hard to improve breast imaging technology.

Any final thoughts?

The more we know about breast cancer risk factors and how they may be modified, the more women will be empowered to minimize their risk of this disease. Like them, I am encouraged by new discoveries in this area.

researchers from multiple disciplines to work jointly on these studies. Information about cancer risk generated by these studies will inform our efforts to develop effective prevention and intervention strategies.

• With our expanding knowledge of genetic risk for cancer comes the challenge to use this information to help patients at risk. As a first step, NCI has added to our Physician Data Query (PDQ) database a directory of cancer genetics providers whom individuals may consult to gain additional information and guidance about currently available genetic tests to determine risk for certain cancers. PDQ also has established a new editorial board on cancer genetics, composed of experts in the numerous disciplines involved in this area; the board currently is developing information summaries about genetic factors associated with breast and colon cancer.

• NCI has launched an initiative to support basic biobehavioral studies on cancer related behaviors. These studies promise to provide a greater understanding of the complex interplay of genetic, neurobiological, and environmental factors that underlie the initiation and maintenance of smoking, dietary, and exercise practices. Such knowledge will be valuable for developing novel pharmacological and behavioral cancer control interventions.

• Training scientists to expertly explore important questions in cancer genetics is vital to advancing our knowledge of cancer genetics. Within our intramural program, the NCI offers two types of training fellowships. The Epidemiology and Biostatistics Fellowship provides pre- and postdoctoral training to conduct research on environmental and host determinants of cancer. The Cancer Genetics and Epidemiology Fellowship provides interdisciplinary training to conduct studies on genetic determinants of cancer and the role of gene-environment interactions.

Consequences: Investing versus Waiting

We cannot turn back from the frontier of genetic medicine. Our plan for cancer genetics, designed to identify all major cancer susceptibility genes, will enable us to help prepare our Nation and its health care system to embrace the benefits and proactively address the potential pitfalls of genetic medicine. Failure to establish our national cancer genetics plan now will have grave and far-reaching consequences. If we do not make this investment, we will not be able to respond to individuals who want to know if they are at increased risk for cancer due to an inherited predisposition. Without this investment, we will be unprepared for the ethical, legal, and other challenges associated with genetic testing. Without this investment, we will be unable to answer the questions health care providers and individuals will have about what to do with this potent information. Without this added investment, we will be unable to offer participation in important clinical trials and careful counseling to millions of Americans who will seek guidance and answers. Without this plan, we will be severely limited in our ability to clarify decades of observations about environmental contributions to cancer incidence to better identify preventable causes. Finally, without this added investment, we will not be able to utilize fully and rapidly the advances in cancer genetics to improve our understanding of cancer and loosen its grip on our people.

Failure to seize this opportunity will slow the pace of research at all levels, and many people who could have been helped will not be. Ultimately, we will have missed new possibilities for prevention, early detection, and treatment. This is a pivotal opportunity to provide leadership in addressing the fundamental societal issues that accompany genetic testing. We are quickly approaching an era when genetic testing will be widely available. Already, tests for certain gene mutations are available outside the research setting, and the benefits and drawbacks of using them are hotly contested. By establishing a clear, integrated plan, we will pave the way for the ethical use of genetic testing and provide the basis for responsible growth and development in this new frontier of medicine. The cancer genetics initiative offers a plan to build firmly on our recent discoveries and, as importantly, to generate new ones.

CANCER GENETICS RESOURCES FY 2000

Cancer Genetics Network **$8.0M**
- Conduct collaborative studies to further understand the genetic basis for cancer susceptibility
- Develop cancer genetics educational programs
- Develop informatics associated with the Network

Population and Family-Based Registries **$12.0M**
- Expand existing registries
- Increase access to these registries
- Utilize registries for gene discovery

Genetic Annotation Initiative **$5.0M**
- Identify genetic variations in cancer-related genes
- Adapt technologies for clinical detection and measurement of genetic variation

Comprehensive Molecular Analysis **$11.0M**
- Integrate cytogenetic and physical maps of the human genome for more precise mapping of all cancer chromosomal aberrations
- Develop technologies for the comprehensive analysis of chromosomal aberrations
- Adapt and support translation of technologies for use in clinical and population studies
- Conduct pilot studies linking comprehensive molecular analysis of tumors to population-based studies and clinical data
- Develop informatics to analyze and integrate molecular analysis data with epidemiologic and clinical data
- Develop and make widely available a data-base of cancer chromosomal aberrations

Gene Environment Interactions **$19.5M**
- Collect and maintain population-based repository of biological specimens
- Develop and implement questionnaire for environmental risks
- Measure exposure to environmental risk factors
- Develop tools for the molecular analysis of environmentally induced alterations of genes
- Assess impact of complex interactions between genes, environment and lifestyle on cancer risk
- Develop informatics associated with this effort

Training and Educational Programs **$7.5M**
- Develop additional public educational resources
- Assist healthcare providers in gaining expertise in genetics and counseling
- Develop pre- and postdoctoral programs for training in cancer genetics

Management and Support **$4.0M**

CANCER GENETICS TOTAL: **$67.0M**

OPPORTUNITY 2

PRECLINICAL MODELS OF CANCER

The Opportunity

Our research and discovery process has identified an initial array of important cancer genes, and we now are poised to discover all of the genes that, when mutated, contribute to human cancers. As crucial as we know this work to be, we also know that we must go beyond simply identifying these cancer genes — we must understand how changes in these genes contribute to the transformation of a normal cell into a life-threatening cancer. This critical knowledge will be the underpinning for the next generation of interventions to prevent and treat cancer.

Yet the study of cancer genes and how they change the properties of normal cells has been limited by the types of experimental systems or settings available for such studies. To truly understand how a cancer gene disrupts the normal processes of a cell, we need to manipulate genes in a living system and then study the biological effects of the alterations we introduce. For both technical and ethical reasons, we cannot perform these studies in humans. We need experimental models that mimic the wide variety of human cancers. The lack of these models has been a major roadblock to the discoveries needed to reduce the cancer burden in people. This roadblock now has been overcome by several recent advances that have brought us to a threshold of unprecedented opportunity.

New techniques now enable us to modify the genetic make-up of animals and simple organisms to serve as preclinical models of human cancer, facilitating both basic science investigations and the testing of promising preventive or therapeutic agents. This technology will be used responsibly, and NCI is committed to the humane care and use of animals in research. These models will be extremely important to us, allowing us to study and understand cancer in ways that were impossible even a few years ago.

OBJECTIVES

- Develop new preclinical models of cancer to study gene mutations important in human cancers.
- Provide a natural setting for studying all stages of tumor development.
- Facilitate more rapid testing of cancer prevention and detection strategies and new treatment regimens.

Mouse Models

For example, new advances in mouse genetics offer the opportunity to study tumors in a natural mammalian setting that accurately parallels human cancer development. Before this new technology, we could not make animals susceptible to specific cancers via the same genetic predispositions now known in humans. Our previous use of mouse models largely relied on injecting human cancer cells into mice that are immunologically compromised in order to allow the human cells to survive and grow into tumors. In general, this procedure involved injecting the cancer cells under the skin of the mice. This route obviously does not parallel the development of human cancer, and therefore, it is not surprising that these mouse models have failed to predict accurately the behavior of human cancers and their responsiveness to therapy.

Researchers now can alter mouse genes and introduce the same mutations that occur in human cancer into a mouse. These mutant mice predictably develop specific cancers and pass these susceptibilities to their offspring in the same way that humans may inherit a predisposition to a particular type of tumor. With these models, we can examine every stage of tumor development, from the very early stage when a tumor first appears to the advanced stages when the tumor spreads to distant sites within the body. Importantly, we will be able to analyze the gene mutations that occur at each of these stages, thereby speeding our discovery of the remaining complement of cancer genes.

Understanding the early stages of tumor development will help us develop better tools for detection and diagnosis. Similarly, these mouse models will help us understand the complicated and most deadly later stages of tumor spread and invasion, so that we can develop better therapies to save patients with advancing disease.

Non-Mammalian Models

Models using even simpler organisms like flies, worms, and even baker's yeast are other powerful examples of how we can learn about human cancer by studying non-human systems. As each new cancer gene is discovered, we need to determine why its mutation can lead to cancer. One approach to learning this is to study a relative of that human gene in an organism where its normal role can be determined more easily. One of the great advances in modern biology has been the realization that the function of specific genes has been conserved through hundreds of millions of years of evolution.

At least three examples illustrate the growing value of studying simple organisms to reveal mechanisms of human cancer. Studies of the nematode, *Caenorhabditis elegans*, have identified several genes in the *ced* family — which correspond to genes in mammals — that play important roles in regulating programmed cell death (PCD). Programmed cell death is a normal backup system used by many organisms, including humans, to prevent unrestrained cell proliferation or destroy a highly damaged cell. Cancer cells, however, evade this system. Researchers now are examining the activities of the *ced* genes to gain a greater understanding of PCD in humans, research that will have important implications for our understanding of cancer. Yeast models and breast cancer provide a second example of the benefit of using these simple organisms in cancer research. Although researchers recently determined that inherited mutations in the *BRCA1* gene predispose individuals to breast and ovarian cancers, the biological function of this gene is largely unknown. The *BRCA1* gene,

SPOTLIGHT ON RESEARCH

A Model for Lung Cancer

Recently, a group of NCI-supported researchers made an important contribution to the area of lung cancer research by developing an elegant animal model for studying how tumors develop and progress in the lung and analyzing the effectiveness of potential therapeutic agents for preventing and treating lung tumors. By exposing hamsters to decreased levels of oxygen and to certain nitrosamines — potent tobacco-associated carcinogens — the researchers were able to induce pulmonary adenocarcinomas and small cell carcinomas in the animals. These two tumor types are most commonly associated with tobacco use in humans. Interestingly, the researchers also found that the nitrosamines bind to specific receptors on the surface of the tumor cells; by binding to these receptors, the nitrosamine signals the cell to proliferate. This piece of information provides some intriguing insights into how tobacco-associated carcinogens not only initiate but promote tumor growth.

however, appears to be similar to a *RAD* gene in yeast that is involved in DNA repair. Scientists now will be able to explore this and perhaps other corresponding genes in yeast in an effort to gain a greater understanding of the role of *BRCA1* in humans. Finally, simple organisms are providing important opportunities in the study of colon cancer. Scientists recently discovered that a hereditary form of colon cancer, non-polyposis colorectal carcinoma syndrome (HNPCC), is associated with mutations in the genes responsible for DNA mismatch repair. Now, studies of bacterial and yeast genes that correspond to human mismatch repair genes promise to provide a fuller understanding of the role of these genes in HNPCC and sporadic colon cancer.

These simple organisms are providing valuable biological models that are helping us understand how cells make the decision whether or not to divide. Since cancer cells grow and divide in an uncontrolled way, a detailed understanding of cell division is critical to understanding cancer. We know that many of the cancer genes already identified play a role in cell division. Indeed, over the past 10 years, we have learned that these genes relate to each other as they normally function, forming a network of cell division controls. The many cancers within this disease family share numerous common mechanisms. We now have the opportunity to use these relatively simple and easily manipulated biological systems to determine how cancer-causing mutations force cells to divide at inappropriate times. Findings such as these can then be translated to human systems and refined — a dramatic shortcut to gaining important new knowledge and reducing the time between gene discovery and the development of therapies targeting the specific changes that lead to cancer.

Testing New Treatment and Prevention Strategies

Cancer therapeutics research will benefit significantly from animal models that faithfully represent the great variety of diseases we call cancer. Developing animal models for human cancer predisposition and development will allow us to test prevention strategies and facilitate the development and evaluation of agents that could intervene in and arrest the disease process.

As we enter an era when cancer therapy will be tailored to the particular mutations that permit tumors to develop, we will need these accurate models to test new therapies more rapidly. These systems will allow us to answer critical questions, such as why a particular therapy works in some cancers but not in others. New ideas and new approaches to therapy abound — from manipulating the immune system to gene therapies. We require experimental settings such as these animal models to emulate quickly and safely the real problems and potentials of 21st century therapeutics.

These are only a few of the opportunities for which model systems can be created to further our understanding of cancer and hasten our progress in developing new methods for detection, diagnosis, and treatment. The applications of these models may be virtually limitless.

The Goals

1. Create models of tumor development in mice based on our knowledge of human cancer genes and use these models to study the biology of tumor development.

2. Use the mouse models of tumor development to study methods of cancer intervention:
   a. Test potential strategies for preventive interventions to block the development of tumors.
   b. Analyze new methods to treat tumors after they have developed.
   c. Establish the best approaches for early cancer detection and diagnosis.

3. Use simple organisms as tools for discovery to help understand the normal role of human cancer genes and to determine both how normal cells make decisions to divide and how cancer cells lose the ability to make these decisions correctly.

4. Develop the infrastructure and procedures needed to make these models available to all researchers.

The Plan

The need for this technology and the potential for significant, concrete advances against cancer are great, but at present we cannot fully exploit this extraordinary opportunity for progress. Creating mouse and other models of human cancer is now technically possible, but we lack the infrastructure to develop and distribute efficiently to the research community the range of models necessary to represent human cancer and to validate these as predictive models of human cancer. The expense and logistics of creating and maintaining these animal models is beyond the budgets available to individual researchers. Added investment and infrastructure are essential to support, manage, and coordinate the use of these powerful new preclinical models. Specific steps in our plan include the following:

We require experimental settings such as these animal models to emulate quickly and safely the real problems and potentials of 21st century therapeutics.

• Support the development of mouse and other non-mammalian models. These preclinical models must be tested and refined to ensure that they accurately reflect important characteristics of human tumors.

• Establish repositories, distribution mechanisms, and related procedures to make these models available to all researchers.

• Gather the knowledge and develop the expertise and technology to validate these biological models and to use them to their fullest potential in cancer research.

• Develop a work force that is expert in the genetic manipulation of mice, the manipulation of other relevant genetic systems, complex genetic analysis, and mouse pathology.

Progress in Pursuit of Our Goals

Our many activities in this area during the past year underscore the importance that the Institute — and the cancer research field — place on developing and validating models to study human cancer. All of these efforts are being pursued in response to the field's needs in this area and some have grown directly from the recommendations proposed by the Preclinical Models of Human Cancers Working Group — convened to identify the major opportunities and barriers to developing and disseminating biological models for cancer. Recommendations from this group also formed the basis for an NIH-wide effort to devel op-mouse genomic and genetic resources. Some of our new and continuing projects are described below.

