

NIH Centers of Excellence

Introduction

The National Institutes of Health (NIH) Centers of Excellence are diverse in focus, scope, and origin. In general, they facilitate and coordinate research efforts on a specific disease, a group of diseases, or an area of research. Some were created as NIH-wide initiatives, others by individual Institutes and Centers (ICs), some reflect mergers or redesignations of existing programs, and some were congressionally mandated. The NIH Centers of Excellence described in this report are a subset—those established by statutory mandate.

Some congressionally mandated Centers of Excellence focus on long-recognized, significant challenges to public health, such as Alzheimer's disease and other conditions that have a major impact on aging populations. Other centers focus attention on areas of research that might otherwise be underfunded, such as rare diseases or research on minority health and other health disparities. Depending on when they were established and how many research sites have been funded, Centers of Excellence vary in size, scope, and outcomes.

The specific research goals and activities of the centers vary according to their mandates. In general, however, Centers of Excellence help establish critical research infrastructure, foster collaboration, train physician scientists and other professional staff, and provide shared resources, often through core facilities. Shared resources include systems for data gathering and analysis, instrumentation and computing, and the development of large patient registries. Research at the centers is often multidisciplinary and designed to encourage scientists and clinicians from diverse fields to come together to focus on a common set of objectives.

NIH Centers of Excellence seek to integrate basic and translational research and to move those findings efficiently toward clinical applications, some of which are evaluated in patient populations brought together at the centers. Results from these studies may have spinoffs that increase knowledge about other areas of research. Through outreach and communication efforts, the centers inform researchers and the public of scientific advances and improvements in medical care. Research at the congressionally mandated NIH Centers of Excellence is supported by administrative and program staff at individual ICs. Centers are funded for several years and then must re compete for support.

It is important to note that the creation of Centers of Excellence should only take place after an assessment of whether there is an adequate base of knowledge or number of expert investigators; what research opportunities are being adequately supported through existing or planned funding mechanisms and initiatives; or the appropriateness of alternative funding mechanisms. Congress has recognized they should create centers of excellence only under certain circumstances and provided the NIH Director with a new authority, through the NIH Reform Act of 2006, to review and approve the establishment of all centers of excellence recommended by the agency's institutes and centers.

This chapter provides overviews, outcomes (in the form of programmatic and research accomplishments), recommendations, evaluation plans, and future directions for the six congressionally mandated NIH Centers of Excellence programs, which are described in order of their establishment:

- Alzheimer's Disease Centers (1984)
- Claude D. Pepper Older Americans Independence Centers of Excellence (1989)

- Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (2001)
- National Center on Minority Health and Health Disparities Centers of Excellence (2001)
- Rare Diseases Clinical Research Network (2002)
- New Autism Centers of Excellence (2006), which merged the previously existing Collaborative Programs of Excellence in Autism and Studies to Advance Autism Research and Treatment

Tables listing the Centers of Excellence for each program appear in the appendix at the end of this chapter.

NIH Centers of Excellence

Alzheimer's Disease Centers

Overview

Why the ADCs Were Established

In 1984, Congress directed NIH to foster further research related to Alzheimer's disease (AD). The NIH [Alzheimer's Disease Centers](#) (ADCs) program is authorized by the Public Health Service Act under section 445 (42 U.S.C. 285e-2). The first ADCs were funded in the mid-1980s in response to the congressional directive and knowledge of AD pathophysiology emerging from the work of NIH grantees and other researchers. The prospect of a medical and social crisis triggered by an explosion of AD cases in a rapidly increasing aged population also motivated their creation. The principal objectives of the ADC program are to promote research, training, and education; technology transfer; and multicenter and cooperative studies of diagnosis, treatment, and clinico-neuropathological correlations in AD, in age-related neurodegenerative diseases, and in normal aging.

How the ADCs Function Within the NIH Framework

There are currently 29 ADCs funded by NIH (see Table 4-1). The centers are funded under the P30 and P50 mechanisms for 5 years and then must compete through a peer review process for additional funding. New applicants for ADCs compete with existing grantees, and if existing centers are unsuccessful in competition, new centers are funded to take their places.

Description of Disease or Condition

[AD](#) is the most common form of dementia among older people. It is a neurodegenerative disease that damages the parts of the brain controlling thought, memory, and language. AD is named after Dr. Alois Alzheimer, a German doctor who, more than 100 years ago, studied the brain tissue of a woman who had died of an unusual mental illness, and found abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary tangles). Today, these plaques and tangles in the brain are considered signs of AD, as are other brain changes, including the death of nerve cells in areas of the brain that are vital to memory and other mental abilities and the disruption of functional connections, called synapses, that allow nerve cells to communicate with each other. The disease is also characterized by lower levels of some of the chemicals in the brain that carry messages between nerve cells. AD may impair thinking and memory by disrupting these messages.

There probably is no single cause of AD. The most important known risk factors are age and family history, although education, diet, and environment might also play roles. Scientists are also finding evidence that some of the risk factors for heart disease and stroke—such as high blood pressure, high cholesterol, and low levels of the vitamin folate—might increase the risk of AD. Evidence is also increasing for physical, mental, and social activities as protective factors against AD. Although scientists have learned a great deal about AD, they still do not know what causes the disease and have not identified a cure for it.

Burden of Illness

AD is estimated to affect approximately 4.5 million older people in the United States¹ and 24.3 million people worldwide². Although it is occasionally diagnosed in patients in their forties and fifties, AD most frequently is associated with advancing age. The disease doubles in prevalence with every 5 years past age 65; thus, extending life by 10 years quadruples the probability of the disease occurring. AD is the most frequent cause of institutionalization for long-term care. It destroys the active, productive lives of its victims and devastates their families financially and emotionally. It has been estimated that the United States spends as much as \$148 billion per year for the direct and indirect costs of care for patients with AD³. With the rapidly increasing percentage of the population older than 65, the number of people with AD will increase proportionately, as will the toll it takes.

Scope of NIH Activities: Research and Programmatic

The ADC program provides an environment and core resources to enhance ongoing research by bringing together biomedical, behavioral, and clinical science investigators to study the etiology, progression, prevention, diagnosis, and treatment of AD and to improve health care delivery. ADCs also foster the **development** of new research approaches and provide suitable environments for research fellows and junior faculty to acquire the necessary skills and experience for interdisciplinary AD research.

All 29 ADCs are required to have an administrative core, a clinical core, a data management and statistics core, an education and information transfer core, and a neuropathology core. Some centers include other, optional cores, such as neuroimaging or genetics cores, and some have satellite diagnostic and treatment clinics to assist in the recruitment of minority research subjects. The ADC program comprises two types of centers: Alzheimer's Disease Research Centers (ADRCs) conduct research projects in addition to core resources, and the Alzheimer's Disease Core Centers (ADCCs) consist of cores only and provide access to investigators with well-characterized patients, patient and family information, and tissue and other biological specimens for use in separately funded research projects.

By pooling resources and working cooperatively, the ADCs have produced research findings and developed resources that could not have been achieved by individual investigators working alone. Biological samples from patients with AD have provided the materials for hundreds of non-ADC funded projects. Several major longitudinal studies on the development of dementia in particular populations rely on ADC core facilities and integrate their findings with those of the centers. Examples of shared resources are the brain and specimen banks at each center, which consist of well-characterized specimens collected under standardized protocols. Another resource is the National Cell Repository for Alzheimer's Disease (NCRAD), located at Indiana University, which collects and stores blood, well-documented phenotypic data, DNA, and cell lines from families that have multiple affected members. The repository is part of the National Institute on Aging's (NIA's) [Alzheimer's Disease Genetics Initiative](#) to identify genetic risk factors for late-onset AD. The ADCs have spawned other collaborative efforts that have led to the establishment of research resource entities, such as the [Consortium to Establish a Registry for Alzheimer's Disease](#), the [National Alzheimer's Coordinating Center](#), the [Alzheimer's Disease Cooperative Study](#), and the [Alzheimer's Disease Neuroimaging Initiative](#) (see below.)

¹ [Hebert LE, et al. *Arch Neurol* 2003;60:1119-22](#), PMID: 12925369

² [Ferri CP, et al. *Lancet* 2005;366:2112-7](#), PMID: 16360788

³ For more information, see http://alz.org/national/documents/PR_FFfactsheet.pdf

Much important progress in AD research in the United States during the past 20 years stems from research conducted at the ADCs, as well as from resources and infrastructure provided by the centers. Advances include the linkage and cloning of mutant genes on chromosomes 1, 14, and 21, the presence of which could result in early-onset, familial Alzheimer's disease, and on chromosome 17 in frontotemporal dementia, another common cause of dementia. More recent studies have revealed the importance of the abnormal processing of proteins encoded by these genes and the identification of a specific version of a gene at a location on chromosome 19 as a risk factor for late-onset AD.

ADC scientists have conducted much of the research on protein processing related to plaque and tangle formation, including the discovery of a protein implicated in the pathogenesis of Lewy body dementia—and the recognition of the common properties of the abnormal proteins associated with several neurodegenerative diseases. Important studies relating changes in brain structure to different clinical stages of AD are being carried out in many ADCs, using patients enrolled in the clinical cores, brain imaging studies supported by imaging cores, and autopsy evaluations in neuropathology cores. In recent years, researchers have focused on evaluating cognitive changes associated with normal aging and the transitions to mild cognitive impairment and early dementia, as well as studies to identify factors that contribute to changes in cognitive abilities. Relationships and commonalities between AD and other neurodegenerative diseases are also being emphasized along with studies of contributions of non-neurological comorbid conditions.

NIH Funding for FY 2006 and FY 2007

NIH funding for the ADCs was \$49.6 million in FY 2006 and \$50.1 million in FY 2007.

Outcomes: FY 2006 and FY 2007 Progress Report

Programmatic Accomplishments

Recent programmatic accomplishments for the ADCs include the following examples.

- [National Alzheimer's Coordinating Center \(NACC\)](#): Beginning in 1999, the NACC was established to facilitate collaborative research and to standardize procedures among the 29 ADCs. NACC developed and maintains a large relational database of standardized clinical and neuropathological research data collected from each ADC. This database provides a valuable resource to qualified research scientists for both exploratory and explanatory AD research. The data provided by NACC will permit large studies that use patient samples from diverse populations and multiple ADCs. One goal is to standardize procedures among the ADCs in several ways: (1) the approach to diagnosis of AD; (2) the approach to followup with those who have the disease; and (3) the collection of common data elements, also known as the uniform dataset. Although the unique aspects of the individual ADCs will be preserved, a core of common elements will help promote communication among the ADCs as well as with non-ADC researchers and the public. Autopsy confirmation of many of the cases makes these aggregate data especially valuable.
- [Alzheimer's Disease Cooperative Study \(ADCS\)](#): The ADCS is a major AD clinical trials effort that has grown out of the ADC program. This consortium was initially funded in 1991 to test the safety and efficacy of compounds of little interest to large pharmaceutical companies and to evaluate treatments for cognitive and behavioral symptoms of AD. The trials include drugs that are off-patent, were patented and marketed for another use but might be effective in AD, or novel compounds from individual investigators or small companies that lack adequate resources to conduct clinical trials. The ADCS helps to facilitate the testing of new drugs for the treatment of AD and functions as part of the AD Prevention Initiative, which was established to invigorate

efforts to discover new treatments, risk factors, methods of early detection, and diagnosis of AD. The ADCS also develops strategies for improving patient care and alleviating caregiver burdens and expedites movement of promising new treatments and prevention strategies into clinical trials. The ADCs serve as performance sites for the ADCS.

