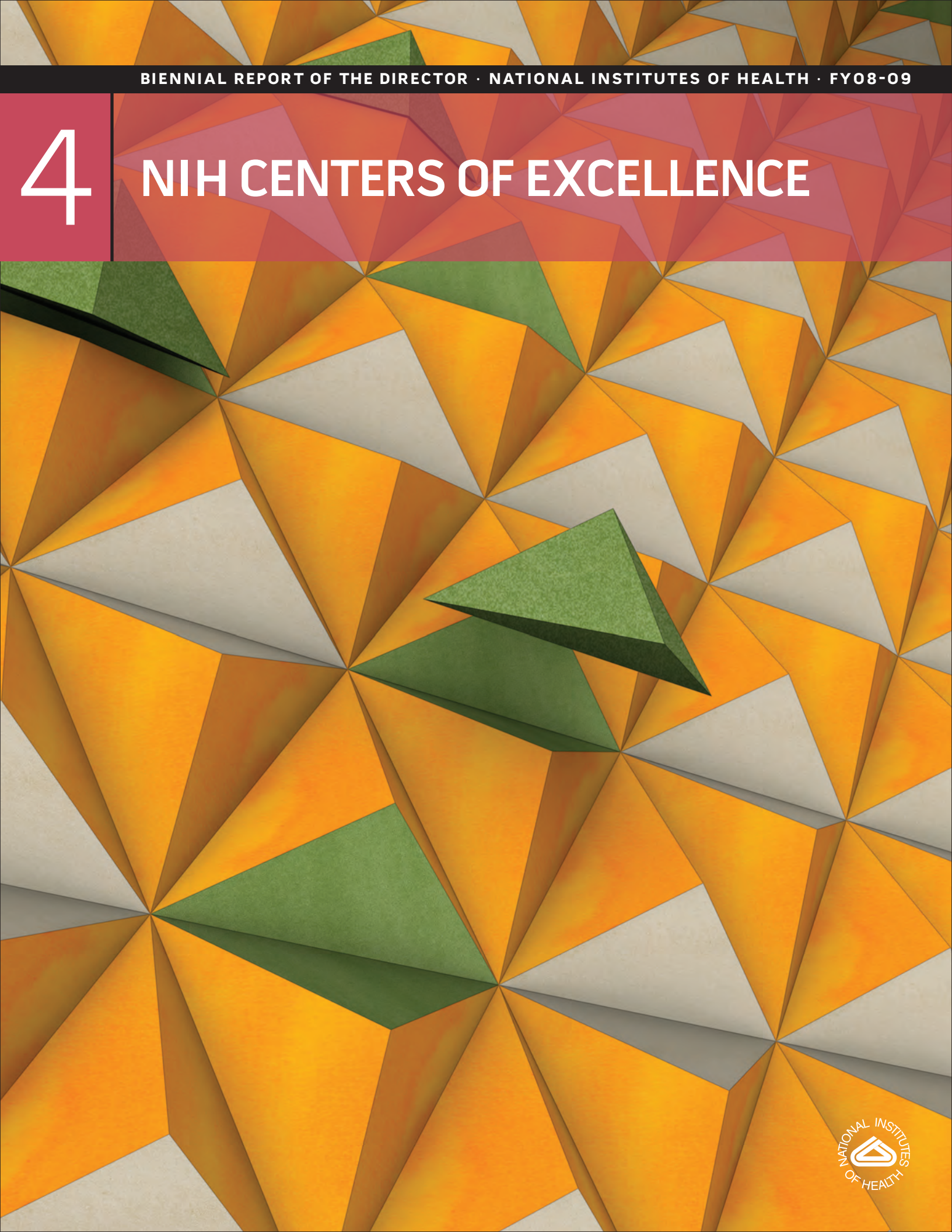
4 NIH CENTERS OF EXCELLENCE



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Volume IV Contents

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Introduction

NIH Centers of Excellence programs 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) and Offices within the NIH Office of the Director (NIH OD); some reflect mergers or redesignations of existing programs; and some were mandated by Congress. The NIH Centers of Excellence programs described in this report are a subset—those established by statutory mandate.