• The mouse is an important model for cancer research. The availability of strains selectively bred for certain characteristics provide a well developed system for mammalian genetic analysis. In addition, scientists can use the mouse to develop models for many human diseases. Among the most exciting of NCI's activities in this area is the Mouse Cancer Genome Anatomy Project, or m-CGAP. NCI has already initiated the landmark human Cancer Genome Anatomy Project that will provide the tools to determine the complete profile of expressed genes in normal, precancerous, and cancerous human cells, with the aim of making it possible to recognize all major steps of tumor development. The m-CGAP is a parallel and complementary effort that will accelerate the discovery of genes and gene pathways involved in human cancer development by taking advantage of our ability to manipulate mouse genes, enabling us to compare mouse cancer stages with those of human cancers at the equivalent body site. NCI also is participating in an NIH-wide initiative to generate a gene-based physical map of the mouse genome. This should greatly increase the usefulness of the mouse for cancer research, and aid the isolation and cloning of mouse genes. Once identified, many human genes will be studied in the mouse and information obtained in such studies can then be applied to human studies.

• Through the Mouse Models of Human Cancers Consortium initiative, NCI is creating a consortium of scientific laboratories and teams of scientists dedicated to developing, validating, and characterizing mouse models of human cancers. These models can be used both to gain greater understanding of the biological pathways and mechanisms associated with cancer development and to test therapeutic, prevention, and early detection strategies. Accomplishing this work will require the efforts of scientists with knowledge and expertise from a variety of scientific areas, including mouse genetics, animal husbandry, mouse and human cancer pathology, and human cancer biology. The consortium addresses the urgent need for a coordinated mechanism to support this important work, and is specifically designed to foster the exploration of innovative, new technologies that will advance research in this area; promote information exchange between participating laboratories; establish linkages to the basic, clinical, prevention, and control research communities; and identify the best ways to provide access to animal models by the cancer research community. To make existing and newly developed mouse models available to all researchers who wish to use them, a mouse models repository and distribution center is planned.

Related activities are planned within the Mouse Genomics Center of NCI's Intramural Program. Researchers in the Center plan to develop mouse models of human cancer, identify and clone tumor suppressor and modifier genes, and develop a resource center dedicated to a variety of activities, including cryopreservation and training.

• The development, care, and maintenance of model systems can be a challenging and expensive venture. Scientists often find, however, that funding provided for this area of research is not adequate to cover unanticipated animal costs. In light of this, the Institute has established administrative supplements for NCI-funded investigators whose research includes the development of preclinical models. These supplements are intended to support institutional costs and maintenance expenses that are higher than originally budgeted in the grant, unanticipated results and new opportunities that arise during the grant period, and opportunities that link the non-mammalian models research community and the mammalian model/cancer research communities.

• In the area of non-mammalian models, NCI is developing an initiative to encourage the use of lower organisms in cancer research. Lower organisms are a valuable tool for a variety of reasons: the genomes of several are or soon will be sequenced; they are easier to manipulate genetically than are more complex organisms; and they possess many of the cellular processes important in the development of cancer in animals and humans. This initiative should provide an opportunity for new collaborations between the cancer research community and investigators whose research uses lower organisms. In addition, the Institute has established an initiative to encourage the use of non-mammalian organisms for use in drug development research. Such research potentially can be useful for identifying cancer-associated genes or gene products that can be targeted in treatment. NCI also is participating in an NIH-wide effort to develop genomic resources to enhance research using lower organisms as models for disease.

• Finally, NCI plans to join an NIH-wide consortium focused on using the zebrafish as a model for studying human developmental or disease processes. The zebrafish is an excellent genetic model, enabling easy identification of mutations that affect either specific organs, biochemical pathways, or specific biological functions. Specifically, NCI has two ongoing initiatives in collaboration with other Institutes. One initiative focuses on developing zebrafish models to help identify and place genes in functional pathways that, when altered, result in uncontrolled or cancerous growth. A second initiative is to provide genomic resources to researchers using zebrafish as a model.

Consequences: Investing versus Waiting

Good biological models quicken the pace of discovery. The use of simple genetic systems has the potential to enhance greatly our understanding of the genetic mechanisms involved in the cancer process

and can be expected to uncover new targets for therapeutic and preventive interventions.

Past research investments have yielded a wealth of innovative ideas and approaches to early detection, prevention, and treatment of disease. We believe animal models represent the most rapid, efficient, and cost-effective way to assess the potential of these innovations. In all areas of medicine, the new ability to create valid models of specific diseases is revolutionizing safety and efficacy testing of these much needed interventions. Failure to make full use of this breakthrough technology in cancer will greatly limit the number and types of novel therapies that we can test. Moreover, we will continue to be hampered in our ability to prioritize promising interventions and assess their readiness for human clinical trials. The backlog of new ideas and new approaches is growing, but we can neither afford nor justify trying them all in humans.

If we fail to enact this plan, we will have abandoned a practical way to test interventions that may allow us to prevent the development and progression of cancer. Without the tools this plan will provide, our understanding of the environmental and dietary factors that alter cancer risk will remain limited.

We are committed to discovering more rapid, more accurate, and more economical means to translate basic research to the benefit of patients, and we believe that animal model technology will increase the flow of ideas into testable clinical applications. If we do not invest in designing new biological models and making them widely available to researchers, we will be tied to a slower pace of progress; too many worthy ideas will have to wait in the long queue for human clinical trials without the guidance that compelling results in animals could provide. We must enact this plan to capitalize on this technology's enormous potential to deepen our understanding of cancer and help us find ways to conquer it.

PRECLINICAL MODELS OF CANCER — FY 2000

Mouse Cancer Genome Anatomy Project (m-CGAP) — **$4.3M**

- Produce 50 cDNA libraries from mouse cancer models
- Produce 100 cDNA libraries from different stages of mouse development and anatomical sites
- Sequence tag 400,000 mouse gene transcripts

Mouse Models to Study the Biology and Treatment of Human Cancers — **$21.0M**

- Improve technology for development and validation of mouse models
- Develop and validate mouse models of human cancers
- Establish database of mouse models
- Utilize mouse models for the identification and evaluation of detection, treatment, and intervention strategies
- Improve access to validated mouse models
- Train a workforce expert in the genetic manipulation of mice, genetic analysis, and mouse pathology

Gene-Gene Interactions: Identification of Modifier Genes — **$6.0M**

- Develop new initiative to identify genes that modify cancer phenotypes in mice

Non-Mammalian Organism Models to Find Oncogenes, Cancer Pathways, and Screens for Anti-Cancer Drugs — **$9.0M**

- Identify and study cancer gene homologs in non-mammalian models
- Develop screens for anti-cancer drugs in these systems

Management and Support — **$1.0M**

PRECLINICAL MODELS OF CANCER TOTAL: — **$41.3M**

OPPORTUNITY 3

IMAGING TECHNOLOGIES

The Opportunity

Medical imaging advances in the past quarter century have been nothing less than astounding. X-ray and other imaging techniques have made it possible to diagnose abnormalities of the bones, organs, and other body structures, often before they have caused irreversible damage. These advances have revolutionized the care of patients, eliminating many of the crude and painful procedures of the past.

In no field of medicine has the diagnostic usefulness of x-ray imaging been more phenomenal than in oncology. In many parts of the body, cancers too small to be detected by physical examination can be pinpointed by imaging and treated before they can spread. Early detection of breast cancer by x-ray mammography saves the lives of many women.

But as we survey our progress thus far and our use of current imaging techniques, what is most striking is the breathtaking potential of imaging technologies to advance still further our capacity to painlessly search out tiny colonies of cancer cells and monitor the effectiveness of our treatments.

OBJECTIVES

- Improve diagnostic imaging technology so that it is both sensitive and specific enough to detect very small numbers of tumor cells.
- Develop functional imaging to observe the characteristics of tumors and the effects of therapy.
- Create an infrastructure to rapidly assess new imaging technologies.

Current Imaging Techniques

Imaging has revolutionized medical diagnosis perhaps more dramatically than any other area of clinical medicine. A radiologist practicing a quarter century ago would dismiss as science fiction the possibility of the richness and precision of information now provided by a routine computed tomography (CT) scan.

We know that several different types of physical processes can interact with living tissue and produce useful images. X-rays can be collected, recorded, and analyzed to produce plain images on film or CT scans. Radioactive materials called tracers, when introduced into the body, seek out a particular organ or structure (such as a tumor) and can yield an image of that organ or structure when the decay of the tracer is detected by special sensing devices. The responses of tissue exposed to a changing magnetic field can be recorded as magnetic resonance images. Sound waves of high frequency (ultrasound) can pass through the body and produce images in real time of rapidly moving or stationary anatomical structures.

As a result of these developments, organs deep within the body can now be biopsied by long, thin needles guided safely to their targets by CT or ultrasound scanning, in many cases eliminating the need for general anesthesia and an open surgical procedure. Adaptations of magnetic resonance imaging (MRI) permit the refined visualization even of the arteries of major organs without the need for painful and potentially hazardous injection of contrast material into

these vessels. Yet we still have far to go to realize the full potential even of the techniques already available to us.

Images of Our Future

For example, most routine imaging techniques show us the anatomic size, shape, and in some cases the density of an organ or an abnormality within an organ. Sometimes the appearance of an abnormality is so characteristic that we can infer what the abnormality is (in other words, it strongly suggests a specific diagnosis), but most often it is not. Certain currently available techniques, such as positron emission tomography (PET) or single photon emission computerized tomography (SPECT) imaging permit visualization of the physiologic or metabolic characteristics of a tissue, including tumor tissue. These characteristics might include, for example, the glucose utilization rate within tumor tissue or the kinds of receptors covering the surface of the tumor. Such information may soon help us choose the most effective therapy, or may tell us, without the need for a biopsy, how a tumor is responding to a recently administered treatment. Gazing further into the future, it is even possible to imagine that metabolic imaging techniques eventually may be extended to identify disrupted cellular signaling pathways or specific patterns of gene expression.

Pictures beamed back to earth from orbiting satellites and interplanetary probes have shown us the medical promise in applying computer technologies to enhance and manipulate images so that they can be better appreciated by people. Extending this technology to medical imaging has potentially profound implications for detecting cancers at their very earliest stages. Neural networks are a component of some artificial intelligence technologies that can be "trained" to recognize patterns. Already, the application of neural networks to patterns imaged using standard x-ray mammography has suggested that neural networks can be "taught" to distinguish between malignant and non-malignant breast images with impressive accuracy. Since we know that mammography saves lives, the demonstrated potential of these new technologies to enhance mammography has compelling implications for extending image enhancement and pattern recognition to other cancer medicine applications.

The potential benefits of enhanced medical imaging in cancer care are extraordinary, and they are attainable. Improved imaging will contribute to a better understanding of human tumor biology, to more accurate cancer detection and diagnosis, and to better prevention and therapy. Paradoxically, this tremendous scientific promise comes at a relatively inhospitable time for the introduction of innovative technologies in medicine. Health care providers are under severe pressure to contain costs and are less willing than in the past to make large capital investments; the promise of more accurate images will not be sufficient to justify new equipment purchases unless there also is evidence that the greater accuracy translates into cost savings or better clinical results. These economic realities are making industrial developers of imaging technologies reluctant to invest in risky projects that have little or no prospect of near-term gain, even if the potential long-term payoff is very high. This issue will need to be addressed to realize the vast potential of imaging in cancer diagnosis and care.

The Goals

1. Discover and develop techniques that will increase the precision, accuracy, and scope of imaging diagnosis.
2. Integrate imaging further into the practice of clinical oncology.

The Plan

To advance medical imaging technology for the benefit of cancer patients and those at risk, we must address three particularly important challenges. Specifically, we must:

• Develop a plan for a comprehensive imaging research program.

• Coordinate the development of imaging technology with medical need.

• Create a suitable infrastructure for the timely and definitive clinical evaluation of emerging imaging technologies.

Progress in Pursuit of Our Goals

Over the past year, NCI launched a number of imaging initiatives in an effort to respond to the important challenges described above. As an initial step, we created a Working Group devoted to imaging technologies. Identical in concept to the very successful Working Groups on cancer genetics, preclinical models, and molecular diagnostics, experts from diverse disciplines have been challenged to help NCI develop a plan for taking full advantage of current and emerging scientific opportunities in imaging technology. In 1997, the Imaging Sciences Working Group formed seven subgroups to focus on screening and early detection, in vivo molecular imaging, emerging technologies, technology development, image-guided treatment, technology assessment, and training. Several subgroups have developed recommendations based on their meetings. NCI is now evaluating how best to implement many of the recommendations offered by the Working Group.

We also developed several large initiatives that will facilitate the advancement of imaging techniques in basic research, diagnosis, and treatment. Several of these initiatives are described below.

• Today, important advances in technology and science are fueling the development and improvement of all kinds of diagnostic imaging tools. Many of these tools promise to be extremely useful in cancer diagnosis. However, before new or refined tools can be used in this capacity, they must be rigorously evaluated for their safety, effectiveness, and cost effectiveness. In the coming year, NCI will create a single, national network for evaluating diagnostic imaging technologies. Composed of academic centers of excellence and affiliated hospitals in the community with particular expertise in clinical imaging, this cooperative group will have two important roles. First, it will work with academic and industrial technology groups to expedite the early clinical testing of promising prototype devices. This effort will provide the critical information necessary to decide whether innovations are promising and, if so, whether they need improvement before large-scale testing. Second, the group will have the capability to conduct these large-scale, definitive evaluations of imaging innovations, usually comparing the innovation to standard techniques, as soon as such testing is justified by the pilot clinical experience. Evaluations should include measures of diagnostic accuracy, medical benefit, and cost effectiveness compared with widely used standard approaches. NCI anticipates that this cooperative network will be well received by commercial technology developers, since it will provide them access to a highly skilled and committed group of clinical investigators for the testing of novel products and approaches. NCI also anticipates significant cost sharing with industry for the support of this activity.

As the past 25 years have amply demonstrated, imaging advances have the potential to profoundly affect the practice of oncology and patient mortality.

• Small animal models are powerful tools in cancer research, but we have yet to fully capture their immense potential for the imaging field. For example, the limited availability of small animal imaging systems considerably constrains their utility to researchers. Such systems would enable researchers to observe and gather information on biological, genetic, or pharmacologic processes in living animals. Realizing the importance of this need, NCI has put into place mechanisms to fund facilities to pursue research evaluating new and existing imaging technologies in small animals, particularly mice. These facilities will enhance capabilities to conduct basic, clinical, and translational cancer research, as well as foster innovative and cross-disciplinary studies in animal imaging research.