- [Alzheimer's Disease Neuroimaging Initiative \(ADNI\)](#): ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging (MRI), positron emission tomography (PET), or other biomarkers to measure earlier, and with greater sensitivity, the development and progression of mild cognitive impairment and AD. Most ADCs participate in the ADNI. Early results suggest that researchers may be able to reduce the costs associated with clinical trials by improving imaging and biomarker analysis. As part of the ADNI study, a standard physical model (i.e., a plastic phantom) was developed to monitor the performance of MRI scanners at multiple clinical sites, ensuring the accuracy of the MRI images. In another preliminary analysis, investigators compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and AD. They found that scans correlated with symptoms of each condition and that images were consistent across sites, suggesting the validity of PET scans for monitoring the effectiveness of therapies in future clinical trials. More than 200 researchers, as well as other interested individuals, have already accessed a public database containing thousands of brain images and related clinical data obtained through blood and cerebrospinal fluid analyses.
- **Late-Onset Alzheimer's Disease (LOAD) Genetics Initiative**: NIH launched the LOAD Genetics Initiative in 2002 to help advance AD-related genetics research. Eighteen ADCs participate in the initiative. The goal is to collect samples from 1,000 families having at least 2 members with late-onset AD as well as 1,000 control subjects. The Columbia University ADRC serves as the coordination center for the Genetics Initiative. As of 2007, more than 3,000 new blood samples from approximately 400 late-onset AD families have been sent to NCRAD. To complete enrollment, characterization, and followup of patients and control subjects in the Genetics Initiative, NIH awarded a resource grant to a group of six ADCs, which formed a consortium. In 2006, the NIH Center for Inherited Disease Research performed whole-genome scans on approximately 2,500 samples from members of these families. An article based on analysis of these [data](#) will be published in summer 2008.
- **Overlapping Dementing Diseases**: NIA and the National Institute of Neurological Disorders and Stroke (NINDS) are exploring the overlap of Parkinson's disease dementia, dementia with Lewy bodies, and AD, as well as the contributions of cerebrovascular disease to the brain pathology seen in AD. Joint initiatives in these overlap areas are under way. The ADCs collaborate with the NINDS-supported Udall Parkinson's Disease Centers to further the goals of examining the overlapping scientific and clinical issues related to AD, dementia with Lewy bodies, frontotemporal dementia, and Parkinson's disease dementia.
- **ADCs Minority Outreach**: A major objective for the ADCs is to recruit minority and ethnically diverse research subjects for AD research. A strategy to address this goal was developed in 1990 by creating a program to add Satellite Diagnostic and Treatment Clinics linked to existing ADCs. The number of satellites has fluctuated; 23 are currently active and are recruiting African American, Hispanic, Native American, and Asian research subjects. NACC data now show that approximately 20 percent of those enrolled in the ADCs are minorities.
- **Education Outreach**: All ADCs have Education and Information Transfer Cores (EITC) that support the development of clinical and research skills related to AD for physicians and other professional staff, as well as outreach to the public, including caregivers. EITC efforts have recently been redefined to emphasize subject recruitment for projects such as the NIA Genetics Initiative, ADCS, ADNI, and other clinical trials and initiatives. Collaborations include ongoing interactions with groups such as the Alzheimer's Association and the NIA's [Alzheimer's Disease Education and Referral Center](#). The ADCs pay special attention to issues of cultural sensitivity, and, where appropriate, the information is structured so it can effectively reach minority populations, including non-English-speaking people. ADCs work with ADEAR to develop materials for broad audiences.
- [New York Consortium for Alzheimer's Research and Education \(NYCARE\)](#): The three New York City ADCs—at Columbia University, Mount Sinai School of Medicine, and New York University—and the New York City

chapter of the Alzheimer's Association joined in 2000 to form NYCARE. The consortium provides continuing medical education programs for community physicians on AD diagnosis, management, and research opportunities.

- **The Alzheimer's Clinical Research and Training Awards Act:** This congressional initiative helps train the next generation of physician-scientists to conduct basic and clinical research on AD and associated dementias. The program provides support for promising clinicians through awards for research, study, and practice at the ADCs. Twelve awards have been made, and most of the awardees are working at ADCs.

Research Accomplishments

Since the establishment of the ADC program in 1984, thousands of research papers have been published on all aspects of AD and related neurodegenerative disorders, ranging from the molecular biology of the disease to family and societal impact, and including many studies of diagnosis and treatment. Research accomplishments include the following important recent studies carried out by ADC scientists.

- **Amyloid-beta Protein Metabolism Studies.** Biochemical, genetic, and animal model evidence implicates amyloid-beta as a pathogenic peptide in AD that can lead to abnormal communication among nerve cells and cell death. In late-onset AD, concentrations of this peptide in brain tissue from AD patients are 100- to 200-fold higher than in control brains. Recently, investigators at the Washington University ADC reported a new method for quantifying the synthesis and clearance rates of amyloid-beta in the normal human adult central nervous system. For the first time, investigators can now accurately measure the production and clearance rates of amyloid-beta in the central nervous system of living humans, indicating that under normal circumstances it is rapidly produced and cleared from the central nervous system. This new technique may prove to be of critical importance to scientists in their efforts to address crucial questions about the underlying pathogenesis of AD, to find possible biomarkers, and to test proposed disease-modifying therapies.
- **Standards for Assessing Cognitive Status in Understudied Populations:** One difficulty in evaluating the cognitive status of people in understudied populations is that the normative values available for standard tests often are not appropriate for other populations. Cultural, linguistic, educational, and other factors differ among groups and consistently have been shown to influence neuropsychological evaluations. Recently, scientists at the Mayo Clinic ADC produced a large set of normative data on older African Americans, using several common neuropsychological assessment tools. The authors note that these normative values may be applicable only to older African Americans raised in the South, making it important to determine whether the new data can be generalized. In addition, over time, even a narrowly defined group might have different characteristics; for example, participants in this sample were educated prior to the Brown vs. the Board of Education decision by the U.S. Supreme Court to end segregation of public school systems. Despite some limitations in its clinical utility, this study represents the first large-scale publication of normative data for an understudied population.
- **Establishing Commonalities Between Frontotemporal Dementias and Amyotrophic Lateral Sclerosis:** Frontotemporal dementias (FTDs) are a group of neurodegenerative diseases that are sometimes misdiagnosed as AD or related dementing disorders. It is estimated that 35-50 percent of FTD cases have a family history of dementia; nearly half have been linked to a mutation on chromosome 17. In recent studies, researchers have linked some cases of FTD to another mutation on chromosome 17. In addition, a new brain protein has been identified, related to the pathogenesis of both FTD and amyotrophic lateral sclerosis (ALS), in which dementia also can occur. It is thought that changes caused by this mutation impair the ability of the cell to degrade abnormal proteins, thereby causing them to remain in the nervous system, where they contribute to the development of FTD and ALS disease processes. Investigators are continuing to study these proteins and other genetic mutations to further identify and understand the mechanisms involved in the development

of FTD, ALS, and other neurodegenerative diseases.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the ADCs

Since their launch in 1984, the NIH ADCs have continued to grow, and many multiple-center initiatives have emerged. In 2002, NIA organized a meeting to help determine the future of the ADC program. Several recommendations were made based on this meeting and have been implemented.

The first recommendation was to create the uniform dataset, which was described earlier in this chapter (see National Alzheimer's Coordinating Center [ADCC]). Another recommendation was to encourage greater flexibility in the structure of ADCs to take better advantage of local strengths, interests, and expertise. For example, ADCs can now enroll and follow special patient populations rather than using only clinic populations, as had been required previously. ADCs also are encouraged to develop programs that change with the scientific knowledge base and to find ways to translate new knowledge into clinical applications—for example, the translation of basic research findings to measure amyloid-beta production and clearance in living patients. ADCs also are being encouraged to make better use of tissue and data resources and to share them. One example of this is the further development and expansion of NCRAD to increase its capacity to bank cell lines, DNA, and serum from all ADCs as well as other sources.

Evaluation Plans

The ADCs were reviewed in great detail by an external advisory committee in 2002 and again in less detail by the National Advisory Council on Aging in 2003. The next review by the National Advisory Council on Aging will take place in May 2008.

Future Directions

In the future, ADCs will continue to place less emphasis on late-stage AD and instead will concentrate more on the transition from normal aging to mild cognitive impairment to full-blown AD, as well as on studies that overlap with other neurodegenerative diseases. NIH will continue to support existing ADCs and to award new grants to applicant institutions that are deemed qualified through the NIH peer-review process.

NIH Centers of Excellence

Claude D. Pepper Older Americans Independence Centers

Overview

Why the OAICs Were Established

In 1955, the U.S. Surgeon General established five Geriatric Research and Training Centers (GRTCs) to advance research on the health care problems of the elderly and to train future academic leaders in geriatrics. In 1989, Congress enacted legislation that redesignated the GRTCs as the Claude D. Pepper Older Americans Independence Centers (OAICs), in honor of former Florida Senator and Representative Claude Denson Pepper for his efforts to promote the health and well-being of older Americans. The OAICs, which are funded in 5-year periods, are authorized under Section 445A of the Public Health Service Act (42 U.S.C. 285e-3) to increase scientific knowledge leading to better ways to maintain or restore independence in older adults (see Table 4-2).

How OAICs Function Within the NIH Framework

The OAICs are funded by NIA through a center grant mechanism (P30). The ultimate goal of the OAIC program is to enhance the translation of basic and developmental research on aging to applications and interventions that increase or maintain independence for older persons.

Each OAIC:

- Provides intellectual leadership and innovation
- Stimulates translation of basic research findings into clinical applications, e.g., research to develop or test interventions or diagnostics based on new findings from aging research or other studies of fundamental biological processes
- Facilitates and develops novel multidisciplinary and interdisciplinary research strategies
- Stimulates incorporation of emerging technologies, methods, and scientific advances into research designs, as appropriate
- Serves as a source of advice to and collaboration with other institutions regarding technology, methodology, analysis, or other expertise
- Provides career development, guidance, and training for future leaders in basic, clinical, and translational research in geriatrics and related fields

Description of Disease or Condition

Aging research focuses on a range of conditions, including geriatric syndromes such as involuntary weight loss, dizziness, and incontinence, as well as diseases and disorders that are more common among older adults, such as

cancer, cardiovascular disorders, stroke, and loss of sensory functions such as hearing and sight. The ultimate goal is to advance the translation of basic and developmental research on aging to applications and interventions that increase or maintain independence for older adults.

Burden of Illness

There are currently 35 million Americans older than age 65. Of these, more than 4 million are older than 85, and approximately 65,000 have attained their 100th birthday. By 2030, the number of individuals age 65 and older is likely to double to 70.3 million and comprise 20 percent of the entire population, in contrast to 13 percent today. The number of the “oldest old”—people age 85 and older—is expected to grow to at least 19.4 million by 2050⁴.

The ratio of older people to other age groups is important to society because older people, particularly the oldest old, may be dependent on family members, the government, or both for financial, physical, and emotional support. In addition, a large part of older people's security depends on programs such as Social Security and Medicare, which are financed through the contributions of working-age individuals. When the entire population of “baby boomers” enters older age, around 2030, the challenge to meet their needs through social, governmental, and other health care services will expand markedly⁵.

Data compiled in 2003 indicate that U.S. health care expenditures totaled approximately \$1.87 trillion, more than any other industrialized country⁶. Researchers predict that increased longevity is likely to require more financing from Federal health care systems, including Medicare and Medicaid⁷. As life expectancy increases, it will be necessary to find ways to keep the additional years of life free of disease and disability. Today, for example, more than half of all Americans older than age 65 show evidence of osteoarthritis in at least one joint⁸. Over half of Americans older than age 50 have osteoporosis or low bone mass⁹. Cardiovascular disease, cancer, and diabetes remain common among older Americans.

Scope of NIH Activity: Research and Programmatic

OAICs are designed to develop or strengthen each awardee institution's programs to focus and sustain progress in a key area of aging research, contribute to greater independence for older persons, and offer opportunities for training and career development in aging research for young scientists. OAICs select a specific focus for their research activities from a range of topics, including:

- Specific aging-related physiologic changes, other factors, or interventions (e.g., physical activity) that affect risk for multiple conditions or disabilities in old age

⁴ Federal Interagency Forum on Aging Related Statistics. Older Americans 2000: Key Indicators of Well-Being. 2000.