Some congressionally mandated Centers of Excellence programs 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 such programs focus attention on areas of research that might otherwise be underfunded, such as rare diseases or health disparities. The mandated Centers of Excellence programs were established at different times and the number of research sites funded vary; thus, each of these programs differ in size, scope, accomplishments, and outcomes.

The Centers of Excellence programs help establish critical research infrastructure; foster collaboration; train researchers, physician scientists, and other professional staff; and provide shared resources, often through core facilities.

The specific research goals and activities of the mandated Centers of Excellence programs vary according to their authorization. In general, however, these programs help establish critical research infrastructure; foster collaboration; train researchers, 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 funded by these congressionally mandated programs often is multidisciplinary and designed to encourage scientists and clinicians from diverse fields to come together to focus on a common set of objectives.

All of the congressionally mandated 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. Administrative and program staff at individual ICs and Offices within the NIH OD oversee and manage each congressionally mandated NIH Centers of Excellence program. Specific centers funded under these mandated programs receive awards for a defined period of years, after which they must recompete for support.

The creation of Centers of Excellence at the discretion of NIH only takes place after an assessment of whether an adequate base of knowledge and number of expert investigators exists; what research opportunities are adequately supported through existing or planned funding mechanisms and initiatives; and the appropriateness of alternative funding mechanisms. Recognizing that it should only create Centers of Excellence under certain circumstances, Congress 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 ICs and Offices within the NIH OD.

This chapter provides overviews, progress reports for the FYs 2008 and 2009 biennial period (covering programmatic and research activities and outcomes), recommendations, evaluation plans, and future directions for the six congressionally mandated NIH Centers of Excellence programs, which are described in the 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 (2003)
- 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 funded under each mandated Centers of Excellence program appear at the end of the narrative on each program.

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 Public Health Service Act authorizes the NIH Alzheimer's Disease Centers (ADCs) program under section 445 (42 U.S.C. 285e-2). NIH funded the first ADCs in the mid-1980s in response to the congressional directive, information on AD emerging from the work of NIH grantees and other researchers, and the prospect of a medical and social crisis triggered by an explosion of AD cases as the population ages. The principal objectives of the ADC program are to promote research, research, training, outreach, and technology transfer. Much of the research takes place through multicenter cooperative studies to better understand the causes and effects of AD and to develop and test new interventions for the diagnosis, treatment, and prevention of AD and other age-related neurodegenerative diseases (diseases in which the cells of the brain and spinal cord are lost) and normal aging.

How the ADCs Function Within the NIH Framework

NIH currently funds 30 ADCs (see Table 4-1). Funding for the ADCs comes from NIA through the P30 (center core grant) and P50 (specialized center grant) mechanisms for 5 years and then must compete through a peer review process for additional funding. New applicants for ADCs compete with existing grantees. If existing centers are unsuccessful in competition, new centers are funded to take their places.

NIH currently funds 30 Alzheimer's Disease Centers through a congressionally mandated program initiated in 1984.

Description of Disease or Condition

AD is the most common form of dementia among older people. It is an age-related, irreversible brain disorder that develops over many years. In the very early stage, people experience memory loss, which can be mistaken for memory changes that occur in normal aging. As the disease progresses, these symptoms gradually lead to dementia, a condition characterized by marked memory loss and behavior and personality changes. The disease also leads to a decline in other cognitive abilities (such as decision-making and language skills) and, eventually, an inability to recognize family and friends and a severe loss of mental function. These losses are related to the breakdown of the connections between neurons (nerve cells) in the brain and to the eventual death of many of these cells. In most people, symptoms first appear after age 60. AD and other dementing disorders are caused by disease processes that affect the brain, although age-related brain and body changes also can affect the development of AD and other dementias.