• An important and rapidly growing area of cancer research is the development of tumor-specific treatment agents. Our increasing knowledge of the biological processes involved in tumor growth and the development of new technologies in drug discovery

are enabling scientists to identify many new agents that may prove to be effective in treating cancer. Before these agents can be used in the clinic, however, they must be rigorously evaluated for their effectiveness and safety. NCI is establishing an initiative to fund studies focused on developing and applying imaging in therapeutic studies. Through this initiative, the Institute is encouraging researchers to use imaging technologies to assess investigational cancer therapeutic agents. The goal is to apply and develop new imaging techniques to determine whether a therapeutic agent reaches a cancer, and once there, how it acts upon the tumor.

Consequences: Investing versus Waiting

As the past 25 years have amply demonstrated, imaging advances have the potential to profoundly affect the practice of oncology and patient mortality. Improved imaging technologies hastened by investing now will bring earlier and more accurate diagnosis of many cancers, fewer invasive procedures for patients, and a heightened ability to monitor tumor response to treatment. Significant advances in imaging are now possible and will translate directly into larger numbers of lives saved, but their development will be stunted without NCI leadership and investment at this crucial time.

If NCI is able to capitalize on the opportunities outlined here, translation of imaging science into clinical reality for people with cancer and those at risk will occur much sooner than is possible at our current level of involvement. The formation of productive consortia between academia and industry will occur much more rapidly if catalyzed by NCI interest and resources. Our participation will ensure the application of emerging technologies to the cancer problem.

IMAGING RESOURCES	FY 2000
Metabolic and Physiologic Imaging	**$14.5M**
• Develop multidisciplinary centers for molecular and functional imaging	
• Develop molecular and functional imaging technologies and reagents	
• Establish multidisciplinary conferences on *in vivo* molecular imaging	
Integration of Imaging With Therapy	**$7.0M**
• Develop and refine image-guided therapy approaches for various cancer sites	
• Develop and apply imaging agents and technologies for the assessment of cancer drugs	
Diagnostic Imaging Network	**$5.0M**
• Utilize for the comprehensive clinical evaluation of new and refined imaging technologies	
Small Animal Imaging Facilities	**$11.0M**
• Develop and refine imaging technologies and reagents for use on small animals	
• Enhance access to small animal imaging systems	
Training	**$4.0M**
• Establish programs for training the next generation of imaging researchers	
Accelerated Technology Transfer	**$1.0M**
• Establish a national forum for information exchange related to imaging technologies and biomedical need	
Management and Support	**$1.0M**
IMAGING TOTAL:	**$43.5M**

OPPORTUNITY 4

DEFINING THE SIGNATURES OF CANCER CELLS: DETECTION AND DIAGNOSIS

The Opportunity

Just as each person's signature and fingerprints are distinct from those of every other person, cells likewise have signatures — unique, identifiable characteristics related to their role in the body. During the transformation of a normal cell into a cancer cell, its signature changes, and that change becomes a unique signal of its presence and character. By reading these signals accurately, we will be better able to detect and diagnose individual cancers. Our progress to date in isolating unique identifiers of cancer cells makes this area of research one of extraordinary opportunity for dramatically improving patient care.

With the tools we now are ready to develop, a single drop of blood from a patient's finger may be all that is needed to find a cancer, assess the threat it poses by comparing its traits to profiles in an on-line library of tumor characteristics, choose the best possible treatment, and monitor the patient's recovery.

Detection

It has been shown time and again that early detection of cancer saves lives. We know that finding tumors when they are smaller and have not spread usually results in a substantially better prognosis for the patient. In short, the earlier a cancer is detected, the better. Accurate early detection methods give us a chance to catch a tumor before it has reached a stage at which effective care is compromised.

Currently, three major approaches are used to detect cancer. The first involves physically detecting the tumor, such as by touch or by x-ray imaging, as in mammography for breast cancer. The second involves recognizing abnormalities caused by the tumor, such as the presence of blood in the stool — a potential sign of colon cancer. The newest method — and the basis of exciting new opportunities for major advances in the early detection of cancer — detects molecular changes that only occur in patients with cancer cells. Several types of molecular changes are known to occur in people with cancer. Cancers produce unique proteins, some of which can be detected in easily sampled body fluids such as blood. We have learned that cancer cells also influence the behavior of both neighboring and distant tissues; blood vessels, the kidney, the brain, endocrine glands, and other organs are all subject to changes as tumors grow. We are quickly discovering tumor-secreted proteins that account for these changes, so that developing sensitive methods for detecting them is now feasible.

In addition, subtle but detectable changes in the DNA, cellular proteins, and other molecules in tissue surrounding the site where a tumor was removed may persist even if only a few precancerous or cancerous cells remain around the margin. Detecting these changes will enable us to determine with greater con-

OBJECTIVES

- Improve early detection of cancer by identifying in body fluids tumor-specific secreted proteins and mutant genes that may signal the presence of small numbers of premalignant cells.
- Use new knowledge of the molecular traits of tumor cells to improve our ability to diagnose cancer, plan patient care, and choose effective therapies.

fidence whether we have removed the entire tumor. Moreover, periodically monitoring patients for these changes may provide early signals of disease recurrence, or alert us to the existence of residual disease at locations distant from the original tumor site. For all of these reasons, the ability to detect a tumor's molecular signature in body fluids or tissue holds huge potential for catching tumors at their earliest, most controllable stages, and thereby improving the care and prognosis of people with cancer.

Diagnosis

The behavior of each cancer — how it responds to therapy, how it changes over time, and whether it threatens the patient — is determined by molecular changes that occur during the tumor's development. At present, our ability to discern these important tumor traits is too limited.

The problem is one of discrimination. We have achieved significant progress in understanding the molecular changes that occur in cancers, but our diagnostic tools are still too crude to provide the clarity of information we need for better patient care. For example, two apparently identical breast tumors may have distinct features that caused them to develop differently and will cause them to respond differently to treatment. The inability to identify such crucial characteristics can result in vastly different outcomes for the patient. We must design more sophisticated tools so that we can pinpoint the tumor traits that dictate treatment choice and predict prognosis.

Leveraging the knowledge gained from our investments in the infrastructure for discovery, we finally are poised to forge these crucial tools. Molecular diagnostics will directly link the molecular characteristics of cancer cells and patient care. In its simplest terms, this new era in cancer diagnostics will provide a profile — a "snapshot" — of the tumor's properties at a particular point in time. This snapshot will show the key differences between a normal cell and the cancer cell. Once identified, the abnormal traits of the tumor cell will be used to plan individual patient care.

Developing a rapid and cost effective method for taking this snapshot of the tumor cell will be an essential step toward major advances in:

• Understanding tumor development by establishing a natural history of tumors for each type of cancer. A snapshot of cancer cell properties taken at each stage of tumor development will chart the steps of cancer growth and enable us to answer key questions. Does one alteration dictate the alteration that follows? When do the most harmful changes take place?

• Classifying tumors into groups based on their fundamental properties. We will then be able to identify tumors that have similar patterns of growth and will respond similarly to various therapies.

• Selecting and developing treatment based on molecular changes that occur during tumor development. Diagnostic tests that identify these key molecular changes will make it possible to make fully informed choices between available therapies and eventually to design new and more effective therapies.

• Assessing progress based on a complete picture of the alterations that promote tumor development and a clear indication of the original cancer site. This information will make it possible to predict more accurately the course of disease and will lead to more effective patient care.

The Goals

1. Develop new methods for detecting tumors at their earliest stages, when the number of tumor cells is small and the chance for cure or control is greatest.
2. Develop diagnostic tests that will enable us to base treatment choice on the fundamental traits of a tumor that determine the course of its development.

The Plan

In the area of detection, our plan has three major components:

• We will expand our current knowledge about the proteins secreted by normal and cancer cells to

develop new cancer detection tools. Using these highly sensitive molecular tests, we will catalog proteins secreted by specific tumor cell types. Individual proteins known to be secreted by a particular tumor cell type can then be measured in blood samples. This approach should be applied to all of the common solid tumors for example, breast, colon, lung, prostate, ovarian, brain, and bladder cancers.

• We will adapt existing gene identification systems, used to find cancer-related genes, to detect extremely small numbers of tumor cells. These methods will enable us to detect accurately and rapidly tumor cells in easily obtained samples of tissue, blood, and/or other body fluids.

• We will design methods of detecting the numerous protein and non-protein molecules made by tumor cells. Detecting these molecules in tissues and body fluids would signal the presence of tumor cells in a patient; the tumor cells' location could then be pinpointed by clinical methods.

To increase the usefulness of diagnostics in caring for patients, our efforts will be focused on two major areas: developing better diagnostic tests and creating the research structure needed to correlate test results with clinical outcomes. The clear goal of the next generation of diagnostic tests will be to classify tumors into groups that behave and respond in similar ways. As we are better able to see how tumors are alike or different, we will have recognizable targets for which we can select and/or develop effective therapies.

Three approaches will be used:

• We will develop methods for detecting the actual mutations responsible for tumor development in the cell's genes.

• We will develop a picture of key genes that are expressed in the tumor and establish a profile of the proteins found in the tumor. The patterns of gene expression should also indicate the tumor's origin.

• We will identify changes in key communication pathways and other regulatory controls in a tumor cell. Communication or "signaling" pathways are like electrical circuits; they are the mechanisms that cells use to make decisions. In cancer cells, these "circuits" function differently than in normal cells in ways that we can identify and monitor.

The plan for improving cancer diagnosis must include the capacity to evaluate whether the new tests result in better patient outcomes. To develop the research infrastructure needed to do this, we need to support research through which the gene alterations, gene and protein expression levels, and signaling pathway changes underlying the new diagnostic approaches can be established. We will need repositories for tissue and tumor samples provided by patients who wish to participate in this research. The repositories will also store clinical records and will serve as a resource for samples and for comparing prognosis with the various tumor markers measured with the new diagnostic tests. Clinical research will be needed to correlate the tumor profiles with response to different therapies. All of this data must be linked through a network that allows information exchange among all of the researchers and cancer care givers developing and using these new methods.

Progress in Pursuit of Our Goals

In the past year, we initiated and continued a number of initiatives to help us achieve our goals in this investment area. The following list describes many of our activities and programs.

• The Developmental Diagnostics Working Group is composed of outstanding basic, translational, and clinical scientists from academia, industry, and government. As a result of their discussions, NCI is supporting the creation and expansion of technologies to measure genetic changes and establish the patterns of gene expression and the functions of proteins in tumor cells.

• The Cancer Genome Anatomy Project (CGAP) (www.ncbi.nlm.nih.gov/ncicgap), now underway, is the Institute's principal vehicle for coordinating and achieving advances in molecular detection and diag-

nostics. The overall goal of CGAP is to determine the complete profile of expressed genes in normal, precancerous, and cancer cells, with the aim of making it possible to recognize all major steps of tumor development. This genetic information can guide future efforts to develop diagnostic indicators and to identify targets for early detection or drug discovery.

One goal of CGAP is to establish the Tumor Gene Index, a complete index of all expressed genes in cancer cells. To perform this task, scientists are extracting RNA from tumor tissue. Once a gene becomes activated, RNA instructs a cell to manufacture a particular protein. By reading the RNA, scientists can identify the genes that are being expressed (at work) in a cancer cell. Then, making copies of the RNA, or complementary DNA (cDNA), helps scientists to decipher the code for the gene.

As scientists identify and read the sequences for genes expressed in a specific cancer, they organize the gene sequences into a library. Each library includes information on the number of genes discovered to date for a specific cancer, codes for each gene, the gene's location, and how prominently a gene is expressed. Although many laboratories around the world are sequencing (or deciphering) the genetic codes of various cancers, it is a laborious, time-consuming, and expensive process. This is why achieving a complete Tumor Gene Index is so important: It will enable scientists to compare cDNA from cancer cells with cDNA from normal cells from the same body site, providing tremendous scientific insights.

Although this project is designed to collect data for all cancers, researchers initially are concentrating on five major cancers — breast, colon, lung, prostate, and ovarian cancers. To date, the Tumor Gene Index includes approximately 86 libraries from well-defined tissue sources. More than 302,500 sequences have been entered in the CGAP public database, representing more than 11,800 newly discovered genes and many thousands of new and unique DNA sequences. This database is an important component of CGAP, providing the cancer community with ready access to all progress that we make in developing this index.

• To take full advantage of the library and sequence resources that we develop through the Tumor Gene Index, we need the tools to analyze adequately these resources. Toward this end, NCI has established funding for research aimed at developing novel technologies — instruments, techniques, and analysis tools — to conduct molecular analyses of tumor samples. These new technologies should enable scientists to use tumor samples to identify alterations in DNA, to monitor the expression of genes and the products in the cell that they encode, determine the function of various cellular proteins, and identify and monitor cellular pathways involved in cancer. The technologies should be cost effective and adaptable to automation and high-throughput. Many of these studies will be supported through NCI's new Phased Innovation Award, developed to support technology research from the evolution of innovative concepts, through feasibility testing, and ultimately to subsequent full-scale development. The Phased Innovation Award has a two-tiered structure: the R21 phase supports pilot technology and feasibility testing; the new R33 phase — the exploratory development grant — supports innovative exploratory and development research initiated under the R21 mechanism. Researchers who are awarded an R21 grant will transition to the second phase of the award (R33) once they reach certain milestones in their project. The Institute also has established a parallel funding mechanism to encourage the participation of small businesses in this scientific pursuit.

• Sequences of human cDNAs have been a key resource to the biomedical research community in its efforts to identify the genes expressed in human cells and the functions of these genes. Full length cDNA clones are important tools because they can be used to develop the full sequence of a given gene. Yet, to isolate, sequence, and assemble these clones requires a considerable investment of a researcher's time and funds. Therefore, NCI has funded initiatives to identify cost effective strategies to generate full coding sequences of genes that may be useful for cancer research. This effort will facilitate the generation of high-quality full coding sequences of genes in a systematic and timely fashion.

PEOPLE'S STORY

LIVING WITH CANCER

Ten years ago, I was diagnosed with colon cancer. I found myself trying to make life-changing decisions about my care in a language I barely understood. I never knew if I had enough information, the right information, or if I even knew what questions to ask.