⁵ U.S. Department of Health and Human Services. 65+ in the United States: 2005, Current Population Reports, Special Studies. U.S. Department of Health and Human Services/NIH/NIA and the U.S. Department of Commerce/Economics and Statistics Administration/U.S. Census Bureau: December 2005.

⁶ For more information, see <http://www.cdc.gov/nchs/products/pubs/pubd/hsu/healthexpenditures.htm>

⁷ [Spillman BC, Lubitz J. N Engl J Med 2000;342:1409-15](#), PMID: 10805827; [Feder J, et al. Health Aff 2000;19:40-56](#), PMID: 10812780

⁸ For more information, see http://www.niams.nih.gov/Health_Info/Osteoarthritis/default.asp

⁹ For more information, see <http://www.nof.org/advocacy/prevalence/index.htm>

- Interactions of multiple diseases, disabilities, and interventions (e.g., medications) in older persons and their relationship to the risk of morbidity, progression of disability, and efficacy of prevention or treatment strategies
- Factors contributing to the amelioration or delay of multiple deleterious aging changes by modulating risk factors or fundamental aging mechanisms
- Causes, prevention, and treatment of a geriatric syndrome that is related to multiple pathologies or disabilities
- Causes, assessment, prevention, and treatment (including rehabilitation) of a specific type of disability in older people
- Issues related to specific conditions that contribute to a loss of independence in older persons, e.g., the role of aging changes in the etiology of debilitating physical condition(s); special problems in the diagnosis, treatment, or prevention of the condition in old age; complications, disability, or symptoms from the condition found principally in older people

NIH Funding for FY 2006 and FY 2007

NIH funding for the OAICs was \$13.6 million in FY 2006 and \$13.7 million in FY 2007.

Outcomes: FY 2006 and FY 2007 Progress Report

Programmatic and Research Accomplishments

- The [Duke University OAIC](#) supports studies to develop and evaluate interventions designed to help older Americans anticipate, cope with, and recover from disability arising from late-life disease and aging. An analysis of several biomarkers has linked these biomarkers to osteoarthritis; research is continuing to evaluate genes for their potential association with osteoarthritis and facioscapulohumeral dystrophy, one of the most common inherited neuromuscular disorders, which primarily affects the skeletal muscles of the face and upper arms. A Demonstration and Information Dissemination Project has helped to translate research findings from programs such as the Osteoporosis Intervention Study into clinical practice. The Genetic Ascertainment of Large African American Family for Osteoarthritis and Early Onset Cardiovascular Disease project of the Duke OAIC has analyzed the genetics of one of the largest intact extended families in the United States and is evaluating this family for evidence of osteoarthritis and early-onset heart disease.
- The **Harvard University OAIC** promotes research to help elderly individuals maintain independence well into late life by supporting a series of studies focused on the development of interventions to overcome common disabling geriatric conditions. Examples include studies of the causes and consequences of delirium after coronary bypass surgery; the relationship between cardiovascular risk factors and the development of frontal lobe dysfunction (impairments in executive function, gait, and continence) in African American elders; and the use of subsensory mechanical noise to improve somatosensation—such as the ability to perceive pain and temperature variations—and balance in healthy older people and patients with diabetes and stroke. For example, one study indicates that caution should be used in administering isoflurane, a common inhalation anesthetic, to individuals with excessive levels of amyloid-beta protein in the brain, including AD patients, among others¹⁰.

¹⁰ [Xie Z, et al. *J Neurosci* 2007;27:1247-54](#), PMID: 17287498

- The **Johns Hopkins University OAIC** supports research to determine causes and potential interventions for frailty in older adults. New studies include a project to develop methods that will infer parameters to measure frailty and to test hypotheses about the causes of frailty in older adults. Another project involves compiling genetic data from several resources, including the Women's Health and Aging I and II studies, InCHIANTI, the Baltimore Longitudinal Study of Aging, and HealthABC, to provide sufficient analytical power to detect causes of frailty. A pilot study to describe the relationship between brain-derived and peripheral cholesterol levels and cognitive and physical frailty found that high, not low, total cholesterol was associated with better psychomotor speed. The next step is to determine whether these findings also extend to physical speed and might be a predictor of physical frailty. Another pilot study to evaluate the role of glucocorticoid resistance in frail elderly people demonstrated that frailty is strongly associated with increased daytime salivary cortisol levels and that it is much more strongly related to these increases than to chronological age.
- The **University of California, Los Angeles OAIC** supports the development and testing of clinical interventions to prevent disability. Its activities include a study to refine an intervention for optimizing nursing home staff efficiency in providing feeding assistance to residents and then to test the efficacy of this model in a randomized clinical trial to determine quality of life and health outcomes. A separate, pilot, randomized clinical trial involves an intervention to improve visual functioning in older people. Information from this preliminary study will be utilized in a larger randomized clinical trial to determine whether visual and overall functioning of older people can be enhanced through a multidimensional intervention that corrects reversible causes of visual impairment, improves lighting in the home environment, and provides access to low-vision aids. Another ongoing study evaluates an age-appropriate intervention designed to improve diabetes self-care practices by enhancing the self-efficacy, empowerment, and diabetes-specific knowledge among African Americans older than age 65, a group that tends to experience substantially worse process and outcomes of care. The OAIC provides ongoing operational assistance to the new Resource Center for Minority Aging Research, one of six centers funded for the 2002-2007 cycle of this NIH initiative.
- The **University of Maryland, Baltimore OAIC** conducts mechanistic and outcome-based research in exercise rehabilitation and provides research training in gerontology and geriatrics to improve the lifestyle and functional independence of older Americans with disabilities. The center emphasizes exercise rehabilitation based on preliminary findings that exercise can improve the devastating health consequences and functional declines associated with stroke, hip fracture, and peripheral arterial occlusive disease—chronic conditions that often decrease functionality and independence in the elderly. Preliminary studies show that specific exercises such as treadmill exercise training improves lower body strength and increases fitness reserves among gait-impaired stroke patients and that an upper body workout improves motor function in the partially paralyzed upper extremities of stroke patients who have completed conventional rehabilitation and are 1-5 years beyond the incident stroke. Evidence of improved brain function accompanying task-specific exercise provides further support to the observation that recovery not only is enhanced through exercise but also continues months and years after the stroke. Thus, task-oriented exercise programs that improve upper and lower body functional capabilities and quality of life might allow these patients to remain at home and function independently, maintaining their lifestyle, reducing caregiver burden, and lowering their utilization of health care resources.
- The **University of Texas OAIC** research focuses on age-related sarcopenia, a progressive loss of muscle mass that leads to muscle weakness, limited mobility, and increased susceptibility to injury, and the contribution of sarcopenia to loss of independence in older persons. OAIC researchers discovered in an animal model that a specific protein, UNC-45, previously demonstrated to be critical to the proper formation of muscle, acts as a chaperone for muscle proteins known as myosins and helps myosins fold into stable structures that clump together to form thicker filaments that give heart and skeletal muscle its striated appearance. Normally,

electrochemical signals cause the myosin filaments to contract, producing, for example, a heartbeat or an arm movement. When myosin proteins are not yet fully stable, a cellular cleanup system, known as the ubiquitin proteasomal system, may mistake them as unstable or malfunctioning and break down the myosin. Further study of the cellular basis of muscle weakness and loss of muscle mass in aging is under way. Researchers affiliated with another study are using a porcine model to clarify the mechanisms by which amino-acid supplementation can regulate muscle protein synthesis with the goal of designing appropriate nutritional support in a variety of clinical settings. The OAIC also supports the Longitudinal Study of Mexican American Elderly Health, a population-based longitudinal study that focuses on predictors of continued physical independence among 3,000 older Mexican Americans living in five southwestern States.

- The **Wake Forest University OAIC** mission is to assess the risk factors of physical disability in older adults and to develop and test effective prevention therapies. Among the studies supported by the center is research on chronic obstructive pulmonary disease, a major cause of morbidity and mortality in the United States. Investigators are evaluating the effectiveness of a lifestyle intervention to increase physical activity to a greater extent than a traditional exercise therapy program and are comparing the impact of these two interventions on physical function, self-reported disability, health-related quality of life, and exercise capacity. The Pharmacological Intervention in the Elderly is a randomized controlled trial in older patients with diastolic heart failure to evaluate the effect of the drug enalapril on heart structure and function, exercise tolerance, and quality of life. Enalapril is one of the angiotensin-converting enzyme inhibitor drugs primarily used to treat hypertension and congestive heart failure. The goal of an observational pilot study is to examine physical function in obese individuals after a specific type of gastric bypass surgery to determine whether intensive weight loss associated with bariatric surgery will improve physical function. In addition, the Wake Forest center established the Maya Angelou Research Center on Minority Health to address issues related to racial and ethnic health disparities.
- The **Yale University Center OAIC** focuses on causes, prevention, treatment, and disability outcomes of multifactorial geriatric conditions. Research from this OAIC has contributed significantly to understanding the extent and frequency of transitions in and out of disability by identifying factors influencing these transitions and those predicting successful recovery from disability affecting activities of daily living. Findings from the studies provide a basis for developing multifactorial interventions to prevent disability. Multifactorial interventions to prevent falls in community settings are currently supported through the Yale OAIC; injuries and fractures resulting from falls are a major cause of disability among older adults. Epidemiologists and biostatisticians at the Yale OAIC are developing new statistical approaches to analyze data from multifactorial interventions and to identify contributions from individual components and thus to guide the refinement of these interventions.
- The **University of Michigan Center OAIC** seeks to advance research on health care problems of older adults. Among their projects is one to study the loss of balance and its consequences in older adults and to utilize a wearable motion sensor to capture important parameters of this process. A pilot project on elucidating the cellular and molecular events that regulate normal epidermal growth seeks to determine how alterations in these events precipitate hyperplastic growth, particularly as it occurs in aged skin. In another pilot study, investigators are examining genetic factors in hypertension among three generations of African American women.
- The **OAIC Coordinating Center at Wake Forest University** strengthens the OAIC program by facilitating information exchange and research collaborations among individual OAICs. The Coordinating Center builds on elements that are common to individual OAIC themes and assists in the development and implementation of projects in shared areas of interest. Major activities of the Coordinating Center are the coordination and

enhancement of the training programs across OAIC sites and the organization of seminars and other activities for trainees at the OAIC Annual Scientific Meeting

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the OAICs

One recommendation of NIA's Geriatrics and Clinical Gerontology Program is to establish the Coordinating Center function as a part of the competitive OAIC Request for Applications (RFA) process. RFA AG-07-008 includes requests for applications for continuing the Coordinating Center functions. Another effort is to explore plans to expand the OAIC program.

Evaluation Plans

The general progress of each OAIC is reviewed by program staff at the time of noncompeting renewal. In addition, a formal midcycle review is conducted by a panel of experts external to the OAICs at 2-3 years into the funding cycle of each OAIC. The purpose of the review is to assess the progress of individual OAICs in meeting the goals set forth in their funded applications and to identify areas of concern that could be addressed prior to the next competing renewal. A written summary of the review is provided to each OAIC principal investigator for use in directing his or her center.

Future Directions

The number of qualified applicants for OAIC sites is increasing, and NIH expects that additional centers will be added gradually to bring the total number to 12 by 2010. NIH plans to continue funding the Claude D. Pepper OAICs through a continued, competitive peer-reviewed process open to new and renewal applications.

NIH Centers of Excellence

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

Overview

Why the Wellstone MDCRCs Were Established

The Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Pub. L. No. 107-84) specified provisions for expanding and intensifying research on muscular dystrophy and mandated that NIH establish Centers of Excellence for research on muscular dystrophy. Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs) in the Omnibus Appropriations for FY 2004 (Pub. L. No. 108-199). Former Minnesota Senator Paul D. Wellstone, who died on October 25, 2002, was a driving force behind the Muscular Dystrophy Community Assistance Research and Education (MD-CARE) Act (see Table 4-3).