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 unexplained mental illness. Dr. Alzheimer found unusual features of her brain tissue—many deposits of sticky proteins in the spaces between neurons, now known as beta-amyloid plaques, and tangled bundles of fibrils (thin fibers) within neurons, now known as neurofibrillary tangles. However, it was not until the 1960s and 1970s that scientists began to recognize AD as a disease associated with aging.[1] Today, plaques and tangles in the brain are considered signs of AD, as are other brain changes, including the death of neurons in areas of the brain that are vital to memory and other mental abilities and the disruption of connections, called synapses, that allow neurons to communicate with each other. The disease also is characterized by low levels of some of the chemicals in the brain that carry messages between neurons. AD impairs thinking and memory by disrupting these messages.

Scientists are 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 for AD. Evidence also is increasing that physical, mental, and social activities may protect people from AD.

AD probably has no single cause. The most important known risk factors are age and family history, although education, diet, and environment also might play a role. Scientists also are 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 for AD. Evidence also is increasing that physical, mental, and social activities may protect people from 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.

Burden of Illness

Recent estimates from a nationally representative sample in the Aging, Demographics, and Memory Study (part of the ongoing NIH-supported Health and Retirement Study) suggest that one in seven Americans age 72 or older has dementia and about 2.4 million have AD.[2] Other investigators, using projections from community-based studies, estimate that 5.1 million Americans ages 65 or older will have AD in 2010.[3] Despite the differing methodologies and results of their studies, experts agree that the number of people with AD will increase significantly if current U.S. population trends continue and no prevention methods emerge. Our aging society makes AD an especially critical issue because the number of people with the disease doubles for every 5-year age interval beyond age 65. The U.S. Census Bureau estimates that the size of the population ages 65 and older will double to about 72 million people in the next 25 years. Moreover, the fastest growing segment of the U.S. population is comprised of people 85 years of age or older.

Scope of NIH Activities: Research and Programmatic

The ADC program provides infrastructure and core resources to enhance ongoing research by bringing together basic biomedical, behavioral, and clinical scientists to study the causes, 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.

NIH requires all 30 ADCs to have the following cores: administrative, clinical, data management and statistics, education and information transfer, and neuropathology. Some centers include other optional cores, such as neuroimaging or genetics cores, and some have satellite diagnostic and treatment clinics to help recruit minority or rural research participants.

The ADC program comprises two types of centers. Alzheimer's Disease Research Centers conduct research projects in addition to providing core resources. The Alzheimer's Disease Core Centers consist of cores only and provide investigators with access to 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 with other ADCs, these centers have produced research findings and developed resources that individual investigators working alone could not have achieved.

By pooling resources and working cooperatively with other ADCs, these centers have produced research findings and developed resources that individual investigators working alone could not have achieved. ADCs have provided biological samples from patients with AD for hundreds of non-ADC funded projects. Several major long-term studies on the development of dementia in specific populations rely on ADC core facilities and integrate their findings with those of the centers.

Examples of resources shared among ADCs are the brain and specimen banks at each center, which consist of well-characterized specimens collected under standardized protocols. Another resource shared by the ADCs is the National Cell Repository for Alzheimer's Disease (NCRAD) at Indiana University, which collects and stores blood, DNA, and cell lines from families with several affected members and from unaffected control participants. NCRAD also stores well-documented phenotypic data, which includes the observable traits or characteristics of a person, such as age and gender, as well as the presence or absence of a disease. The repository is part of the NIH Alzheimer's Disease Genetics Initiative, which was established to identify genetic risk factors for late-onset AD, and the recently funded Alzheimer's Disease Genetics Consortium, which conducts large-scale whole-genome studies on AD.

The ADCs have helped create additional collaborative research resources or projects, 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. Descriptions of these and other efforts are provided below.

Much important progress in AD research in the United States during the past 25 years stems from research conducted at the ADCs, as well as from resources and infrastructure provided by the centers. Through ADC research, scientists have identified mutant genes on three chromosomes whose presence could result in the rare early-onset, inherited AD; discovered a version of a gene on chromosome 19 that is a risk factor for the more common late-onset AD; and determined that mutant genes on chromosome 17 are associated with frontotemporal dementia, a group of rare dementia disorders that affect the parts of the brain that are associated with language and behavior. Other studies have revealed the importance of the abnormal processing of proteins encoded by these genes.