The journey of every person with cancer is unique. NCI knows that patients and their families need rapid access to understandable, unbiased cancer information to become educated about their disease, to make informed treatment decisions, and to find sources of care and support. As a central part of its mission, NCI provides millions of people each year with an array of print, audiovisual, and electronic information services. At the same time, physicians and other health professionals have recognized the need for better tools, tailored to the needs of patients with different cultures and educational levels, to help explain complex treatment options at the bedside.

When I was first treated, I had a lot of pain from the surgery and an awful infection at the colostomy opening. From the chemotherapy, I was nauseated all the time and so fatigued I could barely get up. Some days I knew I would make it through, but other days were total despair.

In recent years, intensive research has yielded effective treatments for some of the most dreaded side effects of cancer treatment. For example, while cancer or its treatment may cause pain, in the vast majority of cases, it now can be relieved through a variety of medication strategies and other techniques. NCI continues vigorously to sponsor research to discover even more effective ways of controlling pain. Clinical guidelines for managing cancer pain were established in 1994, and NCI has actively supported projects to educate patients and physicians about pain control and to encourage the guidelines' implementation in community practice.

Medications are now available that effectively relieve the debilitating vomiting associated with some cancer therapies. Similarly, treatment-induced anemia, the principal cause of fatigue among cancer patients, can now be reversed with medications. Our ability to control these difficult side effects has greatly improved both patients' willingness to undergo treatment and their quality of life. In addition, by enabling patients to tolerate stronger chemotherapies than would otherwise be possible, these advances have also contributed importantly to progress in treatment.

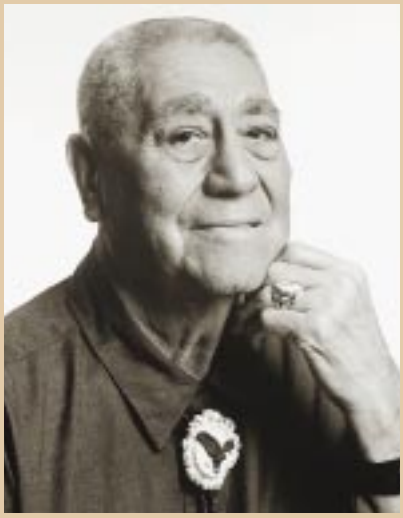
The people at work were very supportive while I was in treatment, but when I came back to work, I found I had to "prove myself" all over again, even though I'd been doing this job for three years and came back to a full work schedule.

The end of treatment can bring new and unexpected challenges for patients. In two recent studies, most of the cancer survivors surveyed felt their job helped them maintain emotional stability during treatment. But the studies also found that survivors still face bias from both employers and co-workers, who think they will no longer be able to do their job as well or will need special accommodations. In fact, most survivors are able to resume a full work load and have no more work absences than other employees.

Since the surgery and chemotherapy, I don't feel the same about myself. It has been hard to re-establish intimacy with my spouse. You know, we've both read

a lot about cancer, but when you're looking each other in the eye... well, that's different.

As a result of cancer or its treatment, survivors may experience unsettling changes in body image because of surgical scars, skin or hair changes due to radiation or chemotherapy, arm or leg swelling called lymphedema, or the loss of a limb or breast. Some chemotherapies can also dampen libido and cause fatigue that may last well after treatment is completed. Depression related to these changes can also hinder efforts to restore, initiate, or maintain intimate relationships. The importance of these issues to survivors' overall quality of life is increasingly recognized, and research efforts to find ways to help survivors make positive adjustments to body image and other changes are gaining momentum.



Some people with cancer hesitate to go to a support group, but once you go, you know there's a place where you can go to talk about your concerns.

I had a recurrence a month before my five year anniversary. My first thoughts weren't, "I'm going to die." I thought, "Oh no, more surgery, more treatments, more complications." And I was concerned about putting my family through all of that again.

Some survivors report that facing the challenge of cancer a second time is harder than the first. NCI's Office of Cancer Survivorship was established to promote research on the myriad physical, social, psychological, and economic issues faced by survivors throughout their lives, with the goal of improving quality of life for this growing population. NCI also recognizes that recurrences or second cancers can be equally devastating to family members, who themselves have struggled to move forward after a loved one's battle with the disease. Research on the health and psychosocial effects of cancer on family members is in its early stages.

Some people with cancer hesitate to go to a support group, but once you go, you know there's a place where you can go to talk about your concerns. As wonderful as families and friends can be, no one can understand like someone who's been there.

Support groups provide strength and understanding to many thousands of cancer survivors. In communities across the country, support groups have been formed to meet the needs of child and adult survivors with particular types of tumors, diverse cultures, or other special circumstances. Groups just for family members have also been established. For some survivors, cancer support activities — leading peer support groups, writing newsletters, or becoming advocates — become an integral part of their recovery and life after cancer. A few studies have suggested that support group participation may even extend survival.

There's more information and support than there was when I was diagnosed, but it seems to me there is still a long way to go to help patients and families cope with this disease.

• Alterations in our own genes underlie the development of cancer. Usually, such changes accumulate in cells over many years, and often are present before a clinically identifiable tumor ever appears. Detecting and characterizing these altered cells during the earliest stages of the disease would offer us a great opportunity to find a cancer when the potential for a full recovery is greatest. Therefore, we have established mechanisms to fund research aimed at developing sensitive early detection techniques that can effectively identify, and ultimately characterize, tumor cells in easily sampled body fluids.

Through this initiative, we have the opportunity to convert our growing knowledge of tumor cell biology into practical advances in patient care. Over time, these advances will transform many aspects of clinical cancer medicine.

• Scientists in the cancer field have a need for readily available tissue samples for research use. In an effort to support this ongoing need, the NCI established extensive tissue repositories, and over the past year, began a number of projects to expand and enhance these repositories. For example, the Institute renewed funding for five years for the Cooperative Breast Cancer Tissue Resource (CBCTR), a tissue repository that also includes considerable clinical and outcome information associated with the specimens. The information is available to scientists in a searchable database on the Web. Already, this resource has proved to be extremely useful to the research community, providing investigators with the opportunity to rapidly validate a test to identify patients likely to respond to a new targeted therapy. NCI will fund a pilot project to assess the feasibility of establishing a prostate tissue resource similar to the CBCTR. Also planned is a collaborative effort by NCI and the Office of Research on Women's Health to support a field test of a model informed consent form for research use of tissues obtained in the course of routine care. The model consent form and a fact sheet about use of tissues in research were developed by a committee of the National Action Plan on Breast Cancer. This consent will help to ensure that specimens obtained now can be used in future research.

• NCI is developing an Advanced Technology Center (ATC) to integrate many of NCI's laboratories, scientists, and research projects in the fields of molecular genetics, molecular pathology, biotechnology, and informatics into one physical space. The ATC creates a rich research environment that can exploit state-of-the-art technology necessary to uncover the genetic signatures of human cancers.

• Because grants to develop innovative technologies often are overlooked in the traditional, peer review process, the NCI has initiated the Unconventional Innovation Program. This program will support research aimed at discovering innovative and unconventional technologies that can facilitate cancer research. Although the utility of such technologies may not be evident for 10 to 20 years, these high-risk projects may have an exceptional impact on future cancer research.

Consequences: Investing Versus Waiting

We have known for years that certain tumors, such as testicular cancer in men and choriocarcinoma in women, have distinct signature molecules circulating in the blood, and we have been using these characteristic markers to detect and treat disease much earlier than if we had to wait for visible or palpable lumps. We have every reason to believe that all cancers have distinctive signatures that can be used to detect tumors at the earliest possible stage to ensure the best possible outcome for patients. Improved methods for diagnosing tumors are on the horizon. We need to make this vision a reality.

Through this initiative, we have the opportunity to convert our growing knowledge of tumor cell biology into practical advances in patient care. Over time, these advances will transform many aspects of clinical cancer medicine. We will be able to diagnose based on biology, not just on the microscopic appearance of a tumor. By pinpointing the molecular changes that occurred during tumor development, we will be able to predict with accuracy how a tumor will behave and what the patient's outcome will be. We will select therapy based on the tumor's individual biological properties, rather than on empirical guesses. We will uncover new therapeutic targets and make it possible to base clinical trials on tumor characteristics and the patient's cancer risk.

Without national investment, this fundamental transformation of cancer medicine will occur far more slowly, and many lives will be lost unnecessarily. A portion of the work necessary to effect these developments would proceed in academia and industry, but less rapidly and with less intensity and coordination. Certain necessary steps may not occur at all; it is unlikely that the essential research infrastructure to support a cancer detection and diagnostics effort of this type (tissue banks and the information links between banks, tumor registries, and the clinical trials program) can be organized and supported by another means.

Without this investment, cancer treatment choices will continue to be based on unsatisfactory and incomplete methods of diagnosis. We will not be able to separate tumors into classes based on their molecular differences. Since these differences are the reasons that tumors behave and respond differently, our insights into treatment choice and outcome will continue to be blurred. Progress will not be stopped, but an important opportunity for real advancement will be missed.

SIGNATURES OF CANCER CELLS FY 2000

Tumor Gene Index (TGI) **$21.5M**
- Develop human full-length cDNA libraries
- Sequence full transcript of 20,000 genes identified in TGI
- Develop vector systems to shuttle cDNA libraries into various expression systems
- Develop sample preparation methods for tumor specimens to support molecular analysis
- Develop gene expression profiles for five tumor types (breast, prostate, ovarian, lung, colon)
- Support informatics systems to make information more widely accessible and user-friendly

Molecular Discovery **$8.0M**
- Develop comprehensive methods to identify gene mutations, changes in gene expression, and to identify signaling and regulatory pathways that correlate with cancer sites
- Develop analysis and modeling tools to interpret information from comprehensive molecular analysis

Tissue Repositories **$7.0M**
- Develop and expand repositories to enhance accessibility by cancer research community
- Develop secure informatics systems to link specimen information to clinical data

Diagnostics **$10.0M**
- Develop highly specific and sensitive tests for assaying specific molecular profiles
- Begin to develop new molecular classification schemes for all cancers

Detection **$20.5M**
- Determine secreted proteins that correlate with the presence of cancerous or precancerous lesions
- Develop highly specific and sensitive assays to detect cancer-related proteins in body fluids
- Develop highly specific and sensitive assays to detect tumor cells in body fluids
- Develop highly specific and sensitive assays to detect molecular products of tumor cells in body fluids
- Develop detection research network

Long-Range High Impact Technologies **$6.0M**
- Fund long-range, high-risk projects for the development of remote detection technologies

Management and Support **$2.0M**

SIGNATURES OF CANCER CELLS TOTAL: $75.0M

NCI's Challenge

Without doubt, we are in a golden age of discovery, one unique in human history. Knowledge about the fundamental nature of cancer is exploding. Technology is giving us new instruments with which to see and understand cancer. Investments made to achieve our accumulated knowledge and technical capacity are beginning to pay off — cancer mortality rates overall, and rates for many individual cancers are finally falling, although not as quickly as we would like.

Without question, these successes have resulted from the application of research — research on how lifestyle and environment affect cancer risk, on ways to prevent and detect cancers more readily, and on how to treat cancers more effectively. NCI has engaged the best minds from diverse disciplines to assess how best to foster discovery, facilitate its application to the care of people with cancer and those at risk, and topple barriers to progress. Throughout these intense deliberations, all of us who are dedicated to the fight against cancer returned to this central question: "What more must we do to convert this golden age of discovery to the golden age in the prevention and care of cancer?"

Research into the causes of cancer is the best route to effective prevention. Research into detection techniques is enhancing traditionally successful therapy by enabling us to detect cancers at their earliest, most curable stages. Research into the life and death of cancer cells is leading to incremental success in curative therapy. Our successes have shown us that no one approach is likely to conquer the many different diseases we call cancer. We know progress can be made, and we know it will have its roots in discovery. But it is clear that the gap that still exists between discovery and application will not be closed unless we now set in place structures that will speed the engine of discovery, create bridges among all components of the cancer research enterprise, and encompass the care of those with cancer and those at risk into our national research system.

We believe firmly that the most rapid movement toward cancer prevention and cure will happen only when the current gap between discovery and application is spanned. To do this, we must create a system of bridges among all aspects of research — between research and clinical practice, between research and industry, between researchers in laboratories throughout the Nation, and between the research enterprise and the American people. We must nurture and

strengthen the ties among these diverse research areas, and between the research enterprise and those whose lives cancer touches, to ensure that the benefits reaped by our new ideas and new technologies flow directly into the reduction of suffering from cancer.

In this section of NCI's budget, we present our plan to meet the challenge of building those bridges that eventually will conquer cancer.

The Challenge and the Plan

The challenge before us is immense. How will we convert our knowledge of cancer into advances in prevention and care on the scale that is needed to conquer cancer? We must fully embrace a new era — one in which scientific knowledge, rather than empiricism, more closely directs our efforts in the fight against cancer. As research reveals more about the inner workings of cells and the ways they behave, the challenge before us is to convert this knowledge quickly into practical, affordable, and effective interventions that restore cancer patients to health or prevent the development of these diseases in all segments of our population.

To meet this challenge, we must have a research base that can bring the best of our developing knowledge — the best ideas, technologies, and people — to the problems of cancer prevention and care. We must supply the structures and mechanisms that will not just span the gap between discovery and application but will transform the process by which we bring discoveries to the benefit of people and allow us to conquer all types of cancer.

To respond to this challenge, we must increase our investment in six key areas:

NCI's Challenge (dollars in millions)

Additional Increases Beyond Core and Investment Requests	FY 2000
1. Investigator-Initiated Research	138.9
2. Cancer Centers: Restructuring and Expansion	79.5
3. National Clinical Trials Program	316.5
4. Cancer Informatics and Information Flow	35.0
5. Studying Emerging Trends in Cancer	28.5
6. Training, Education, and Career Development	95.1
TOTAL ADDITIONAL INCREASE FOR THE NCI CHALLENGE	**$693.5**

Investigator-Initiated Research

An enhanced level of support for all types of investigator-initiated research remains a fundamental need. Research in the laboratory, clinic, and community provides the platform on which translational research and clinical testing stand. In basic investigation, we now need to complete the picture of how the cell works and how its molecular circuits go awry in cancer. This is an enormous undertaking, but it is the foundation of future medicine — the pivotal base from which we will create the interventions that translate our knowledge into real improvement in cancer prevention and care. We also need to make important additions to our research portfolios in areas that will support the crucial process of translation — the generation of clinical hypotheses from basic information and the testing of these hypotheses in applications for people.

Today, NCI can only support approximately the top 25 to 30 percent of competitive grants through the Research Project Grant pool. To ensure that excellent ideas have the chance to be tested, and new investigators are attracted to research on cancer, we need to fund the top 45 percent.