How the Wellstone MDCRCs Function Within the NIH Framework

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NINDS, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) fund two Wellstone MDCRCs each, using the U54 Specialized Centers Cooperative Agreement award mechanism. A Steering Committee oversees scientific coordination of the Wellstone MDCRCs, sets goals, and makes strategic decisions about activities such as establishing collaborations. The committee consists of the directors and co-directors of each center, NIH science officers, and a public member. The External Advisory Committee, which is composed of experts in muscular dystrophy research and a patient advocate, helps inform NIH programmatic decisions regarding the Wellstone MDCRC program.

Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of the skeletal muscles, which control movement. Some forms occur in infancy or childhood, whereas others may not appear until middle age or later. Diseases addressed by the Wellstone MDCRCs include, but are not limited to, the following conditions.

- **Duchenne and Becker muscular dystrophies:** Duchenne muscular dystrophy is the most common childhood form of muscular dystrophy. It is an X-linked recessive disease, primarily affecting males who inherit a genetic mutation from their mothers. Boys with Duchenne muscular dystrophy lack the protein dystrophin, which is essential for keeping muscle cells intact. Duchenne muscular dystrophy usually becomes evident when a child begins walking. Patients typically require a wheelchair by age 10 to 12 and die in their late teens or early twenties. Becker muscular dystrophy, a less severe disease, occurs when a partially functional form of dystrophin is produced.
- **Myotonic dystrophy:** Myotonic dystrophy is the most common adult form of muscular dystrophy, although it

can strike at any age. It is marked by myotonia (an inability to relax muscles after contraction) and muscle wasting and weakness. Myotonic dystrophy varies in its severity and manifestations. It can affect other body systems in addition to skeletal muscles, including the heart, endocrine organs, eyes, and gastrointestinal tract.

- **Facioscapulohumeral muscular dystrophy:** Facioscapulohumeral muscular dystrophy initially affects muscles of the face (*facio*), shoulders (*scapulo*), and upper arms (*humeral*). Symptoms usually develop in the teenage years, and some affected individuals become severely disabled.
- **Limb-girdle muscular dystrophies:** All limb-girdle muscular dystrophies show a similar distribution of muscle weakness, affecting both upper arms and legs. Many forms of limb-girdle muscular dystrophy have been identified; some affect children, whereas others manifest in adulthood.
- **Miyoshi myopathy:** Miyoshi myopathy, one of the distal muscular dystrophies, causes initial weakness in the calf muscles. It is caused by defects in the same gene that is responsible for one form of limb-girdle muscular dystrophy, suggesting that research progress against one form of muscular dystrophy may lead to a better understanding of other forms as well.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Symptomatic treatments such as physical therapy, use of appliances for support, corrective orthopedic surgery, and drugs improve the quality of life for some individuals. However, even though some drugs, such as steroids, can slow the progression of Duchenne muscular dystrophy, there are side effects. Several therapeutic approaches, including gene therapy, cell-based treatments, and strategies to inhibit muscle degeneration, have shown promise in cell culture systems and animal models. Clinical trials of some therapies have begun, including the use of drugs to reduce muscle damage, cell-based replacement therapies, functional compensation for the lack of dystrophin by increasing the body's production of certain proteins, increasing muscle mass via inhibition of other proteins that negatively regulate muscle growth, and strategies to bypass the mutations that cause disease.

Burden of Illness

Duchenne and Becker muscular dystrophies affect boys at a rate of 1 in 3,500 to 1 in 5,000. More than 4 million births occur annually in the United States, and about 400 to 600 boys are born with Duchenne or Becker muscular dystrophy every year¹¹. Myotonic dystrophy affects approximately 1 in 8,000 people worldwide¹², whereas facioscapulohumeral muscular dystrophy affects approximately 1 in 20,000 people and affects men and women equally¹³. The MD-CARE Act called for the Centers for Disease Control and Prevention (CDC) to collect and analyze information on the number, incidence, correlates, and symptoms of individuals with muscular dystrophy. This surveillance system, once fully operational, will provide additional burden of illness data.

Scope of NIH Activities: Research and Programmatic

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDCRCs are expected to promote communication and collaboration, develop and share research resources, and contribute to the training of new muscular dystrophy researchers¹⁴. Each Wellstone MDCRC includes at least one basic research project and one clinical research project, with a minimum of three individual but interrelated research projects, an

¹¹ For more information, see <http://www.cdc.gov/ncbddd/duchenne/who.htm>

¹² For more information, see <http://ghr.nlm.nih.gov/condition=myotonicdystrophy>

¹³ For more information, see <http://www.nlm.nih.gov/medlineplus/ency/article/000707.htm>

¹⁴ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-03-001.html>;
<http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-04-008.html>

administrative core, and at least one scientific resource core that serves as a resource for the national muscular dystrophy research effort.

Collectively, the Wellstone MDCRCs are engaged in research on various forms of muscular dystrophy, including some not listed above. Designed to accelerate progress toward effective treatments for muscular dystrophies through increased synergistic collaboration and coordination of research activities, they promote side-by-side basic, translational, and clinical research. Each center coordinates efforts to help bring together investigators at multiple sites.

Examples of research topics addressed at the various centers are as follows.

- The **University of Pittsburgh** center focuses on developing gene therapy techniques as well as research on muscle stem cells as potential therapies for Duchenne muscular dystrophy. The center is also preparing to conduct a clinical trial of gene therapy for limb-girdle muscular dystrophy.
- The **University of Rochester** center focuses on myotonic dystrophy and facioscapulohumeral muscular dystrophy. Researchers are examining cellular and molecular factors that contribute to these diseases and are conducting a clinical trial of the drug IPLEX (mecermin) for patients with myotonic dystrophy.
- The **University of Washington** center focuses on gene therapy techniques and has begun several new collaborative projects focused on the mechanisms underlying facioscapulohumeral muscular dystrophy
- Researchers at the **Children's National Medical Center** are analyzing genetic and cellular factors that contribute to the progression of Duchenne muscular dystrophy and the response of patients to treatment.
- The **University of Iowa** center focuses on gene and stem cell therapeutic strategies for Duchenne, limb-girdle, and other muscular dystrophies. It provides diagnostic services for physicians around the country and banks biopsy samples that can be used for research.
- The **University of Pennsylvania/Johns Hopkins University** center focuses on strategies to promote muscle growth or inhibit muscle protein degradation, approaches that could be applicable to a range of muscular dystrophies and other muscle disorders. It also provides state-of-the-art animal model physiological testing services as a resource for other researchers.

The Wellstone MDCRC program reserves funds to support new collaborative projects involving center investigators and pilot projects by non-center investigators. Center directors are also encouraged to collaborate with other muscular dystrophy researchers or representatives from voluntary health organizations to apply for Administrative Supplements to support small workshops or conferences focused on specific topics in muscular dystrophy research¹⁵.

Each of the Wellstone MDCRCs has core facilities that provide unique resources or services for the muscular dystrophy research community. Resources include repositories of research data and biologic resources from patients with various muscular dystrophies; imaging, diagnostic, bioinformatics, and computing capabilities; and viral vector development and production. The Wellstone MDCRC program also aids therapeutic development by maintaining a muscular dystrophy dog colony and providing sophisticated functional testing of mouse models.

NIH Funding for FY 2006 and FY 2007

In FY 2006 and FY 2007, NIH invested a total of \$9.6 million and \$8.5 million, respectively, in the Wellstone MDCRC program. The three original Wellstone MDCRCs (Rochester, Washington, and Pittsburgh) also received up to

¹⁵For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-AR-05-008.html>

\$500,000 per year from the Muscular Dystrophy Association. This supplemental funding ended in December 2006.

Outcomes: FY 2006 and FY 2007 Progress Report

Programmatic Accomplishments

Programmatic accomplishments include awards of NIH Administrative Supplements for Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships at Wellstone MDCRCs to advance the careers of four basic and clinical scientists who study muscular dystrophy.

New collaborative projects supported by the Wellstone MDCRC in FY 2006 and 2007 include the following:

- A collaborative effort between investigators at the Wellstone MDCRC at Children's National Medical Center and researchers in Japan to evaluate a gene modification technique (i.e., exon skipping) in a dystrophic dog model
- Collaboration between the Iowa Wellstone MDCRC and Ohio State University to develop more effective diagnostic techniques for limb-girdle muscular dystrophy and Miyoshi myopathy
- A partnership between University of Pittsburgh and University of Pennsylvania investigators to study myostatin inhibition using the dog colony supported by the Pittsburgh Center

In 2006, the Wellstone MDCRC Administrative Supplements program to support workshops and research conferences funded a workshop entitled "High Throughput Drug Screening for the Muscular Dystrophies" at the Children's National Medical Center. Industry, academic, and government researchers, as well as patient advocates, participated. The center is planning a second workshop, which will address the development of standard protocols for testing therapies in animal models.

The availability of Wellstone MDCRC core facilities has been publicized at national meetings, through Web sites that the centers have established, and through the [Wellstone MDCRC Web site](#). Sharing these research tools fosters collaborations across departments or schools at a single institution and among investigators and health care providers at several institutions. For example, the Muscle Tissue/Cell Culture/Diagnostics Core at the University of Iowa Wellstone MDCRC serves as both a local and a national resource for muscular dystrophy research. In addition to maintaining a muscle tissue repository of well-characterized tissues and cells representing the spectrum of muscular dystrophy diagnoses that are available for research, the center provides diagnostic services that are not readily available through clinical laboratories and is facilitating the development of new diagnostic tests.

Research Accomplishments

The Wellstone MDCRCs conduct basic, translational, and clinical studies related to a variety of muscular dystrophies. Each center has at least three distinct but interrelated research projects. Examples of research accomplishments in FYs 2006 and 2007 are noted below.

- In the past 2 years, investigators at the University of Rochester MDCRC have begun a clinical trial to test the drug Iplex in patients with myotonic dystrophy. The dose escalation phase of this safety and feasibility trial suggests that the drug is well tolerated. The next phase of the trial will test an optimal dose in patients with myotonic dystrophy. Because Iplex improves muscle regeneration, it may be useful in many types of muscular dystrophy.