Through ADC research, scientists have identified mutant genes on three chromosomes whose presence could result in the rare early-onset, inherited AD and discovered a version of a gene on chromosome 19 that is a risk factor for the more common 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 development of Lewy body dementia (which can cause confusion, rigid muscles, slower movement, and tremors). ADC researchers also identified the common properties of the abnormal proteins associated with several neurodegenerative diseases, which are characterized by damage or loss of neurons in the brain and spinal cord. Additional support through ARRA funding to the Johns Hopkins ADC will enhance research efforts in studies of brain pathology.

In recent years, ADC researchers have evaluated cognitive changes associated with normal aging and the transitions to mild cognitive impairment (early difficulties with thinking and remembering) and dementia. They also have identified factors that contribute to changes in cognitive abilities.

Currently, many ADCs are carrying out important studies relating changes in brain structure to different clinical stages of AD. For these studies, researchers are examining patients enrolled in the clinical cores, brain imaging supported by imaging cores, and autopsy evaluations in neuropathology cores. ADC researchers also are examining relationships and commonalities between AD and cerebrovascular disease or other neurodegenerative diseases as well as contributions of co-existing non-neurological conditions that occur in people with AD.

The ADCs are exploring commonalities between AD and other dementias that involve Lewy bodies and between AD and Parkinson's disease dementia. In this regard, collaborations are underway with the NINDS-supported Udall Parkinson's Disease Centers to examine the overlapping scientific and clinical issues.

Many (18) ADCs also participate in the NIH Late Onset Alzheimer's Disease (LOAD) Genetics Initiative, which was launched to help advance AD-related genetics research. LOAD aims to collect samples from more than 1,000 families having at least two members with late-onset AD as well as 1,000 control participants. The Columbia University AD Research Center serves as the coordination center for LOAD. To complete enrollment, characterization, and follow-up of

patients and control participants in the LOAD Genetics Initiative, NIH awarded a resource grant to a consortium of six ADCs. As of 2009, more than 5,000 new blood samples from approximately 800 late-onset AD families have been sent to the National Cell Repository for Alzheimer's Disease, another important resource for the ADCs. In a search for risk factor genes, ADC researchers are analyzing data derived from whole-genome scans of LOAD samples.

The ADCs are contributing phenotypic information and DNA specimens from participants enrolled in ADC studies to a major new genomic project carried out by the NIH-funded Alzheimer's Disease Genetics Consortium, which will perform whole-genome scans using specimens from up to 10,000 human subjects enrolled in the ADCs as well as from other major population studies.

The ADCs also are contributing phenotypic information and DNA specimens from participants enrolled in ADC studies to a major new genomic project carried out by the NIH-funded Alzheimer's Disease Genetics Consortium (ADGC). The ADGC will perform whole-genome scans using specimens from up to 10,000 human subjects enrolled in the ADCs as well as from other major population studies. In FY 2009, ARRA funds were awarded to the ADGC to add 3,800 AD patients and an equal number of people free of disease, thus making this one of the largest collections of samples available for genome-wide association studies in an effort to identify the susceptibility and protective genes influencing the onset and progression of late-onset disease.

Another major objective for the ADCs is to recruit minority and ethnically diverse research participants for AD research. To achieve this goal, NIH created the Satellite Diagnostic and Treatment Clinics and linked them to the ADCs. The number of satellites has fluctuated; 23 currently are active and are recruiting African American, Hispanic, Native American, and Asian research participants. National Alzheimer's Coordinating Center data now show that approximately 20 percent of those enrolled in the ADCs are minorities. Also, the ADCs conduct research related to minority concerns in cooperation with the NIH-supported Research Centers on Minority Aging Research. In addition, ARRA funds were awarded to two ADCs to help understand the factors that affect recruitment of minority populations in their studies. These two supplements will be used to study recruitment of African American participants at a satellite clinic at the University of Kentucky's ADC and at the Boston University ADC.

National Alzheimer's Coordinating Center data now show that approximately 20 percent of those enrolled in the ADCs are minorities.