Sometimes, however, important research flows not from the laboratory of an individual investigator but from the collaboration between two or more Cancer Centers or other scientific organizations. Collaborative efforts are particularly important to the development of new cancer treatments and preventive agents. NCI supports such collaborations in part through its Program Project Grant (see p.20) and cooperative agreement mechanisms. To encourage and facilitate multidisciplinary collaborations, we wish to double the number of competing Program Project Grants and Cooperative Agreements.

Our Progress Toward Meeting the Challenge

Over the past year, NCI has been working to meet the challenge of providing enhanced levels of funding for both investigator-initiated and collaborative research efforts. In order to move toward our goals of funding the top 45 percent of single investigator grants and doubling the number of collaborative research efforts through the Program Project Grant and Cooperative Agreement mechanisms, we have taken the following steps:

• NCI has shifted its funding priorities to increase significantly the number of new, investigator-initiated single project research grant applications that receive funding. In FY 1998, we anticipate funding over 1,000 competing grants, or the top 29 percent of the competing applications in the Research Project Grant (RPG) pool. In FY 1999, NCI plans to continue its emphasis on investigator-initiated research, as well as maintain our support of Program Project Grants, and continue our increase in the number of funded Cooperative Agreements.

This is the research that ultimately will transform biological insights into new diagnostics, treatments, and preventives.

• NCI is continuing to support first-time investigators and ensure that a steady stream of new investigators and ideas flows into the RPG pool through the use of the NIH-wide R01* coding system. The NIH

SPOTLIGHT ON RESEARCH

Angiogenesis

Cancer cells promote the process of angiogenesis — the formation of new blood vessels — by disrupting the normal balance between the naturally occurring molecules that stimulate this process and those that inhibit it. Angiogenesis is exploited early in the process of metastasis, enabling the cancer cells to form blood vessels needed to gain nutrients and growth factors for continued growth.

Researchers are focusing on a number of important opportunities in this area, including: identifying the signals that initiate formation of tumor blood vessels; identifying and exploiting possible differences between blood vessels in healthy tissues compared with those in tumors; designing methods to inhibit "vascular endothelial growth factor" — a powerful agent that stimulates angiogenesis by binding to and activating growth of endothelial cells; developing agents that can impede the effects of angiogenesis-stimulating growth factors in the body; and developing new techniques to increase the production of naturally-occurring anti-angiogenic factors to prevent tumor spread. A number of agents are being tested in mice for their anti-angiogenic potential. Among these are angiostatin and endostatin, which effectively halt tumor spread in mice.

BUDGET FOR INVESTIGATOR — INITIATED RESEARCH

We are requesting $138.9 million beyond the Core budget and Extraordinary Opportunities for Investigator-Initiated Research in FY 2000.

These funds will enable us to:

- Fund approximately 1,800 new and competing renewal research project grants at peer-reviewed approved recommended levels, at an average cost of $355 thousand.
- Fund the top 45 percent of single investigator grants.
- Increase the research project grant by an average cost of 10 percent over FY 1999.
- Double the number of competing Program Project grants and collaborative agreements.
- Fund more translational research projects.

TOTAL ADDITIONAL FUNDING FOR INVESTIGATOR-INITIATED RESEARCH: $138.9 Million

Center for Scientific Review, which manages the initial review of individual investigator grants, codes incoming R01 applications from first-time investigators as R01*, a designation that indicates to reviewers that an applicant is a new investigator. Reviewers may take this fact into consideration while evaluating the proposal for investigator experience and track record, but otherwise, the application receives the same rigorous review as other applications. Once funding decisions have been made, NCI assesses the funding rate for R01* grants to make sure that they are funded to the same overall success level as the rest of the RPG pool; if not, additional grants are funded through our exception process.

• NCI is working to ensure that meritorious grants of high program priority that do not score high enough in the review process to receive funding based solely on merit, but are very close to the payline, are still considered for funding through the exception process. In addition, NCI has instituted a "second chance" review process, known as Accelerated Executive Review, to expedite the review of responses to peer review concerns for those unfunded initial grant applications whose merit ratings fall near the grant pay line.

• Working together with NCI, the NIH's Center for Scientific Review will establish a peer review group (study section) for translational research in clinical oncology in FY 1999. This group will specialize in the review of grant applications that move findings from the laboratory into the clinic. This is the research that ultimately will transform biological insights into new diagnostics, treatments, and preventives. The new study section will assure the necessary broad expertise for assessing new ideas in translational cancer research and clinical trials.

Cancer Centers: Restructuring and Expansion

There are currently about 70 research centers nationwide that have the critical mass of NCI-supported research to benefit from core support under NCI's Cancer Centers grant mechanism. Of these, NCI currently awards cancer center support grants to 58 institutions. We believe that this program should grow over the next few years to include all institutions for which this program could be significantly beneficial. Therefore, we wish to expand the Cancer Centers Program to include 70 Centers by FY 2001, thereby improving their geographic distribution and increasing their versatility as agents of discovery.

Our Progress Toward Meeting the Challenge

The restructuring and expansion of the Cancer Centers Program has been an important focus for the Institute in the past year. For example:

BUDGET FOR CANCER CENTERS: RESTRUCTURING AND EXPANSION

We are requesting $79.5 million for this area for FY 2000.

These funds will enable:

- $30.0 million to be used to expand existing co-supported NCI-sponsored Centers.
- $9.0 million to be used to develop 6 new Cancer Centers.
- $2.5 million to be used to help 5 additional institutions begin the process of qualifying for designation as an NCI Cancer Center.
- $30.0 million to expand the Specialized Programs of Research Excellence (SPOREs) program (see p.26).
- $3.0 million for the planning of new types of Centers for form exceptionally strong research networks with the ability to deliver quality health care in a managed care environment. These Centers will link academic institutions with community hospitals.
- $5.0 million to be used for management and support.

TOTAL FOR CANCER CENTERS RESTRUCTURING AND EXPANSION: $79.5 Million

• In an effort to revitalize the Cancer Centers Program, NCI has implemented new, more flexible program guidelines, recommended by a blue-ribbon panel of national cancer experts who reviewed the Program. This new flexibility provides the opportunity for more research institutions to qualify for funding within this program and to compete for planning grants to strengthen their capabilities and potential to become NCI Cancer Centers in the future.

• The Institute has funded two new Cancer Centers; with this increase, NCI now supports 58 Centers throughout the Nation. Several other institutions have planning grants to help strengthen their research programs so that they potentially can qualify as an NCI Center. NCI also increased the number of NCI-designated Comprehensive Cancer Centers from 31 to 35. To qualify as a Comprehensive Cancer Center, an institution must have significant scientific strength in basic, clinical, and population studies as well as strong interdisciplinary collaboration across scientific boundaries. In addition, Centers must have in place effective cancer information, education, and outreach activities for the regions and communities they serve.

• A number of new types of Centers now in the planning phase are being designed as partnerships, often linking free-standing and academic institutions with community hospitals. These new Centers can form extremely strong research networks with the ability to deliver quality care in a managed care environment.

• We are in the process of extending the SPORE program to include ovarian cancer. $2.5 million has been set aside to fund a SPORE in ovarian cancer in FY 1999.

National Clinical Trials Program

The importance of a strong clinical trials program — and our urgent need to improve and expand the Nation's current clinical trials infrastructure — cannot be overstated. Clinical trials are the crucial final steps in the process of developing new cancer treatments, preventive measures, and detection and diagnostic techniques. At present, approximately 300,000 people participate in all NCI-sponsored clinical trials.

As the place where promising new strategies from the laboratory bench are applied to real human problems at the bedside, clinical trials offer cancer patients access to promising, state-of-the-art care and provide us with the opportunity to create tomorrow's prevention and treatment interventions and add greatly to our understanding of cancer.

Why, then, do so few eligible people — only about two percent of cancer patients — participate in treatment clinical trials? The barriers to participation, some of which are discussed below, are not insurmountable. But we need a robust clinical trials infrastructure to speed the way. We need to ensure that every American who wishes to participate in a clinical trial is able to do so. In short, we need to break down the barriers to clinical trial participation for patients and health care professionals.

Clinical trials provide us with the opportunity to create tomorrow's prevention and treatment interventions.

A serious barrier to progress is the growing reluctance of health care payers and providers, particularly managed care organizations, to pay even the routine clinical care costs of patients participating in early clinical trials, thus limiting patients' access to research studies. But treatment and prevention advances must not be sacrificed to the cost consciousness now driving the health care industry. Therefore, NCI is actively negotiating with representatives of the industry to arrive at mutually agreeable solutions. NCI maintains that it is the legitimate responsibility of the insurance industry to reimburse the costs of routine medical care of cancer patients in all phases of high-quality research trials. For certain innovative trials in which patient care costs are significantly higher than routine care for the same condition, it may be appropriate to consider cost sharing between the insurer and the research sponsor. However, regardless of cost, for people with advanced or otherwise untreatable cancers, a clinical trial may represent the best available treatment.

An expanded and strengthened clinical trials program will challenge us in:

Prevention and Early Detection. As we are able to identify more individuals who are at risk of developing cancer, whether because of their genetic profile, their environment, their behavior, or other factors, we need trials of chemopreventive agents, dietary interventions, and new technologies to prevent their cancer, or to find it early, before it has had time to spread.

Diagnosis. New, minimally invasive diagnostic techniques emerging from NCI's research must also be tested in people.

Treatment. For most types of cancer, current treatments are inadequate. New and highly promising strategies for cancer treatment are emerging through our ever-increasing understanding of basic biology; we must speed their development by testing them in people as rapidly and efficiently as possible.

Presently about 100,000 people are participating in treatment clinical trials with an average yearly accrual of about 20,000 patients. Initially, we are aiming for a five-fold increase over the next five years in the number of people receiving the latest treatments under development through the NCI-supported Cooperative Treatment Trials Program.

New Therapeutic and Preventive Agents for Cancer. Our clinical trials system not only allows us to refine current therapies but provides the mechanism to test new ideas rapidly. The explosion of biological discovery presents us with an additional challenge for the development of new therapeutic and preventive agents for cancer. As academia and industry increasingly realize the potential for discovering of cancer therapeutics inherent in biology, chemistry, and engineering, the

USING TAMOXIFEN TO PREVENT AND TREAT CANCER

The road of scientific discovery is often long and demands both perseverence and open dialogue among researchers and clinicians in order to reach a goal. This was true in the more than 30-year process of discovery and development of tamoxifen. First developed as a breast cancer treatment, tamoxifen now has been proven to help prevent breast cancer in women at high risk for developing the disease. The discovery of tamoxifen's dual role as a cancer treatment and preventive was fostered by the dedicated efforts of many researchers around the world who pursued the use of tamoxifen as a treatment and ultimately recognized its potential for breast cancer prevention, and by the efforts of thousands of patients who volunteered for clinical trials testing tamoxifen.

Tamoxifen, first discovered in 1962, is an anti-estrogen — a substance that stops estrogen from working in specific tissues by preventing the hormone from docking in estrogen receptors found in these tissues. Because of this activity, tamoxifen was first tested as a contraceptive; surprisingly, however, women in the clinical trials who took tamoxifen became more fertile.

Realizing that tamoxifen was not an effective contraceptive, scientists looked for other ways the compound could be used. Through these investigations, they discovered that tamoxifen's anti-estrogen activity appeared to be selective: it only stopped estrogen from working in certain tissues, such as breast tissue. Knowing that estrogen must bind to its receptors in breast cancer cells to promote tumor growth, and that tamoxifen prevents estrogen from reaching its receptors, scientists began to wonder if the drug might stop breast cancer growth. Therefore, researchers began looking at the drug's ability to combat the growth of human breast cancer cells in animals, as well as in cancer cells grown in the laboratory. In both settings, tamoxifen successfully robbed the cancer cells of the estrogen they needed for tumor growth. These results led to testing of tamoxifen as a treatment for patients with advanced breast cancers. These first clinical trials were successful, and in 1977, the Food and Drug Administration (FDA) approved tamoxifen for advanced breast cancer therapy.

Tamoxifen's success as a treatment for advanced breast cancer fueled many scientists' desire to continue looking for new ways to use the drug to help cancer patients. Tamoxifen was next tested with success as an adjuvant therapy, a treatment given following surgery. Taken as an adjuvant, tamoxifen extended patient survival time, prompting researchers to begin testing it as a treatment for women with estrogen-dependent breast cancers that had spread to the lymph nodes. Its success as an adjuvant therapy and in treating women with lymph-node involvement led to FDA approval of tamoxifen's use for these patients in the early 1980s. As the results of the different trials were reported, open dialogue between researchers in the laboratory and clinic became critical to refining the design of new trials and uncovering trends in the data.

Picture courtesy of Zeneca Pharmaceuticals

When this growing pool of data was analyzed, three themes began to emerge: women who received tamoxifen had increased rates of survival; women who took the drug had fewer recurrences of cancer; and, it seemed that tamoxifen might prevent breast cancer — an observation supported by evidence from animal studies.

Responding to this analysis, researchers at the National Surgical Adjuvant Breast and Bowel Project (NSABP) launched B-14, a pivotal trial to see if tamoxifen therapy enabled women whose estrogen-dependent breast cancers had not yet spread to live longer and have fewer recurrences of cancer. The results of B-14 not only demonstrated that tamoxifen did indeed increase survival and decrease recurrence, it also showed that women who already had cancer in one breast and took tamoxifen following other treatment regimens had a 40 percent decrease in the number of breast cancers diagnosed in the opposite (unaffected) breast. This confirmed that tamoxifen did appear to prevent breast cancer and that prevention studies were needed for women who had not yet had breast cancer, but were at high risk for developing the disease.

Now that more than two decades of study had proven tamoxifen to be a safe and effective treatment for early-stage breast cancers and a preventive for women who already had the disease, researchers and clinicians were ready for a study to answer the next question: could tamoxifen prevent breast cancer in women who had not yet developed the disease? Thus, in 1992, NSABP launched the NCI-funded Breast Cancer Prevention Trial (BCPT).

Over 13,000 women at high risk for developing breast cancer volunteered for the BCPT and were randomly assigned to receive either tamoxifen or a placebo. After following the progress of these women and analyzing the data, researchers showed that tamoxifen reduces the rate of developing primary breast cancer by 45 percent in women who are at high risk for developing the disease. The success of tamoxifen for preventing breast cancer among high-risk women led to the early announcement of the trial's results. Despite potential side effects, such as an increased risk of developing endometrial cancer in women over age 50, and a risk of developing blood clots in the major veins and lungs (similar to hormone replacement therapy), tamoxifen's results mark an historic achievement in cancer prevention.