- Two other clinical trials, including one to test a gene therapy for limb-girdle muscular dystrophy, are preparing to begin recruiting patients.
- Wellstone MDCRC investigators have made numerous other advances with respect to gene therapies for other muscular dystrophies. Many strategies that 2 years ago were being tested in mice are now being evaluated in dogs. Wellstone MDCRC researchers are refining their technologies and are identifying how genes should be administered. They also are discovering interactions between gene therapy vectors and human immune responses and have developed an immunosuppression protocol that shows promise in dogs¹⁶.
- Researchers at the University of Pennsylvania/Johns Hopkins University Wellstone MDCRC have tested a class of compounds known as protease inhibitors (i.e., Bowman-Birk inhibitors) that show promise in animal models of Duchenne muscular dystrophy and are planning to begin a clinical trial.
- The Wellstone MDCRCs are also contributing basic research findings to the understanding of muscular dystrophy. For example, during a search for stem cell traits that predict effective muscle regeneration, University of Pittsburgh researchers determined that cell sex (i.e., whether the cells originated in a male or a female donor) has a profound influence on whether muscle stem cells can produce muscle fibers in a mouse model of Duchenne muscular dystrophy¹⁷. The results could influence future research on the use of cell transplants for treating muscular dystrophy and affect the overall field of stem cell biology and regenerative medicine by prompting other investigators to consider and report the sex of the cells used in their research.
- In other basic research, investigators at the University of Rochester conducted a comprehensive genome-wide scan of biopsies from patients with early-stage facioscapulohumeral muscular dystrophy. The scan results are dispelling a widely held belief that a deletion on chromosome 4 triggers the development of facioscapulohumeral muscular dystrophy by disrupting expression of neighboring genes¹⁸. Results from this study have connected vascular abnormalities commonly observed in the retinas of patients with facioscapulohumeral muscular dystrophy who have the skeletal muscle weakness and wasting characteristics of the disease and may eventually lead to new treatments of this disease.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the Wellstone MDCRCs

Due to NIH efforts to improve the Wellstone MDCRCs' effectiveness, efficiency, and outcomes, centers funded in FY 2008¹⁹ will differ somewhat from their established counterparts in the following ways:

- Whereas the Wellstone MDCRCs established in 2003 and 2005 have three research projects, an administrative core, and a scientific research core, institutions applying for the program in FY 2008 are required to have at least one research project and specific core activities.
- Because the number of basic findings that are ready for translation has increased dramatically since the last competition, NIH removed the basic research requirement to allow the Wellstone MDCRCs to focus more of their efforts on translational research.
- The need for a clinical or patient-oriented project remains unchanged in the new solicitation, but because the required number of projects has been reduced from three to one, center applicants are free to propose larger, more expensive clinical research activities.
- Whereas the existing centers could apply for a training supplement to support the career development of a

¹⁶ [Wang Z, et al. *Mol Ther* 2007;15:1160-6](#), PMID: 17426713

¹⁷ [Deasy BM, et al. *J Cell Biol* 2007;177:73-86](#), PMID: 17420291

¹⁸ [Osborne RJ, et al. *Neurology* 2007;68:569-77](#), PMID: 17151338

¹⁹ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-08-002.html>

postdoctoral and nontenure track investigator, the training aspect of the next round of Wellstone MDCRCs will be formalized by Research Training and Education Cores that will support a predoctoral student and a postdoctoral fellow at each site. This addition was made in response to suggestions from the Steering Committee, combined with an analysis of existing training opportunities in the field of muscular dystrophy research.

- To better promote coordination of information and resources among the Wellstone Centers and throughout the muscular dystrophy research community, each applicant institution is required to provide letters documenting how one of its proposed core resources will fill a high-priority need in the muscular dystrophy research community.

As the Wellstone MDCRC program gains momentum, NIH plans to reexamine the role and composition of the External Advisory Committee to ensure that it continues to contribute to the growth and success of the program.

Evaluation Plans

NIH reissued the RFA for the Wellstone MDCRCs in FY 2007. The competition was open to new applicants, and the three centers that were originally established in 2003 had to compete again for funding. Major review criteria for the Wellstone MDCRCs include the degree to which an institution demonstrates its ability to engage in substantive collaborations to address key issues in muscular dystrophy and its potential to serve as a national infrastructure and training resource.

Future Directions

As noted above, the reissued RFA for Wellstone MDCRCs reflects several changes to further strengthen the program. NIAMS, NINDS, and NICHD intend to fund up to three Wellstone MDCRCs. NHLBI will participate by supporting meritorious cardiopulmonary research in successful applications. Grantees will join a network of existing Wellstone MDCRCs to foster the translation of new scientific findings and technological developments into novel treatments for the muscular dystrophies

NIH Centers of Excellence

National Center on Minority Health and Health Disparities Centers of Excellence Program

Overview

The National Center on Minority Health and Health Disparities (NCMHD) promotes the health of minorities as well as of other populations that experience health disparities and leads, coordinates, supports, and assesses NIH efforts to eliminate health disparities. To accomplish these goals, NCMHD:

- Conducts and supports basic, clinical, social sciences, and behavioral research
- Promotes research infrastructure and training
- Fosters emerging programs
- Disseminates information
- Reaches out to minority and other communities that experience health disparities

The Centers of Excellence program is one of several programs central to NCMHD's scientific investment strategy for addressing and ultimately eliminating health disparities.

Why the NCMHD Centers of Excellence Were Established

The NCMHD Centers of Excellence were mandated by Pub. L. No. 106-525, the Minority Health and Health Disparities Research and Education Act of 2000, which also established NCMHD. Solicitations for proposals for the NCMHD Centers of Excellence were first published in the NIH Guide in 2001, and the first awards were made in FY 2002. When the program was launched, it was referred to as the Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT). With the FY 2007 re-competition, the program was renamed the NCMHD Centers of Excellence.

The NCMHD Centers of Excellence were established to develop novel programs across the country that would make significant advances and contributions in preventing, reducing, and ultimately eliminating health disparities in several priority diseases and conditions. The centers are helping to build the Nation's research capacity by establishing novel partnerships between different types of institutions—for example, Historically Black Colleges and Universities (HBCUs) and research-intensive institutions—and by engaging the efforts of community and faith-based organizations. The NCMHD centers provide opportunities to partner in the conduct of rigorous basic scientific research, human and animal subject-based research, and applied population and community-based research. The centers program also provides opportunities for increasing the pool of investigators from populations that experience health disparities through research training, faculty development, disseminating health information, and increasing the participation of these populations in clinical trials.

Since 2002, NCMHD has established a total of 88 centers of excellence located in 31 states, the District of

Columbia, Puerto Rico, and the U.S. Virgin Islands. The program began using three different funding mechanisms for Resource-Related Centers, Exploratory Centers, and Comprehensive Centers. The use of these different funding mechanisms has allowed NCMHD to help level the playing field among institutions with varying experience in biomedical research and to leverage the different skills and capabilities of the Nation's geographically and culturally diverse institutions. In FY 2007, 50 NCMHD Centers of Excellence were active (see Table 4-4). The Resource-Related Centers funding mechanism has been discontinued. The types of institutions are broad and include majority research institutions, medical schools, HBCUs, Hispanic-serving institutions, Tribal colleges, and liberal arts colleges.

How the NCMHD Centers of Excellence Function Within the NIH Framework

The NCMHD centers are managed in accordance with NIH policies and procedures for all funded research grants awarded through the R24, P20, and P60 mechanisms. Their progress is assessed annually, and updates are provided to the NCMHD Advisory Council. Like many other NIH Centers of Excellence that are supported through these mechanisms, a typical project period runs for 4-5 years. The project periods for NCMHD centers (P20s and P60s) that were established in 2002 and 2003 ended in 2007, and many of them recompleted in FY 2007.

Description of Disease or Condition

As described in various solicitations published in the *NIH Guide*, the NCMHD centers conduct research on the following priority diseases and conditions: cardiovascular disease, stroke (ischemic and intracerebral), cancer (all cancers, including breast, prostate, and cervical), diabetes, HIV/AIDS, infant mortality, mental health, and obesity (in men and women). In FY 2006, with the release of the new solicitations for the NCMHD centers program, research on lung disease, liver disease, psoriasis, scleroderma, and glomerular (kidney) injury was encouraged as a result of congressional interest and the fact that these diseases and conditions disproportionately affect racial and ethnic minorities but had not been widely studied.

Burden of Illness

Recent statistics on disparities for select diseases and conditions are provided in the following tables, which highlight the need for research on minority health and health disparities.

<i>Ischemic Stroke Death Rates</i>²⁰	
<i>Race/Ethnicity</i>	<i>Rate (per 100,000)</i>
White	73.7
African American	95.8
American Indian/Alaska Native	48.6
Asian/Pacific Islander	45.8
Hispanic	39.7

²⁰ [Ayala C, et al. Am J Epidemiol 2001;154:1057-63](#), PMID: 11724723

Intracerebral Stroke Death Rates ²¹	
Race/Ethnicity	Rate (per 100,000)
White	13.2
African American	22.5
Asian/Pacific Islander	20.1
American Indian/Alaska Native	10.4
Hispanic	12.0

Breast Cancer Death Rates by Race/Ethnicity ²²	
Race/Ethnicity	Rate (per 100,000 Women)
All Races	25.0
White	24.4
African American	33.5
Asian/Pacific Islander	12.6
American Indian/Alaska Native	17.1
Hispanic	15.8

Prostate Cancer Rates by Race/Ethnicity ²³	
Race/Ethnicity	Rate (per 100,000 Men)
All Races	26.7
White	24.6
African American	59.4
Asian/Pacific Islander	11.0
American Indian/Alaska Native	21.1
Hispanic	20.6

²¹ Ibid

²² Ibid. For more information, see http://seer.cancer.gov/statfacts/html/breast.html?statfacts_page=breast.html&x=16&y=16

²³ For more information, see http://seer.cancer.gov/statfacts/html/prost.html?statfacts_page=prost.html&x=18&y=17

Obesity in Men ²⁴	
Group	Percent
All	30.2
White	31.0
African American	31.2
Mexican	30.5

Obesity in Women ²⁵	
Group	Percent
All	34.0
White	31.5
African American	51.6
Mexican	40.3

Scope of NIH Activities: Research and Programmatic

The scope of activities at NCMHD centers includes the conduct of original and innovative basic, behavioral, clinical, or population-based research directed toward improving minority health, eliminating health disparities, or both. Support is provided for full-length research and pilot projects, research training, student and faculty development activities, and outreach and community engagement. Special emphasis has been placed on research addressing comorbidities within populations with health disparities.

NIH Funding for FY 2006 and FY 2007

NIH funding for the NCMHD Centers of Excellence Program was \$53.7 million in FY 2006 and \$59.9 million in FY 2007.

Outcomes: FY 2006 and FY 2007 Progress Report

Programmatic Accomplishments

Significant programmatic accomplishments include increases in the number of training programs for students and junior faculty; the number of partnerships between universities and colleges and communities with health disparities; the number of senior racial and ethnic minority investigators from major research institutions, HBCUs,

²⁴ For more information, see Table 73 at <http://www.cdc.gov/nchs/data/hus/hus06.pdf>

²⁵ Ibid

Hispanic-serving institutions, and Native American institutions engaged in minority health and health disparities research; and the number of individuals and community organizations from health disparity communities engaged in research. NCMHD Centers of Excellence have been successful in leveraging their NIH funding to attract new dollars from other government agencies and private foundations to support research on minority health and health disparities.

Research Accomplishments

Funding of the NCMHD centers has resulted in many research accomplishments. The centers conduct research on minority health and the biologic and nonbiologic factors contributing to health disparities. For example, a review by researchers at the University of California at Los Angeles Center for Research, Education and Training and Strategic Communication on Minority Health Disparities examined the role of discrimination on health and the causes of race-based disparities. Researchers at the University of Puerto Rico-Medical Sciences Campus, in partnership with the Cambridge Health Alliance—an NCMHD-funded partnership—have developed a new theoretical mechanistic model accounting for the asthma disparities observed in minority children, particularly within subgroups of Latino children. The researchers applied a modified Institute of Medicine model to explain asthma disparities as a complex interaction among four major factors: (1) the health care system, (2) the practices and beliefs of primary care providers, (3) patient-based individual variables (i.e., physical factors such as genetic factors and sociocultural factors such as beliefs and practices), and (4) external environmental factors. This model has been used to guide the development of the comprehensive, multilevel, community-based intervention program²⁶.

In addition to these and other published scientific articles, NCMHD centers are also making significant gains in their communities by increasing awareness of the existence of health disparities and of the need to increase efforts to improve minority health and eliminate health disparities. The examples below highlight some of these efforts. In particular, NCMHD centers are creating new health-related messages and disseminating them to their communities through radio, public and cable TV, newsletters, Web sites, and even YouTube. Some centers produce bilingual versions of all of their messages. Many innovative approaches are being undertaken. For example, one center has produced two plays testing the role of the arts in bringing about change in health behaviors. Other centers are using immersion experiences in urban settings as a means to develop cultural competency and increase awareness and understanding of health disparities issues.