All ADCs have Education and Information Transfer Cores (EITCs) that provide research training for new investigators, as well as outreach to the public, including caregivers. EITC efforts also have been redefined recently to facilitate participant recruitment for projects such as the NIA Genetics Initiative, Alzheimer's Disease Cooperative Study, Alzheimer's Disease Neuroimaging Initiative, and other clinical trials and initiatives. Collaborations include ongoing interactions with groups such as the Alzheimer's Association and NIH's Alzheimer's Disease Education and Referral Center. The ADCs pay special attention to cultural sensitivity and, where appropriate, structure their information to effectively reach minority populations, including non-English-speaking people.

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 jointly formed the New York Consortium for Alzheimer's Research and Education in 2000. The consortium provides continuing medical education programs for community physicians on AD diagnosis, management, and research opportunities.

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the ADCs was $51.0 million in FY 2008 and $51.9 million in FY 2009, including $0.7 million from ARRA funds.

FY 2008 and FY 2009 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments for the ADCs include the following examples.

- **National Alzheimer's Coordinating Center (NACC):** In 1999, NIH established NACC to facilitate collaborative research and standardize procedures among the ADCs. NACC developed and maintains a large 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 support large studies that use patient samples from diverse populations and multiple ADCs. NACC collects standardized data (the Uniform Data Set or UDS) collected over time from research participants who are examined annually.

  Currently, the ADCs are following about 15,000 research participants, and NACC is storing these data. NACC has adopted new procedures for widening access to the database by non-center scientists. NACC has funded 18 collaborative multicenter studies using its own resources, and an additional 8 NIH-funded collaborative research project R01 grants are linked to NACC.

- **Alzheimer's Disease Cooperative Study (ADCS):** All of the ADCs are performance sites for the ADCS, which is the cornerstone of NIH's major AD clinical trials effort. ADCS is a large clinical trials consortium that expanded from the ADCs and now includes sites throughout the United States and Canada. The clinical research outcomes of ADCs are inextricable from the outcomes of ADCS.

  NIH developed the ADCS to advance research on drugs that might be useful for treating patients with AD, particularly drugs that industry might not develop. The study tests agents that lack patent protection; drugs that are under patent protection but marketed by manufacturers for other diseases; and novel compounds developed by individuals, academic institutions, and small biotechnology companies. The ADCS also develops new evaluation instruments for clinical trials, as well as novel approaches to clinical trial design.

  Since its inception, the ADCS has initiated 30 research studies, 23 drug trials, and 7 instrument-development protocols. Studies currently underway at ADC performance sites include:

  - A trial examining whether treatment with docosahexaenoic acid, an omega-3 fatty acid, will slow decline in AD.
  - A trial evaluating the efficacy and safety of intravenous immunoglobulin, which contains naturally occurring antibodies against beta-amyloid, in patients with mild-to-moderate AD.
  - A multicenter trial evaluating home-based assessment methods for AD prevention research in people ages 75 and older.

- **Alzheimer's Disease Neuroimaging Initiative (ADNI):** Most ADCs participate in ADNI, which is an innovative public-private partnership that is examining the potential of serial magnetic resonance imaging (MRI), positron emission tomography (PET), or biomarkers to measure earlier, and with greater sensitivity, the development and progression of mild cognitive impairment and AD. As is true of the ADCS, the activities and outcomes of ADNI are inextricable from those of the ADCs. ADNI completed enrollment in August 2007 and now is monitoring the 823 participants using MRI and PET imaging and laboratory and cognitive tests. This will generate a comprehensive database that will serve as an important public resource to spur further research. Already, many of the tools and methods developed by the study are fueling similar efforts in Japan, the European Union, and Australia.

  In 2007, ADNI obtained additional funds to conduct a genome-wide association study (GWAS) and analyze the genetic variations among ADNI participants. This effort will provide the most extensive and robust dataset of its kind in AD research and will be a critical resource for ADC investigators among others. Supplemental funding from NIH allows the collection of cerebrospinal fluid from participants, while funding from a third NIH supplement is used to

explore the use of PET imaging and Pittsburgh compound B (PiB, an amyloid imaging agent) as tools for developing biochemical and imaging markers.