However, tamoxifen's story has not yet come to a close. Researchers already are creating and testing a second generation of breast cancer prevention agents, such as raloxifene, which may help prevent the disease without some of tamoxifen's potential side effects. Later this year NCI will launch the Study of Tamoxifen and Raloxifene (STAR), a trial comparing the two drugs' ability to prevent the onset of breast cancer in high-risk, post-menopausal women, as well as comparing their side effects.

As we continue our quest for a drug that will help prevent breast cancer for all women, we can mark the discovery and development of tamoxifen as a major milestone, one that has established a whole new avenue of prevention research that should continue to foster prevention discoveries and successes well into the future.

TRANSLATING DISCOVERIES

An important goal for NCI is to translate basic discoveries rapidly and efficiently into the development and testing of new drugs. Over the past year, we instituted two ambitious programs to help us toward this goal. The first program, the **"Rapid Access to Intervention Development"** (RAID) program, is designed to facilitate the translation to the clinic of novel, scientifically meritorious treatment interventions developed in academic settings. Through collaboration with the originating academic laboratory, NCI will provide resources for the pre-clinical development of drugs and biological agents, removing the most common barriers between laboratory discoveries and clinical testing of promising agents. The second new program, our novel **"Chemistry-Biology Centers,"** will bring together the best scientists in these two disciplines to focus their efforts on cancer drug discovery. By enabling chemists and biologists to work collaboratively on research projects, these Centers promise to enhance the rate of discovery of truly novel therapeutic and preventive agents. We have awarded four grants in this program and anticipate awarding another three awards in the coming year.

number of discoveries that are worth developing into therapeutics or preventives will exceed the capacity of the biomedical research community. For example, academic investigators do not themselves have the resources for animal testing of new compounds that they discover, nor the resources for large scale drug synthesis and pharmacologic, formulation, and animal toxicology assessment that must precede clinical testing in people.

These functions ordinarily are performed by drug or biotechnology companies, but the willingness of a company to assume these costs depends on many factors other than the inherent promise of the discovery itself. NCI's long experience with cancer drug development will enable us to expedite significantly the flow of discoveries from laboratory to clinic.

We propose, therefore, a significant expansion of NCI's preclinical development capacity. Our goal is to begin clinical trials with 20 promising new agents. NCI is now soliciting proposals from the research community and will select through a competitive process the most promising drug candidates. NCI will then commit to developing these particularly promising drug candidates to enable their testing in the clinic.

Our Progress Toward Meeting the Challenge

In the past year, NCI has taken a number of steps to strengthen and enhance its Clinical Trials Program. Our accomplishments are described below.

• NCI convened a panel of experts to review the Clinical Trials Program. The review group, composed largely of extramural scientists, was charged with rigorously evaluating our current program and recommending ways to create a more efficient and effective clinical research effort. The review group made a number of recommendations concerning grant review, clinical research funding, and project design, oversight, and administration. In December 1997, an implementation group composed of scientists both inside and outside NCI was brought together to identify the best ways to implement the review group's

recommendations. (For more information on the Clinical Trials Program Review, see http://deainfo.nci.nih.gov/advisory/boards.htm).

• NCI is working with industry and academia in reconfiguring and expanding its systems for early clinical trials development to ensure that the best ideas and the most interesting and promising discoveries are introduced rapidly into the clinic and receive testing.

• The Institute also has put into place a number of plans and programs to strengthen and augment our clinical trials efforts. Because laboratory and correlative studies are integral to the clinical trials effort, we have provided eight new supplemental funding awards for these studies. We also established a new Clinical Cooperative Group, the American College of Surgeons Oncology Group, to conduct surgically-oriented clinical trials, and have increased funding to our other Cooperative Groups.

• We continued to sustain approximately 200 ongoing clinical trials in our intramural program. To increase patient accrual to intramural trials, we established an outreach effort targeting physicians and advocates. As part of this effort, we established an 800 phone line that provides information to callers and provides prospective patients with the opportunity to speak with a nurse or a trial's principal investigator. Over the past year, NCI has received an average of 400 calls each month on this phone line.

• The Institute also continued its intensive efforts in the area of cancer prevention trials, recruiting individuals to clinical cancer prevention and control trials. More than 27 agents currently are being tested for their effectiveness in preventing cancer and over 400 possible preventive agents are being evaluated in the preclinical phase. Further, with the aid of a chemoprevention implementation group, NCI is working to determine how it can improve its efforts to develop and test new chemopreventive agents.

BUDGET FOR THE NATIONAL CLINICAL TRIALS PROGRAM

We request $316.5 million for the National Clinical Trials Program in FY 2000.

- Include $30.0 million in the Research Project Grant pool to support investigator-initiated cooperative trials.
- Provide $100.0 million to the Clinical Cooperative Groups to cover research costs for an additional 20,000 patients.
- Include $70.0 million to bring current Clinical Cooperative Groups up to full funding levels.
- Provide $46.0 million to support cancer prevention trials, primarily through NCI's Extramural Research Program. We anticipate targeting 20,000 individuals per site for prostate, breast, colon, and lung cancer prevention trials over four years (80,000 total).
- Include $25.5 million to bring participants in the Community Clinical Oncology Program up to full funding levels.
- Use $20.0 million for clinical trials conducted by the NCI Intramural Research Program.
- Devote $20.0 million to enhance the national capacity to translate discoveries into new drugs and into the clinic for initial testing in people.
- Use $5.0 million for management and support

TOTAL FOR NATIONAL CLINICAL TRIALS PROGRAM: $316.5 Million

In addition, NCI started and continued several large clinical trials through the Community Clinical Oncology Program (CCOP). The CCOP network for cancer prevention and control research includes CCOPs and minority-based CCOPs, as well as the university members and affiliates of the Clinical Cooperative Groups. This network currently implements 40 active prevention protocols, including the Prostate Cancer Prevention Trial and the screening trial for Prostate, Lung, Colorectal, and Ovarian Cancers (PLCO). Recently, investigators conducting the Breast Cancer Prevention Trial, another NCI-funded large-scale trial, stopped the study earlier than expected when the data showed that tamoxifen, a chemopreventive agent tested in the trial, yielded a 45 percent reduction in breast cancer among the study's participants. In a new trial soon to begin, scientists will compare the effectiveness of tamoxifen with that of raloxifene, an agent with similar breast cancer prevention benefits but with potentially less risk of adverse events, such as the development of endometrial cancer.

Informatics and Information Flow

The power of computer-based communications and the capabilities of the World Wide Web are making possible unprecedented levels of research cooperation. Slow and cumbersome paper-based systems of data collection for multi-center studies will give way to electronic communication, facilitated by enhanced links between sites of care delivery (hospitals, offices, and clinics) and the research databases of investigators. Currently, however, incompatible and outdated informatics systems are in use throughout NCI's Clinical Trials Program. Because of this, the planning and execution of large-scale studies with multiple Cooperative Groups are exceedingly labor-intensive and time-consuming pursuits. We need to institute state-of-the-art informatics systems for clinical trials that promote full compatibility among all participants in the program.

To address the opportunities and challenges presented by the revolution in electronic communications, NCI now is planning a new architecture for the flow of information in its clinical trials programs — a Cancer Informatics Infrastructure (CII). In collaboration with other Federal agencies, and with the participation of many scientists and clinicians, NCI is developing the CII to expedite the undertaking of all types of intervention studies — prevention, diagnosis, and treatment. NCI is modernizing information links with its investigators in a manner that will be compatible with standards set by the international committee now studying this issue for North America, Europe, and Japan. We also are revising our criteria and standards for reporting adverse events. The result will be common terminology and reporting requirements that will greatly increase the speed, efficiency, and accuracy of results reporting.

The twin goals of the CII are to lower the barriers for patients, families, at-risk individuals, and physicians wishing to learn about available clinical trials, and to create an infrastructure that facilitates information exchange among researchers, clinicians, and the public. The CII will greatly enhance NCI's current activities to provide the general public with up-to-date information about new research results, available clinical trials in diagnosis, treatment, and prevention, and contact points for additional information. For example, instructional modules on computers, tailored to individual needs, can supplement current standard techniques for teaching people about difficult concepts like the risk of getting a disease given a certain genetic predisposition. When housed in kiosks in public places like libraries or malls, computers can inform the public about research results or studies of personal interest and relevance. Such kiosks could also be an effective way to reach people in underserved areas. NCI is already exploring this possibility in collaboration with the library system in the state of Maryland.

With the active participation of several patient advocate groups, NCI is engaged in an effort to create a "patient friendly" version of PDQ, NCI's comprehensive cancer information database, containing information in non-technical language on cancer and on opportunities for participating in investigational studies of new approaches to prevention, diagnosis, and treatment. Once in place, the CII will be an invaluable resource for the Nation's cancer clinical trials.

Our Progress Toward Meeting the Challenge

NCI is working intensively to create and develop a unified, multifaceted, and versatile information system. Among our recent accomplishments:

• We have developed several new components of the CII to improve our efficiency in reporting clinical trials data. These include the Clinical Data Update System — developed to improve the efficiency of the drug development process in treatment and prevention trials — and the Adverse Drug Experience Reporting System — an electronic reporting mechanism designed to capture and transmit rapidly standardized data regarding adverse experiences with NCI investigational agents. A newly revised set of Common Toxicity Criteria is now available on the World Wide Web at http://ctep.info.nih.gov for the use of any interested investigator or sponsor; we expect this to become the worldwide standard for measuring and reporting the side effects of treatment. In addition, we have begun the development of a module to facilitate efficient communication among physicians involved in clinical trials.

• We have embarked on an initiative to restructure our clinical trials information program to take full advantage of advances in computing technology. As a key part of this initiative, we have instituted a comprehensive overhaul of the PDQ database. In February 1998, we conducted a formal needs assessment for the "new and improved" database, drawing on the expertise of nearly 200 experts representing diverse interests. Through the needs assessment, we identified the functional requirements for an "ideal" system and addressed the scope and level of the core content; user interface issues such as interactivity and navigability; and access issues, including mechanisms for addressing barriers to access. The development of the "new PDQ" is ongoing.

• NCI has created a new clinical trials resource on the Internet — **cancerTrials** (http://cancertrials.nci.nih.gov) — which provides information about ongoing prevention, detection, diagnosis, and treatment clinical trials — including links to databases of ongoing studies — as well as general information about clinical trials.

• In response to a report from the Office of the Inspector General (OIG) regarding improvement of telephone access to the Cancer Information Service (CIS), we have launched an initiative to renew the CIS, NCI's nationwide information and referral service (1-800-4-CANCER). The OIG report offered several recommendations to which we have responded by:

BUDGET FOR INFORMATICS AND INFORMATION FLOW

We are requesting $35.0 million to facilitate this effort.

- Use $15.0 million to support multicenter clinical trials activity, as well as development of expert systems, data collection, and analysis systems.
- Devote $15.0 million to ensure widespread availability of cancer information for patients and their families.
- Use $5.0 million for management and support.

TOTAL FOR INFORMATICS AND INFORMATION FLOW: $35.0 Million

— Upgrading telephone and computer technology to improve access.
— Improving baseline technical and performance measurements for the CIS telephone service.
— Developing a more efficient system of collecting community services referral information by partnering with other organizations within and outside NCI that develop and maintain resource materials for the CIS to use in responding to calls. Our overall goal is to ensure that the information line, available in all 50 states and Puerto Rico, provides optimal service for the more than 2,000 patients, physicians, and members of the public who call each day seeking cancer information.

• We are building an outcomes research program to assess the importance of our clinical practices on patient outcome and to evaluate how factors such as different payment systems affect cancer care.

Studying Emerging Trends

Through surveillance activities, NCI monitors trends in cancer incidence, survival, risk factors, and death among populations — changes in our national cancer burden — and the factors that influence these measures. Our primary means of studying such trends is the Surveillance, Epidemiology, and End Results (SEER) database (http://www-seer.ims.nci.nih.gov), which tracks the impact of cancer on the general population. For over 25 years, SEER has enabled us to identify environmental carcinogens, to track the cancer-related effects of tobacco on men and women, to identify geographic areas with higher than average rates of cancer, to study patterns and outcomes of cancer care, and to identify risk groups for research and public health intervention programs, all while maintaining the highest level of confidentiality and privacy.

SEER should be not only a means of understanding the past but serve as a window into the future. We want to ensure that SEER and related health information systems not only track changes in cancer rates accurately, but also contain information that will enhance researchers' ability to generate hypotheses and interpret observed changes in trends over time.

Developing and linking databases containing different kinds of health-related information on populations can provide a very powerful tool for analyzing factors (risk factors, screening, diagnosis, treatment, and health practices) that influence cancer rates, planning and evaluating population-based prevention and control interventions, and conducting other special analyses. For example, linkages between SEER and the comprehensive Medicare administrative database are already providing valuable information on relationships between health care resource utilization, costs, and medical outcome. The Breast Cancer Surveillance Consortium, an enhanced information system created to monitor the accuracy and performance of mammography screening in community practice, has led to the development of data linkages among radiology practices, pathology laboratories, and cancer registries to obtain data on the spectrum of care from screening through treatment. We need to extend these specialized surveillance efforts to include information on other cancer sites and on underserved and special populations.

Advances in information technology will enable linkages like these to be established much more easily than in the past and in time will facilitate the creation of databases through electronic transfer of information from electronic source documents. As always, procedures and policies will be needed to ensure individual privacy and confidentiality as these new systems develop.

Our Progress Toward Meeting the Challenge
In the past year, NCI has taken a number of important steps to improve and enlarge our surveillance efforts. For example:

• NCI has established a Surveillance Implementation Group composed of NCI staff and extramural scientists to help us develop plans and research priorities to guide NCI's surveillance efforts in the future. Members of this Group are addressing key issues about evaluating NCI's surveillance activities

and expanding the SEER database, risk factor and screening data linked to outcomes, surveillance methodology, and partnerships and collaborations. Responding to the recommendations of this group will help to ensure that we are keeping pace with the needs of the cancer research community.