Additional examples of research accomplishments include the following:

- Researchers at the New York University NCMHD EXPORT Center for the Study of Asian American Health and the NYC Asian American Hepatitis B Program reported that approximately 15 percent of Asians living in New York City are chronically infected with the hepatitis B virus. Between January 22 and June 30, 2005, they tested 1,836 individuals for hepatitis B virus through collaborating clinics. The prevalence rate of chronic hepatitis infection was higher for males than females, higher for persons ages 20-39 years than for those age 40 years and older, and higher for those individuals born in China than for those born in other Asian countries²⁷.
- The findings from a study conducted at the Mount Sinai NCMHD center show that the inferior survival of minority women with breast cancer is in part due to racial disparities in the use of adjuvant treatments for

²⁶ [Canino G, et al. *Soc Sci Med* 2006;63:2926-37, PMID: 16956704](#)

²⁷ For more information, see <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=PubMed&Cmd=ShowDetailView&TermToSearch=16691180&>

early-stage breast cancer (underuse for minority women). Women referred to medical oncologists were less likely to experience underuse of necessary adjuvant treatments. However, women who were minorities, lacked insurance, and had higher levels of comorbidity were at greater risk for underuse. The researchers concluded: “Minority women with early-stage breast cancer have double the risk of white women for failing to receive necessary adjuvant treatments despite rates of oncologic consultation similar to those for white women. Oncology referrals are necessary to reduce treatment disparities but are not sufficient to ensure patients' receipt of efficacious adjuvant treatment.”²⁸

- A recent cross-sectional survey of a community-based random sample of 230 African American and Hispanic female heads of household living in a geographically defined area (the three urban public housing communities in Los Angeles County, CA) documents significant disparity in screening for cervical cancer among underserved minorities, particularly Hispanic, uninsured, and older women. The continuity of obtaining medical services and receiving from physicians remains the core factor significantly associated with obtaining cervical cancer screening. The results underscore the need for continued efforts to ensure that medically underserved minority women have access to cancer screening services²⁹.
- The Connecticut Center for Eliminating Health Disparities among Latinos, funded by NCMHD, is conducting a Diabetes Peer Counseling Study. Following are the specific aims of the study:
 - Develop a comprehensive, culturally tailored model of diabetes management that integrates the work of community-based peer counselors and clinical specialists into a multidisciplinary health care team in order to directly respond to factors limiting successful diabetes management identified through an intensive needs assessment conducted in the Hispanic community
 - Implement an intervention that provides education and support to Hispanic adults diagnosed with type 2 diabetes in clinical and home settings
 - Evaluate this intervention for its impact on program adherence and improved clinical, cognitive, and behavioral outcomes sustained over time
 - Modify the peer counseling service based on the evaluation and implement it as a best-practices model for diabetes management support of diabetic Hispanics

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the NCMHD Centers of Excellence

The NCMHD Centers of Excellence have evolved and increased in number since they were first established in 2002. In 2004, NCMHD convened a meeting of center directors and grants management staff to network, learn more about NCMHD, and share common interests and challenges in health disparities research. From this meeting emerged a number of recommendations and ideas that either have been incorporated in the NCMHD Centers of Excellence RFAs or continue to guide NCMHD in developing future program components and activities for the centers.

To improve the effectiveness of the NCMHD centers, NCMHD decreased the required number of cores (discrete components that together make up a center) from four (research, administrative, training, and community engagement) to two (research and administrative) but allowed additional cores to be added with appropriate justification. To ensure research leadership and excellence, NCMHD required the development of full research

²⁸ [Bickell NA, J Clin Oncol 2006;24:1357-62](#), PMID: 16549830

²⁹ [Bazargan M, et al. Prev Med 2004;39:465-73](#), PMID: 15313085

projects, provided funding for pilot projects, required that the plan for selecting pilots be peer reviewed, and allowed for the solicitation of pilot projects from health disparity researchers at other institutions. To increase outcomes contributing to minority health or the elimination of health disparities, NCMHD encouraged a multidisciplinary approach to conducting research. This approach emphasizes research on the biological, behavioral, and social determinants of health across the lifespan and includes individual, family, and population studies on factors that are relevant to one, or more, disease or condition. Each NCMHD Center of Excellence is required to develop and maintain a Web site to assist in building collaborations and in disseminating findings and information to health disparity researchers and individuals from health disparity populations.

Evaluation Plans

The NCMHD Centers of Excellence will be evaluated biennially by NCMHD program and evaluation staff by examining the number and type of peer-reviewed publications, books and book chapters, and conferences and presentations on health disparities; community engagement, such as health fairs and other types of dissemination of health promotion materials; community participation in research and clinical trials (if applicable); and training of minority junior faculty, postdoctoral fellows, and graduate and undergraduate students.

Future Directions

Future directions of the NCMHD centers will focus on intensifying research efforts to reduce health disparities with an emphasis on increased partnerships, as described below.

Scientific Knowledge To Be Gained Through the NCMHD Centers

It is expected that new biomedical and behavioral knowledge will be discovered for improving minority health and for eliminating health disparities within and across the priority areas of cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity, as well as lung and liver diseases, psoriasis, scleroderma, and glomerular injury. An important area of emphasis is reducing comorbidities in populations that experience health disparities.

The national health program “Healthy People 2010” identified six critical determinants of health: biology, behaviors, social environment, physical environment, policies, and access to care. It is expected that research conducted at NCMHD Centers of Excellence will generate new knowledge about the interactions of significant biological factors with behavioral and social variables, how they affect each other, and how these interactions influence and contribute to minority health conditions and health disparities. This new knowledge is expected to lead to the development of biopsychosocial interventions and strategies for improving minority health and eliminating health disparities.

Possible Themes for Future Research

Themes for future research directions are the continuation of interdisciplinary minority health and health disparities research, including basic, clinical, and behavioral and social sciences research, to advance understanding of disease development and progression and the development of interventions for preventing or delaying the onset and progression of disease. Another theme is designing studies to improve approaches for disease prevention, diagnosis, and treatment. Researchers at the NCMHD centers also plan to study how disparities in health outcomes occur, including but not limited to behavioral and social factors; genetic variations; underlying biological factors; gender, ethnic, and familial factors; environmental exposures; and policy and social factors. The latter include, for example, exposure of children or adults to abuse, discrimination, or other potential stressors. These studies would seek to identify the biological underpinnings of differential responses to stressors and to therapies (e.g., for hypertension, diabetes, renal transplantation, depression) and the differential prevalence of

disease and comorbidities.

The success of future research conducted at NCMHD Centers of Excellence will depend in part on the development of improved methodological tools, measures, validated instruments, and novel research designs for disentangling the contribution to health disparities of biologic factors, behaviors, and social factors. Also important will be population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the United States, in particular, the Mississippi Delta, Appalachia, the U.S.-Mexico border region, and tribal communities. Also important will be studies to eliminate or decrease the impact of factors, including natural disasters, that contribute to the excess risks, morbidity, and mortality associated with living in such regions.

NIH Centers of Excellence

Rare Diseases Clinical Research Network

Overview

Why the RDCRN Was Established

The need for Centers of Excellence for rare diseases research has been voiced since the mid-1980s. A disease is defined as rare if it has a prevalence of fewer than 200,000 people in the United States. There are almost 7,000 rare diseases known today. Approximately 80 percent of rare diseases are thought to have a genetic origin.

In 1989, the National Commission on Orphan (or rare) Diseases considered the lack of specialized centers for the diagnosis and treatment of rare diseases to be a serious barrier to the advancement of research on rare diseases. The commission found that 15 percent of patients with rare diseases did not obtain a correct diagnosis until after 5 years or more. An additional 30 percent of patients waited from 1 to 5 years before obtaining a diagnosis.

In 1999, the NIH Special Emphasis Panel on the Coordination of Rare Diseases Research endorsed the need for Centers of Excellence. The panel recommended funding for Specialized Research and Diagnostic Centers of Excellence for Rare Diseases for major categories of rare diseases. The proposal in 1999 was to establish Centers of Excellence on a graduated basis, starting with 10 regional centers in the first year and followed by incremental increases of 10 centers per year until 40 research Centers of Excellence were established. The panel also emphasized that centers should work closely with patient advocacy groups.

Some of the panel's recommendations were realized when President George W. Bush signed the Rare Diseases Act of 2002, Pub. L. No. 107-280, and when NIH established the Rare Diseases Clinical Research Network (RDCRN).

How the RDCRN Functions Within the NIH Framework

The RDCRN involves collaboration among the NIH Office of Rare Diseases (ORD), NCRR, NICHD, NINDS, NIAMS, NIDDK, and NHLBI. In 2003, the original RDCRN, funded through a U54 cooperative agreement, consisted of seven Centers of Excellence (consortia) and a Data and Technology Coordinating Center (DTCC). In 2004, three additional consortia were funded (see Table 4-5). During the first 2 years of operation, each consortium focused on developing clinical protocols for a subset of related rare diseases. RDCRN incorporated standards across consortia and developed and instituted an adverse event reporting system.

The RDCRN contains more than 70 sites distributed across the United States and in other countries. The goals of the sites are to make investigational studies and treatments more accessible to patients with rare diseases and to facilitate the recruitment of patients for clinical trials.

The RDCRN Steering Committee consists of the principal investigator of each consortium, NIH representatives, and a patient advocacy representative. The committee meets on a monthly basis via teleconferencing and two times per year in person.

Other cross-network committees ensure collaboration, cooperation, efficiency, and quality for RDCRN research.

They include the Human Subjects Committee, the Participant/Community Liaison Committee, the Standards Committee, the Web Site Committee, the Training Committee, a project managers committee, and the Coalition of Patient Advocacy Groups. Since 2006, 17 training modules on individual protocols and important issues of common interest have been developed and are available to RDCRN participants through the Network Media Center.

Description of Disease or Condition

Rare diseases affect many tissues, organs, and organ systems. Researchers affiliated with the RDCRN study more than 40 rare diseases. These include Angelman, Rett, and Prader-Willi syndromes; myelodysplastic syndrome and other bone marrow failure conditions; lymphangioleiomyomatosis, rare genetic disorders of the airways, and other rare lung diseases; episodic ataxia, Andersen-Tawil syndrome, and nondystrophic myotonias; several vasculitides; urea cycle disorders; antiphospholipid syndrome and other rare thrombotic diseases; rare pediatric liver diseases; and rare genetic steroid defects.

Burden of Illness

The burden of illness for rare diseases is difficult to estimate because of the large number of these disorders and the limited availability of prevalence and incidence statistics for each disease. Estimates of prevalence or incidence exist for only a minority of rare diseases, and the burden of illness and associated costs are complex. Occasionally, estimates have been produced by patient advocacy organizations or principal investigators applying for funding either to NIH or the U.S. Food and Drug Administration's Office of Orphan Products Development. The National Organization for Rare Disorders estimates that 20-25 million people are affected by a rare disease.

Overall, rare diseases are devastating because of their severity and because diagnosis may take a long time, well after symptoms have appeared. Additionally, there may be no available treatment once the disease is diagnosed.

Scope of NIH Activities: Research and Programmatic

The RDCRN brings together health care researchers who are skilled in diagnosing and treating particular groups of rare diseases. Additionally, the consortia gather groups of patients with similar or related disorders, foster basic scientific investigation, encourage synergy in translational research, and enhance opportunities for collaborative clinical investigation.

The DTCC is designed to enable sharing of study results nationally and internationally in a timely and uniform way. Although data and technology coordination is primarily the responsibility of the DTCC, each center as well as NIH IC program officers also participate in overall coordination.

More than 30 patient advocacy groups are affiliated with the RDCRN and have formed the Coalition of Patient Advocacy Groups to support outreach efforts to patients with rare diseases, their families, and the public. A representative of the group serves on the RDCRN Steering Committee and acts as a liaison between the committee and participating advocacy groups.

NIH Funding for FY 2006 and FY 2007

As the Rare Diseases Act of 2002 stipulated, each consortium award has been made for 5 years. Total funding in FY 2006 was \$14.1 million and \$9.4 million in FY 2007.

Outcomes: FY 2006 and FY 2007 Progress Report

Programmatic and Research Accomplishments

To date, the network has produced 25 publications, posters, and abstracts. In 2006, NIH launched the first [clinical studies of the RDCRN](#), and, by September 20, 2007, 26 clinical protocols had been approved, of which 24 were recruiting patients. Twenty more protocols are under development. To date, 2,357 subjects have been enrolled in research studies.

Many consortia participating in the RDCRN have developed longitudinal studies as well as clinical trials to test the safety and efficacy of new therapeutic agents. The consortia have established training programs for clinical investigators who are interested in rare diseases and have developed a [Web site](#) to inform the public, physicians, patients, and investigators about rare diseases.

The DTCC has developed and enabled new technology, tools, and services for the RDCRN, including electronic data entry, remote direct laboratory transfer, vocabulary and laboratory standards, statistical support, Web site development and maintenance, and database querying tools. The DTCC, in collaboration with each consortium, has also implemented a patient contact registry that allows individuals to register to receive information about new or ongoing clinical studies in addition to periodic educational updates.

To facilitate patients' transportation needs, Angel Flight NIH has widened its services to include the RDCRN. Volunteer pilots donate their time, planes, fuel, and operating expenses to transport patients and family members free of charge to and from medical and research facilities in the RDCRN so that no patient is denied medical access to ongoing research projects because of lack of air transportation.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the RDCRN

In anticipation of the completion of the first 5 years of the network, ORD and the participating NIH ICs assessed the current design of the RDCRN and published a [Notice of Intent](#) to announce that an RFA would be published. The new [RFA](#) will be open to the current participating centers as well as to new applicants and builds on lessons learned during the initial 5 years. With the completion of the first 5 years of the network, the re-issuance of the RFA, and a probable increase in the number of participating NIH ICs, NIH continues to respond to the needs of the rare diseases community and the legislative mandate of the Rare Diseases Act of 2002.

Evaluation Plans

Because the RDCRN was established so recently, it has not been formally evaluated. The ORD estimates that it takes approximately 3 years for a clinical study on a rare disease to be developed, fulfill requirements for approval, and enroll patients. Another 10 years are required to assess the overall impact of the research conducted within the RDCRN.

Eventually, the contribution of the RDCRN to rare diseases research will be determined by the following criteria:

- Completion and outcomes of the 45-50 studies
- Successful recruitment of adequate patient populations
- Number of trainees who complete their training programs
- Seminal impact of scientific publications on future rare diseases research
- Contribution of the DTCC to research in terms of a coordinated data management system, the ability to

capture and integrate many different forms of data, and the development and broad acceptance of novel technological approaches to distributed computing, federated databases, and data mining.

Although no formal evaluation of the RDCRN is planned soon, a review of the consortia and the DTCC will occur in 2008/2009, when applications of currently participating consortia are peer reviewed along with those of new applicants. New awards will be made in 2009.

Future Directions

ORD and the partner ICs will continue to coordinate the network's clinical research and encourage the training of new rare diseases researchers. Depending on IC interest in applications, the RDCRN may be expanded to comprise more than the current 10 consortia, thereby encompassing a larger number of rare sites across the United States and in other countries with additional research protocols as well as rare diseases under study.

NIH Centers of Excellence

Autism Centers of Excellence

Overview

Why the ACE Were Established

Recent studies suggest that autism spectrum disorders (ASD) may affect approximately 1 in 150 children in the United States³⁰. Because of the urgent need to better understand the causes of ASD and develop treatments for these serious and disabling disorders, Congress passed the Combating Autism Act of 2006 (Pub. L. No. 109-416), which emphasized the need for expanding research and improving coordination among NIH Centers of Excellence focused on ASD. The new Autism Centers of Excellence (ACE), scheduled for funding in FYs 2007 and 2008, will focus on identifying the causes of ASD and developing new and improved treatments.

Under the new ACE program, NIH will consolidate two existing programs in autism research, the [Collaborative Programs of Excellence in Autism](#) (CPEA) and [Studies to Advance Autism Research and Treatment](#) (STAART). NIH launched the CPEA program in 1997 to support significant, collaborative research on the possible causes of autism, including genetic, immunological, and environmental factors. In 2000, Congress passed the Children's Health Act (Pub. L. No. 106-310), which called on NIH to expand, intensify, and coordinate autism research activities, and to establish at least five Centers of Excellence for autism research. In response, the five NIH institutes participating in the NIH Autism Coordinating Committee (NIH ACC)—NICHD, the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Mental Health (NIMH), and NINDS—launched the STAART Centers Program to unite expertise, infrastructure, and resources focused on major questions about autism, including treatment research.

Although the CPEA and STAART programs collaborate extensively and will be consolidated under the new ACE program, the CPEA is not congressionally mandated. Therefore, this report will focus on the goals, activities, and accomplishments of the congressionally mandated NIH Centers of Excellence for autism research, namely the STAART and ACE Programs (see Tables 4-6 and 4-7).

How the Centers Function Within the NIH Framework

The Children's Health Act of 2000 also established an Interagency Autism Coordinating Committee (IACC), which includes Federal agencies and members of the public appointed by the Secretary of the U.S. Department of Health and Human Services (HHS). At the request of Congress, the IACC developed an [Autism Research Matrix](#) in 2003. The matrix serves as a guiding framework for directing autism research funded by NIH. ACE grantees will focus on the goals of the Autism Research Matrix, particularly in the areas of identifying causes of ASD and developing treatments.

The NIH ACC conceptualized the program goals of the STAART and ACE programs, and the ICs share responsibilities

³⁰For more information, see <http://www.cdc.gov/MMWR/preview/mmwrhtml/ss5601a2.htm>

for administration and oversight. For example, NIMH administers the individual STAART centers, and NICHD administers the Data Coordinating Center (DCC). Thus, there is input from multiple ICs in managing these programs, which are funded through cooperative agreements. Grants that support centers affiliated with the ACE program are administered through a program officer and grants management officer at the awarding IC. The STAART and ACE programs represent less than a quarter of the total NIH commitment to autism research. The rest is distributed across contracts, grants of many types, and cooperative agreements.

Description of Disease or Condition

Autism was first described in 1943 by Leo Kanner as a disorder “characterized by extreme aloneness and a desire for the preservation of sameness, with a variety of behavioral (cognitive, affective) symptoms derived from them³¹.” Over time, the description of this complex neurodevelopmental disorder has broadened. ASD includes a group of developmental disorders of early childhood that vary in severity, share common clinical features, and persist throughout the lifetime of the individual. These disorders share the core clinical characteristics of impairment in verbal and nonverbal communication skills and social interactions, and restricted, repetitive, and stereotyped patterns of behavior. ASD ranges in severity; “classic” autistic disorder is the most disabling, whereas others, such as Asperger's disorder, have fewer or milder symptoms. Among children at the more severe end of this spectrum, mental retardation, seizures, and self-injurious behaviors are common.

Symptoms of ASD often are first identified by a child's primary caregivers. There may be delays or plateaus in a child's attainment of developmental milestones, such as the onset of speech. In some cases, the first signs of an ASD occur in young children who appear to regress after they seem to have been developing normally. For most children, the diagnosis of an ASD can be reliably made by age 3. The current diagnostic criteria and classifications of ASD represent progress in identifying a core set of developmental symptoms that, in the past, might have been diagnosed differently because the criteria were more narrowly defined than they are today.

Burden of Illness

ASD causes tremendous economic and social burdens for families and society at large. Although ASD varies greatly in character and severity, it occurs in all ethnic and socioeconomic groups and affects every age group. Currently, there is no coherent and comprehensive system of care for affected individuals. People with autism may receive private and public services in special education settings, hospitals and university medical centers, and residential treatment facilities, among others.

Some scientists and economists have estimated that the combined direct and indirect costs to care for all Americans with ASD during their lifetimes exceed \$34 billion and that each individual accrues approximately \$3 million in costs over his or her lifetime³². Families often incur large debts related to medical and educational services not covered through public programs or medical insurance. In addition to financial challenges, autism often leads to profound emotional hardships for patients and their families.

Current CDC estimates of the prevalence rate of ASD are as high as 6.7 children per 1,000³³. The total number of individuals in the United States with an ASD diagnosis is unknown. However, CDC estimates that up to 560,000

³¹ [Kanner L. Autistic disturbances of affective contact. *Nervous Child* 1943;2:217-50](#)

³² [Ganz ML. *Arch Pediatr Adolesc Med.* 2007;161:343-9, PMID: 17404130](#)

³³ CDC, 2007

individuals age 21 and younger have an ASD (assuming a prevalence rate of 1 in 150, a birth rate of 4 million children per year in the United States, and a constant prevalence rate over the past 20 years). Prevalence estimates, which refer to the number of affected individuals at a given point in time, have increased markedly since the early 1990s, but it is unclear whether there is also an increase in incidence, a measure of the number of new cases across time in the same population. It is also unclear whether the rise in prevalence is due to factors such as the use of the broader category of ASD or earlier and better diagnosis of ASD. A similar increase in ASD prevalence has occurred in other countries. Boys are approximately four times as likely as girls to have an ASD³⁴.

Scope of NIH Activities: Research and Programmatic

The primary goals of the STAART Centers Program are to support cohesive teams of accomplished biomedical, behavioral, and clinical investigators to pursue common objectives in ASD research, and to establish a research network that is capable of implementing large treatment, diagnostic, genetic, neuroscientific, and other studies of ASD that were previously not feasible. The new ACE program will improve the efficiency of administering the STAART and CPEA centers by consolidating them into one program and will broaden the pool of researchers involved in ASD research.

Each STAART center supports clinical and basic studies, including at least one study focused on treatment. The centers provide core resources that enhance ongoing research by providing critical infrastructure, including centralized patient recruitment and tracking, with standardization of clinical data. The centers are multidisciplinary and include outstanding investigators in related disciplines.

Although the Children's Health Act of 2000 required a minimum of five centers, NIH funded eight centers because of the exceptional quality of the applications. Scientific investigations of the STAART Centers Program focus on genetics, neurobiology, behavioral interventions, drug therapies, and diagnosis, in accord with the legislation. Each center conducts a unique set of studies, including investigations to determine how parents can better assist children with ASD, research on the neurobiological causes of ASD and the impact of early intervention, and projects to examine the possible role of serotonin in ASD, including a neuroimaging study of serotonin pathways and receptors comparing people with Asperger's disorder to people with more typical development.

To identify genes that confer susceptibility to the development of autism, STAART centers use and contribute to the [NIMH Center for Collaborative Genetic Studies](#), a repository of DNA, cell cultures, and clinical data that serves as a national resource for researchers studying the genetics of complex mental disorders. This collaborative program, established partly through an innovative public-private partnership, provides a major resource for qualified investigators. Another important resource for studies on ASD is the DCC, which provides data management and statistical support for autism research activities, including those conducted at the STAART centers. The DCC supports pharmacologic, multisite, randomized control trials and works with the data collection and analysis personnel at each center to standardize data forms and formats so that centralized data storage can be accessed.

NIH Funding for FY 2006 and FY 2007

The total funding for autism COEs—STAART Centers (U54s), DCC (U01), and the ACE program, which includes centers (P50s) and networks (R01s)—was \$12.8 million and \$25.5 million in FY 2006 and FY 2007, respectively.

³⁴[Fombonne E. *J Clin Psychiatry* 2005;66 Suppl 10:3-8](#), PMID: 16401144

Outcomes: FY 2006 and FY 2007 Progress Report

Programmatic and Research Accomplishments

The STAART program is contributing to the understanding of ASD by investigating areas such as early detection, efficacy of early behavioral interventions, neural bases of core features, efficacy trials for pharmacotherapy, genotypic and phenotypic responses to treatment, and identification of susceptibility genes. A few accomplishments of the STAART program are highlighted briefly below.