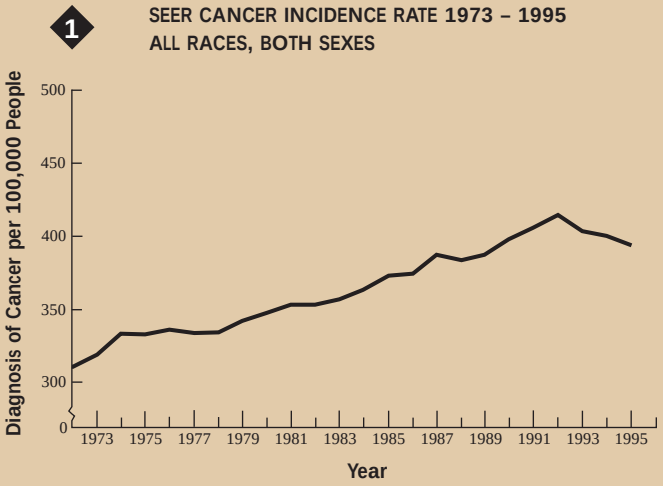
• We expanded the cancer surveillance database systems to collect information on risk factors for prevention and control. A cancer control supplement to the Year 2000 National Health Interview Survey will collect data on family history, genetic testing, survivorship, quality of life, and physical activity, in addition to dietary practices and tobacco use. Through oversampling and specially selected questions, we also are gathering information on Hispanic acculturation. This survey is being developed in collaboration with the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), and other key Federal agencies.

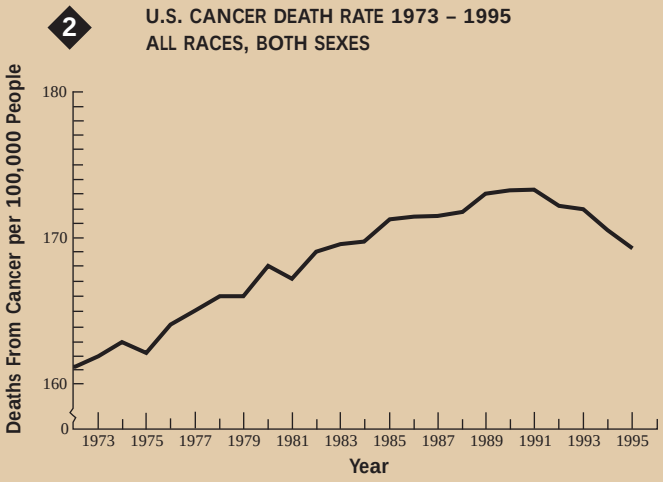
SPOTLIGHT ON RESEARCH

Cancer Statistics

Cancer incidence and death rates for all cancers combined declined between 1990 and 1995, reversing the nearly 20-year trend of increasing cancer cases and deaths in the U.S. The NCI, the American Cancer Society, and the Centers for Disease Control and Prevention recently reported that overall cancer incidence (the number of cases diagnosed per 100,000 people) declined on average 0.7 percent per year from 1990 to 1995 (see Graph 1). The average decline in cancer death rates was 0.5 percent per year from 1990 to 1995 (see Graph 2) with a greater decline for men than women.

Lung, prostate, breast, and colorectal cancers accounted for over one half of the new cases diagnosed and were also the leading causes of cancer death between 1990 and 1995. While incidence and mortality rates for most cancers have dropped, rates of malignant melanoma (now one of the most common cancers in young adults), non-Hodgkin's lymphoma, and kidney and renal pelvis cancers have risen. The previous decline in uterine cancer rates has leveled off. While these numbers, in general, indicate that our current research efforts are taking us in the right direction we now must redouble our efforts and seize the opportunity to further reduce the incidence and mortality rates of all cancers in all people.





• We developed a plan to enhance the Breast Cancer Surveillance Consortium through the collection of more complete data on risk factors for breast cancer incidence, prognosis, and quality of life.

• We began projects aimed at developing a population-based Colorectal Cancer Surveillance Consortium for measuring screening and early detection practices and their impact on colorectal cancer rates. In 1999, we will begin a survey of physicians (including specialists) and health plans, along with some developmental studies to measure utilization in selected populations covered by managed care organizations and Medicare.

BUDGET FOR STUDYING EMERGING TRENDS

We are requesting $28.5 million to facilitate the study of emerging trends in cancer.

- $12.5 million to enhance data collection for the Breast Cancer Surveillance Consortium, enabling collection of more complete data on risk factors for breast cancer incidence, prognosis, and quality of life; and to develop a population-based Colorectal Cancer Health Consortium.
- $11.5 million to improve surveillance research by increasing the utility of new database linkages, enhance infrastructure for managing confidential health data, expand methodological and modeling research related to cancer surveillance, and include geographic information for cancer surveillance.
- $2.5 million to expand SEER special studies on patterns of care for diagnosis, risk factors, screening, and treatment in community practice.
- $2.0 million for management and support.

TOTAL FOR STUDYING EMERGING TRENDS: $28.5 Million

• We have strengthened our capacity for cancer surveillance research studies by awarding a competitive grant to a network of investigators working in large, diverse, not-for-profit, managed care organizations throughout the United States. Other initiatives are designed to address research on cancer outcomes with a major focus on clinical trials.

• We continue to improve SEER and our collaboration with other population-based data systems to provide more complete and accurate information on cancer rates by ethnicity, socioeconomic status, geographic region, and access to care. Our cooperative surveillance activities involve many Federal agencies and other organizations, such as the CDC, the American Cancer Society, and the American College of Surgeons.

• NCI and Environmental Protection Agency staff are co-chairing a Working Group on Childhood Cancer as part of the Task Force on Environmental Health and Safety Risks to Children. The work group has begun several initiatives, including the creation of a national Network for Research on Cancer in Children. This network will build upon existing NCI-sponsored childhood cancer clinical trials groups and serve as a central registry of cases of childhood cancer occurring throughout the U.S. The registry, a multi-agency cooperative effort, also will provide a national resource and a platform to support and facilitate research into environmental causes of cancer in children.

Training, Education, and Career Development

We have been emphasizing the importance of new individuals who will be the leaders in accomplishing the complex tasks of translating discoveries into interventions. We need new kinds of scientists who can cross disciplinary boundaries. Where will they come from?

We must take steps now to ensure that some of the brightest, most creative young people from every segment of the American population enter the cancer research field. We must convince some of them that the field of translational research offers tremendous challenges and rewards. Moreover, we need to persuade individuals from untapped segments of the research community to change direction and join us in these translational efforts. This kind of research is often conducted by physician-scientists and other investigators who possess a broad base of knowledge and expertise in basic science, epidemiology, clinical oncology, and clinical investigation. The training of such individuals takes many years. Despite the scientific and medical rewards of careers in this area, there are also substantial disincentives.

In recent years, changes in the organization and financing of health care have resulted in significantly decreased revenues at many academic health centers. The resulting economic pressures have adversely affected clinical investigators — and, potentially, their research — in those centers. In particular, today's investigator frequently finds protected time for research to be an exceedingly hard commodity to secure. Unless clinical investigators receive the support they need to carry out research, many of the high-quality treatment, detection, diagnosis, and prevention studies that we desperately need will be delayed or even dropped. Therefore, we must create and maintain an environment that supports and encourages health care professionals who are involved in clinical research. We propose to do this by providing partial salary expenses for "protected" research time for NCI-supported clinical investigators engaged in research in areas such as treatment, prevention, and control. In addition, we must support training for health care professionals at any stage of their career who wish to become involved in clinical research.

Finally, we need to focus additional attention on the needs of minority students and young scientists and make these needs a major thrust of NCI's training activities. Current NCI minority initiatives have shown some success in broadening training opportunities for minority scientists, but greater efforts are needed. We must find ways to attract more minority students into biomedical science and more minority biomedical trainees into cancer research. Successful efforts to do this will need to be ambitiously conceived and will need to start early in the educational process. Enhancement of NCI's training programs for minority trainees is needed in order to provide promising young scientists access to high-quality training opportunities in outstanding laboratories and clinics across the entire biomedical spectrum.

Our Progress Toward Meeting the Challenge

As we prepare for a new century, we know that we must not only maintain but augment our support for the cancer research field's most valuable resource: our scientists. In the last year, we reviewed our established training programs to identify how we could best train young investigators coming into the field and continue to develop the skills of scientists already pursuing cancer research. Through this review, we have developed a strategic plan that is responsive to the special needs of students, young investigators, midcareer scientists, and clinical investigators, enabling them to stabilize and sustain productive research careers. We also have planned strategies to offer greater opportunities for investigators to engage in translational research. Below we discuss our new training initiatives in clinical, population, and translational sciences, and underserved populations, as well as plans to expand existing awards.

• ***Clinical Sciences.*** NCI's clinical training programs focus on medical doctors or other clinical professionals, providing support that spans their entire career, from the earliest stages of an investigator's education and training; to transition support needed by young medical scientists starting their first independent research programs; to protected time for established investigators, allowing scientists to focus on their own research and on mentoring young scientists. These programs include opportunities for individuals to pursue a basic or clinical research career (see Figure 1).

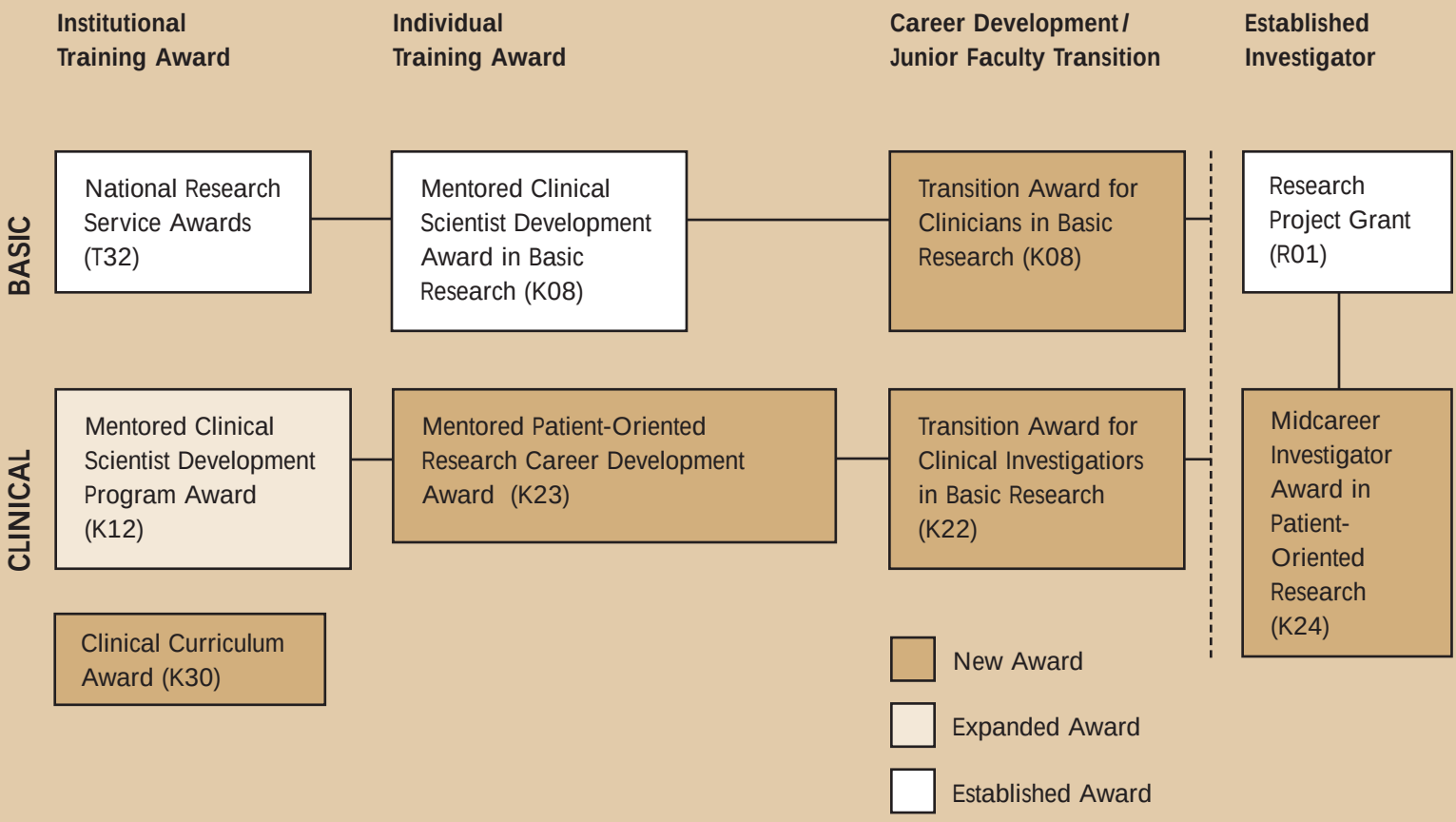
New initiatives include:

— The Mentored Patient-Oriented Research Career Development Award (K23) to develop and strengthen the skills of young scientists entering cancer research, providing them with the training needed to conduct rigorous clinical research.
— The Transition Award for Clinical Investigators (K22) to enable exceptional junior faculty in patient-oriented research to establish their first independent cancer research program. We hope to employ this new "transition" award within the next year.
—The Midcareer Investigator Award in Patient-Oriented Research (K24) to provide established investigators with the important and necessary opportunity to continue their training. Awardees will receive partial salary support for protected research time, an element essential to ensuring that quality clinical research continues into the next century.
—The Clinical Research Curriculum Award (K30) to support curriculum development, improvement, and instruction of in-depth, multidisciplinary core courses for training clinical researchers.

• ***Population Sciences.*** Ensuring a sufficient number of prevention, control, and population scientists is critical to the development of early detection and prevention strategies (see Figure 2). With this in mind, NCI is:

— Expanding the use of the Training Program for Cancer Prevention and Control Scientists (R25) to train individuals at the pre- or postdoctoral levels. This institutional award will provide trainees from basic, public health, and clinical backgrounds with the

FIGURE 1. — RESEARCH TRACKS FOR M.D.s

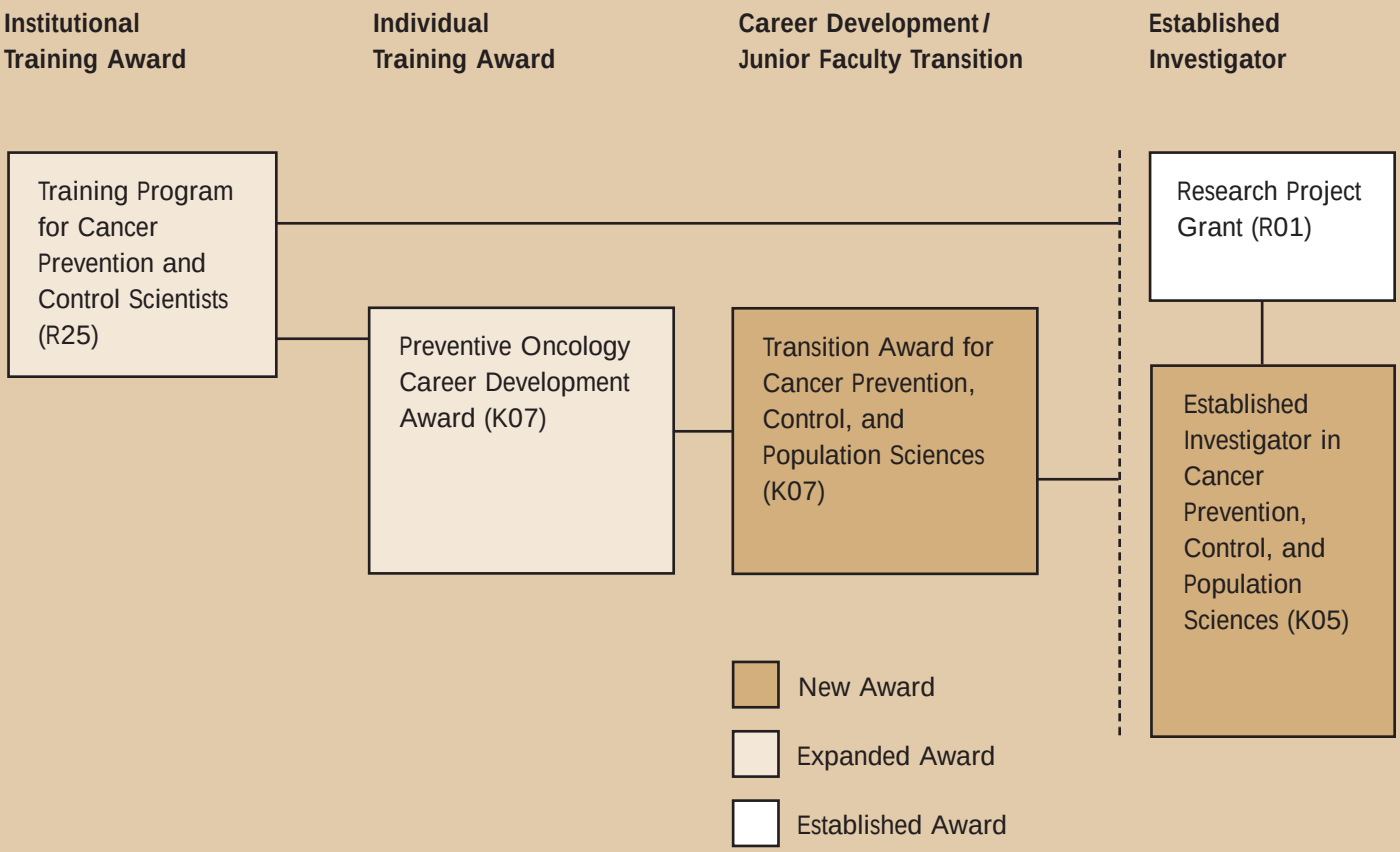


skills necessary to design and implement cancer prevention, control, and/or behavioral intervention research.
— Employing the Preventive Oncology Career Development Award (K07) for young mentored postdoctoral scientists to support development of outstanding candidates for a career in cancer prevention, control, or population sciences research.
— Establishing new "transition" support opportunities for scientists beginning their first independent research programs through the planned Transition Award for Cancer Prevention, Control, and Population Sciences (an enhanced K07). This award will provide awardees with stabilized salary support while they are developing their independent research programs.
— Providing protected time for senior investigators through the planned Established Investigator in Cancer Prevention, Control, and Population Sciences (K05) award.

• ***Translational Sciences.*** The increasing importance of multidisciplinary research for the translation of discoveries from the laboratory to the clinic has led NCI to establish the Translational Scientist Career Award (K01). This award will provide scientists in many disciplines with the support necessary to prepare themselves to develop or participate in translational cancer research. It can be used by basic scientists to redirect research, by individuals to gain new expertise, or by investigative teams that wish to recruit new expertise for a translational project. This new training concept will be developed further in the upcoming year.

• *Underserved Populations.* NCI continues to support extensive training and career development programs

FIGURE 2. — PREVENTION/CONTROL/BEHAVIORAL & POPULATION SCIENCES TRACKS



for minority individuals. To strengthen our efforts, we are proposing a newly structured plan that offers a continuum of training opportunities during high school, undergraduate studies, graduate school, postdoctoral training, and as an independent investigator. We are planning several new awards, and are expanding existing programs. For example, NCI is planning to expand research training for underrepresented minority candidates through the use of supplements to funded, peer reviewed grants supported by NIH. Four new supplements to these established awards will be employed: Center Grant Supplement (P30), for training at the high school and undergraduate levels; Clinical Oncology Supplement (K12), for training clinical scientists at the postdoctoral level; Population Scientist Supplement (R25), for education of population scientists at the graduate and postdoctoral levels; and the Transition Career Award (K01), for assisting minority junior faculty in basic, clinical, and population sciences with the transition from a mentored to an independent research career.

During the last year, we awarded 10 additional grants under the Mentored Research Scientist Development Award (K01) mechanism to support research training for minority postdoctoral investigators.

• ***Existing Awards.*** NCI will continue to maintain a strong basic sciences training program through the National Research Service Awards (NRSA). This base will be further strengthened as NCI, in response to an initiative spearheaded by the NIH, augments efforts to train young scientists by increasing the stipends of predoctoral and postdoctoral trainees under the NRSA by 25 percent. This increase will benefit 1,600 awardees, most of whom are basic scientists.

We anticipate funding an additional eight young scientists through the Howard Temin Award, a training mechanism aimed at fostering the research careers of junior basic, clinical, or behavioral scientists, bridging the gap between the mentored research environment and an independent research career.

BUDGET FOR TRAINING, EDUCATION, AND CAREER DEVELOPMENT

We are requesting a $95.1 million increase in FY 2000 to facilitate training, education, and career development, including activities devoted to trainees from underserved populations:

- $10.0 million will be used for education and training awards to individuals and institutions. Awards will range from $22 thousand to $30 thousand and will be given to 300 to 350 trainees, a portion of whom will be predoctoral students.
- $9.8 million will be used for additional NCI Research Career Awards ("K" Awards), including funds for patient-oriented training and funds for institutions to enhance clinical training opportunities.
- $3.0 million will be used to support intramural research training programs (for example, the NCI Scholars Program).
- $3.5 million will be used to augment the Cancer Education Program (R-25) to further the cancer education curriculum and student development in cancer research.
- $2.7 million will be used to train 20 to 30 individuals in prevention-related research, using both in-house and grant mechanisms.
- $1.1 million will be used to increase the number of investigators supported through Howard Temin Awards.
- $3.0 million will be used to provide additional training support through Research Project Grant awards.
- $54.0 million will be used to provide partial salary support for 450 investigators using the K24 program, including support for prevention and control research.
- $6.0 million will be used to provide "protected" time for clinical investigators in prevention and control.
- $2.0 million will be used for management and support.

TOTAL FOR TRAINING, EDUCATION, AND CAREER DEVELOPMENT: $95.1 Million

Acknowledgments

Producing the Bypass Budget is truly a collaborative effort. This year, this document has benefitted from the insights, contributions, commitment, and review of many people both within the National Cancer Institute and in research institutions and professional organizations throughout the country. Without them, this would have been a lesser document. To each of these individuals goes our thanks for their time, knowledge, and guidance.

Within NCI, three Offices — the Office of Science Policy, the Office of Financial Management, and the Office of Cancer Communications — deserve special recognition for the large roles they have played in developing and assembling this document. In addition, several NCI staff deserve special recognition for their contributions. *Cherie Nichols* provided leadership, motivation, insight, counsel — and when needed — a calming influence and ready ear. Her efforts helped to sustain the project's progress from its inception to completion. This year's Bypass greatly benefitted from the solid coordination efforts of *Jane Lockmuller*. Her many creative ideas for content and design, commitment of energy, and sense of purpose expertly guided this document through its life-cycles. In addition, *Jane Lockmuller*, *Catherine Law*, and *Kate Nagy* conceptualized, wrote, and edited most of the text. Their exceptional skills and dedication were instrumental in producing this document. We are also indebted to *Suzanne Reuben* for her excellent editing and writing contributions.

EDITORIAL BOARD

The Bypass Budget serves two important functions: it describes NCI's large and diverse research portfolio, and identifies the future path we need to take and the opportunities we need to promote to conquer cancer. With this in mind, we enlisted the help of several NCI staff with expert scientific knowledge, an overarching perspective on the Institute's activities and goals, and keen understanding of promising opportunities in cancer research. These individuals — our Editorial Board — contributed substantially to this project, helping to shape the content of this book.

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Dr. Edison Liu

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FY 2000 BYPASS PLANNING COMMITTEE

We thank the distinguished members of our planning committee who helped to ensure that this document clearly and accurately describes the excitement and promise of NCI's current research efforts, the needs and plans of the Institute, and a vision for the direction of the Nation's Cancer Research Program.

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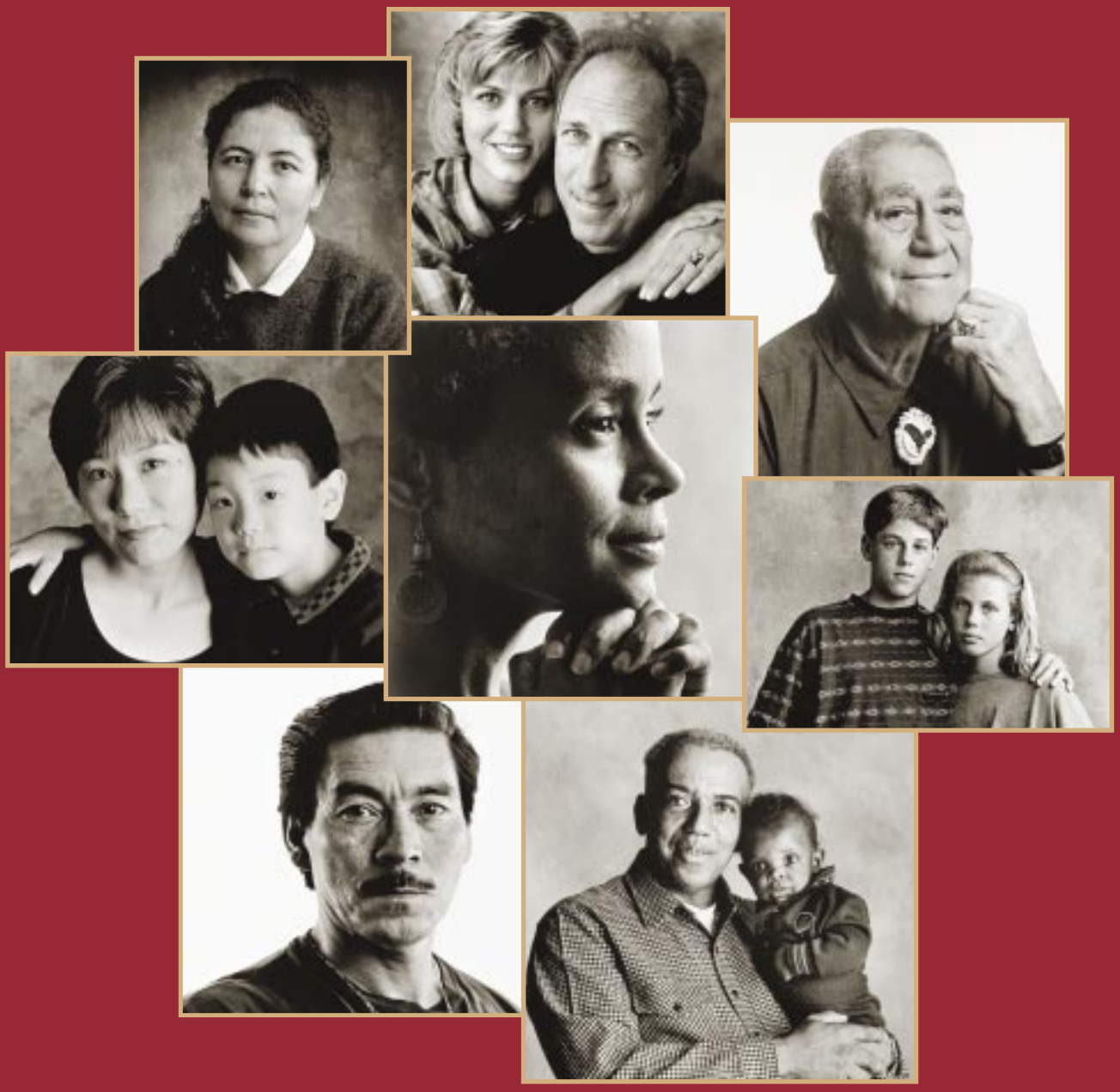
Additional copies of *The Nation's Investment in Cancer Research: A Budget Proposal for FY 2000* can be ordered by fax at 301-330-7968, by e-mail at cisocc@nih.gov, or by phone at 1-800-4-CANCER. Or, you may view the document and previous Bypass Budgets online at http://www.nci.nih.gov by clicking on "What's New."

For additional information on:

- *Cancer:* Visit us online at http://cancernet.nci.nih.gov where patients, health professionals, and the public can find information about the different types of cancer, screening, diagnosis, and state-of-the-art care. Or call NCI's Cancer Information Service at 1-800-4-CANCER to speak with an information specialist.
- *Clinical Trials:* Visit the newly redesigned Physician's Data Query (PDQ) database online at http://cancer net.nci.nih.gov/trials. Or, visit our new clinical trials resource, cancerTrials, at http://cancertrials.nci.nih.gov, which provides information about ongoing prevention, detection, diagnosis, and treatment clinical trials — including links to databases of ongoing studies and general information about clinical trials.
- *Cancer Centers:* Call NCI's Cancer Centers Branch at 301-496-8531 or visit http://www.nci.nih.gov/cancercenters/
- *Grants and Contracts:* Visit NIH's Grants and Contracts page at http://www.nih.gov/grants
- *Training, Education, and Career Development:* Call NCI's Cancer Training Branch at 301-496-8580. A complete list of the Institute's extramural training programs can be found at http://deainfo.nci.nih.gov/flash/awards.htm#TP.



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