- **Early Detection:** The Kennedy Krieger Institute of Johns Hopkins University has conducted a prospective longitudinal study of children who are at high risk for autism because they are younger siblings of children with an ASD. Important implications of this study are that autism screening could be usefully implemented near the first birthday, but screening would need to be repeated near the second birthday to detect children whose development becomes atypical during this interval³⁵.
- **Neurological Characteristics:** Researchers at other STAART centers are evaluating specific neural mechanisms that perform atypically in people with autism. For example, teams at the University of Washington, Boston University, and the University of Wisconsin have used functional MRI to study face perception, which is altered in people with autism. The researchers found that the integration of perceptual and emotional processing mediated by the fusiform cortex and the amygdala, a specific brain pathway, is altered, which may explain the atypical visual scanning of faces that is characteristic of autism³⁶. Research suggests that other brain pathways, such as those of the basal ganglia, may also contribute to repetitive behaviors, a core symptom of autism³⁷.
- **Finding Effective Treatments:** To identify a treatment for autism, STAART investigators have collaborated in a multisite study to evaluate the efficacy of a drug that selectively inhibits the activity of serotonin, a neurotransmitter in the brain that may play a role in the repetitive behaviors associated with autism. The study subjects have completed the treatment phase of the trial and preparation for data analysis is under way. A manuscript with results is expected to be submitted for publication in 2008.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of ASD Research

To improve the effectiveness, efficiency, and outcomes of ASD research, the NIH ACC planned the ACE program to address the need for the following:

- **Enhanced coordination of ASD Research:** Coordination of ASD research is an important priority for all stakeholders. This effort has been spearheaded by the IACC, which facilitates information exchange among the member Federal agencies and patient advocacy groups and coordinates autism-related programs and initiatives.

³⁵ [Landa RJ, et al. *Arch Gen Psychiatry* 2007;64:853-64](#), PMID: 17606819

³⁶ [Hadiikhani N, et al. *Hum Brain Mapp* 2007;28:441-9](#), PMID: 17133386; [van Reekum CM, et al. *Neuroimage* 2007;36:1041-55](#), PMID: 17493834; [Nacewicz BM, et al. *Arch Gen Psychiatry* 2006;63:1417-28](#), PMID: 17146016; [Dalton KM, et al. *Biol Psychiatry* 2007;61:512-20](#), PMID: 17069771; [Webb SJ, et al. *J Autism Dev Disord* 2006;36:881-90](#), PMID: 16897400; [Kleinmans NM, et al. *Neuroreport* 2007;18:987-91](#), PMID: 17558282

³⁷ Hollander E, et al. *Biol Psychiatry* 2005;58:226-32, PMID: 15939406

- **More collaborative studies:** Collaborative studies allow ASD researchers to combine data from their diverse samples and increase statistical power for detecting many types of experimental effects.
- **Improved data standardization and sharing:** In the past, data gathering in autism-related research was separated by format, location, and method of analysis, which makes cross-site data comparisons difficult. The [National Database for Autism Research](#) (NDAR) is building on the gains made by the DCC by creating a common data platform for data gathering and analysis. The NDAR will make it easier and faster for researchers to gather, evaluate, and share autism research data from a variety of sources and will allow the seamless integration of data, research tools, and institutions across the United States and internationally. All ACE Centers and Networks will make data contributions to NDAR.

Evaluation Plans

The Combating Autism Act of 2006 expanded the scope of the IACC. In accordance with the new law, the IACC will develop and update annually a summary of research advances in ASD, as well as a strategic plan, and will monitor and make recommendations about Federal ASD-related activities. The priorities and progress of the ACE program will be an integral component of these annual activities.

In 2010, HHS will provide Congress with a progress report on activities related to ASD, to include contributions from the ACE program. The report will discuss information about the incidence of ASD, average age for diagnosis, average age for intervention, effectiveness and outcomes of interventions by subtypes, and effectiveness and outcomes of newly developed intervention strategies for individuals with an ASD. In addition, NIH will consider how best to assess the effectiveness of the ACE Program and will identify ways to improve implementation of the program.

Future Directions

The strategic plan for autism research to be prepared by the IACC will be developed with broad representation from Federal agencies as well as members of the public. In addition, private organizations that support autism research will be invited to participate in the planning process so that coordination will occur across autism funding groups, both public and private.

NIH created the ACE program to maximize coordination and cohesion of NIH-sponsored ASD research efforts and to broaden the pool of researchers involved in ASD research. Early in 2006, NIH solicited proposals for the ACE centers and networks with an application deadline of August 2006. NIH instructed grantees to direct their research projects toward the goals of the Autism Research Matrix, particularly in the areas of etiology and treatment. NIH made seven ACE awards in 2007 and anticipates making four additional awards in 2008.

The NDAR will be needed to achieve several of the goals of the IACC Autism Research Matrix, such as “establish[ing] resources for genotype/phenotype studies (i.e., bioinformatics, genetic repository).” NDAR also will coordinate data with other Federal databases, such as the [NIMH Center for Collaborative Genetic Studies](#), which stores DNA, cell cultures, and clinical data, and serves as a national resource for researchers who study the genetics of complex mental disorders, including autism.

NIH Centers of Excellence

Appendix

Table 4-1. Alzheimer's Disease Centers of Excellence (ADCs)

Institution and Location	Year Established
University of California, San Diego, CA	1984
Massachusetts General Hospital, Boston, MA	1984
Mount Sinai School of Medicine, New York, NY	1984
University of Southern California, Los Angeles, CA	1984
Johns Hopkins University, Baltimore, MD	1984
Duke University, Durham, NC	1985
University of Kentucky, Lexington, KY	1985
University of Pittsburgh, Pittsburgh, PA	1985
University of Washington, Seattle, WA	1985
Washington University in St. Louis, MO	1985
University of Texas Southwestern Medical Center, Dallas, TX	1988
University of Michigan, Ann Arbor, MI	1989
Columbia University Health Sciences, New York, NY	1989
Oregon Health & Science University, Portland, OR	1990
New York University School of Medicine, New York, NY	1990
Mayo Clinic College of Medicine, Rochester, NY	1990
University of Pennsylvania, Philadelphia, PA	1991
University of California Davis School of Medicine, Sacramento, CA	1991
Indiana University-Purdue University, Indianapolis, IN	1991
Rush University Medical Center, Chicago, IL	1991
University of California, Los Angeles, CA	1991
Boston University Medical Campus, Boston, MA	1996
Northwestern University, Chicago, IL	1996
University of Alabama, Birmingham, AL	1999
University of California, Irvine, CA	2000

Arizona Alzheimer's Center, Phoenix, AZ	2001
University of California, San Francisco, CA	2004
Emory University, Atlanta, GA	2005
University of South Florida, Tampa, FL	2005

Table 4-2. Claude D. Pepper Older Americans Independence Centers (OAICs)

Institution and Location	Year Established
Duke University, Durham, NC	1955 ³⁸
University of Michigan, Ann Arbor, MI	1989
Harvard University, Boston, MA	1990
University of California, Los Angeles, CA	1991
Wake Forest University, Winston-Salem, NC	1991
Yale University, New Haven, CT	1992
University of Maryland, Baltimore, MD	1994
University of Texas Medical Branch, Galveston, TX	1999
Johns Hopkins University, Baltimore, MD	2003
University of Pittsburgh, Pittsburgh, PA	2004
University of Florida, Gainesville, FL	2007

A Coordinating Center was added to the OAIC program in 2005 to promote scientific collaborations among Pepper Center investigators and to facilitate the sharing of unique resources across all sites. The Coordinating Center is currently located at Wake Forest University.

Table 4-3. Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs)

Institution and Location	Year Established
University of Pittsburgh, Pittsburgh, PA	2003
University of Rochester, Rochester, NY	2003
University of Washington, Seattle, WA	2003
Children's National Medical Center, Washington, DC	2005
University of Iowa, Iowa City, IA	2005
University of Pennsylvania, Philadelphia, PA/Johns Hopkins University, Baltimore, MD	2005

³⁸ The only remaining Geriatric Research and Training Center.

Table 4-4. NCMHD Centers of Excellence Active in FY 2007

Institution and Location	Year Established
Arizona State University, Tempe AZ	2007
Case Western Reserve University, Cleveland, OH	2007
Charles R. Drew University of Medicine and Science, Los Angeles, CA	2002
Clark Atlanta University, Atlanta, GA	2007
Columbia University Health Sciences, New York, NY	2003
Florida International University, Miami, FL	2007
Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, MD	2003
Howard University, Washington, DC	2002
Johns Hopkins University, Baltimore, MD	2002
Loma Linda University, Loma Linda, CA	2005
Meharry Medical College, Nashville, TN	2003
Montana State University, Bozeman, MT	2007
Morehouse School of Medicine, Atlanta, GA	2002
Mount Sinai School of Medicine of NYU, New York, NY	2002
New York University School of Medicine, New York, NY	2003
North Carolina Central University, Durham, NC	2002
San Diego State University, San Diego, CA	2002
Texas A&M University System, College Station, TX	2002
Tuskegee University, Tuskegee, AL	2002
University of Alabama, Birmingham, AL	2003
University of Arizona, Tucson, AZ	2003
University of Arkansas Medical Sciences, Little Rock, AR	2007
University of California, Davis, CA	2003
University of California, San Diego, CA	2002
University of Colorado, Denver, and Health Science Center, Aurora, CO	2003
University of Connecticut, Storrs, CT	2005
University of Hawaii, Manoa, HI	2002

University of Maryland, Baltimore, MD	2003
University of Massachusetts, Boston, MA	2007
University of Miami, Coral Gables, FL	2007
University of Michigan, Ann Arbor, MI	2007
University of North Carolina, Chapel Hill, NC	2002
University of North Carolina, Greensboro, NC	2007
University of North Texas Health Sciences Center, Fort Worth, TX	2005
University of Oklahoma Health Sciences Center, Oklahoma, City, OK	2003
University of Pennsylvania, Philadelphia, PA	2002
University of Pittsburgh, Pittsburgh, PA	2002
University of Puerto Rico Medical Sciences, San Juan, PR	2003
University of South Alabama, Mobile, AL	2004
University of South Carolina, Columbia, SC	2005
University of South Dakota, Vermillion, SD	2005
University of Southern California, Los Angeles, CA	2007
University of Texas, Brownsville, and Southmost College, Brownsville, TX	2003
University of Texas, El Paso, TX	2007
University of Texas Health Sciences Center, Houston, TX	2003
University of Texas M.D. Anderson Cancer Center, Houston, TX	2003
University of the Virgin Islands, St. Thomas, VI	2004
Virginia Commonwealth University, Richmond, VA	2007
Winston-Salem State University, Winston-Salem, NC	2007
Yeshiva University, New York, NY	2003

Table 4-5. Rare Diseases Clinical Research Network (RDCRN) Sites

Institution and Location	Year Established
Children's National Medical Center, Washington, DC	2003
Baylor College of Medicine, Houston, TX	2003
University of Rochester School of Medicine, Rochester, NY	2003
Cleveland Clinic Foundation, Cleveland, OH	2003
The Children's Hospital, Aurora, CO	2004

Boston University, Boston, MA	2003
Mount Sinai School of Medicine, New York, NY	2003
Duke University Medical Center, Durham, NC	2004
Cincinnati Children's Hospital Medical Center, Cincinnati, OH	2003
University of North Carolina, Chapel Hill, NC	2004
University of South Florida, Tampa, FL	2003

Table 4-6. Studies to Advance Autism Research and Treatment (STAART) Centers

Institution and Location	Year Established
University of North Carolina, Chapel Hill, NC	2002
Yale University, New Haven, CT	2002
Boston University, Boston, MA	2003
Kennedy Krieger Institute, Baltimore, MD	2003
Mt. Sinai Medical School, New York, NY	2003
University of California, Los Angeles, CA	2003
University of Rochester, Rochester, NY	2003
University of Washington, Seattle, WA	2003

Table 4-7. Autism Centers of Excellence (ACE)

Institution and Location	Year Established
University of California, Davis, CA	2007
University of California, Los Angeles, CA	2007
University of California, San Diego, CA	2007
University of Illinois, Chicago, IL	2007
University of North Carolina, Chapel Hill, NC	2007
University of Pittsburgh, Pittsburgh, PA	2007
University of Washington, Seattle, WA	2007