Results from an ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid might signal the onset of mild AD and established methods and standards for testing these biomarkers (see "Research Accomplishments" for more details). More than 1,000 researchers, as well as other interested individuals, already have accessed a public database containing thousands of brain images, related clinical data, and blood and cerebrospinal fluid analyses.

In FY 2009, ARRA funds were awarded to ADNI to expand the scope of ongoing research by allowing for the enrollment of participants at an earlier stage of mild cognitive impairment (MCI), when symptoms are milder. Furthermore, the funding for this new grant will allow ADNI investigators to extend the length of the original study to better assess changes in individuals over time. The overall impact of the added funding will be increased knowledge of the sequence and timing of events leading to MCI and Alzheimer's disease and development of better clinical and imaging/fluid biomarker methods for early detection and for monitoring the progression of these conditions. This will facilitate clinical trials of treatments to slow disease progression and ultimately will contribute to the prevention of Alzheimer's disease.

Research Activities and Outcomes

Since the establishment of the ADC program in 1984, investigators have published thousands of research papers on all aspects of AD and related disorders. Topics have ranged from the disease's biology to its family and societal impact, as well as many studies of diagnosis and treatment.

Research accomplishments include the following important recent studies carried out by ADC scientists, which highlight research on biomarkers and AD recently carried out by several centers. These studies are only a few examples from a wide spectrum of research studies conducted by the ADCs.

- **Beta Amyloid Deposition Imaging.**[4] The progressive accumulation of a protein called beta amyloid in the brain is a hallmark of AD. Previously, a researcher's ability to measure the amount of beta amyloid in a person's brain could only be accomplished at autopsy. Now, with the development of the new tracer element PiB (Pittsburgh Compound B), researchers can visualize the amount of beta amyloid in the brains of living people. Investigators at the University of Pittsburgh ADC studied PiB binding in the brain using PET imaging to visualize beta amyloid in the brains of living people over age 65. The participants did not have symptoms of AD or other less severe forms of dementia, such as mild cognitive impairment. Of the brains imaged, 21 percent showed evidence of early amyloid deposition in at least one brain area. Demographic characteristics such as gender did not differ significantly between those with and without beta amyloid in their brains. Importantly, the researchers were able to demonstrate that beta amyloid can be identified in the brains of cognitively normal older persons during life and that some older persons can remain cognitively normal despite a significant amount of beta amyloid within their brains. Further studies over a longer period of time now are necessary to ascertain the potential of PiB imaging to identify preclinical AD or, alternatively, to show that beta amyloid deposition alone is not sufficient to predict AD in the future.

Previously, a researcher's ability to measure the amount of beta amyloid in a person's brain could only be accomplished at autopsy. Now, with the development of the new tracer element PiB (Pittsburgh Compound B), researchers can visualize the amount of beta amyloid in the brains of living people.

- **Biomarkers of Presymptomatic AD.**[5] For AD treatments to have the greatest impact, health care providers will need to treat individuals before symptoms appear. Investigators are exploring fluid and neuroimaging measures as possible biomarkers of AD pathology that could aid in identifying individuals during the earliest stages of their disease to direct and monitor therapy. For example, researchers at the Washington University ADC investigated the relationship between brain volume (as measured by MRI) and an array of proteins that are implicated in the eventual development of AD in cognitively normal participants and individuals who have been diagnosed with early AD. They recently

found that lower levels of the toxic protein fragment amyloid beta-42 in cerebrospinal fluid (CSF)—a colorless fluid that circulates through and around the central nervous system, including the brain—in cognitively normal people appear to be associated with lower brain volume, suggesting some damage to the brain. The study indicates that increases in the protein tau take place later in the course of the disease and are more closely associated with clinical onset and progression of AD. Taken together, these results provide additional evidence that amyloid-associated brain damage may occur well before clinical symptoms appear.

- **Cerebrospinal Fluid Biomarkers.**[6] In the first ADNI CSF biomarker study, NIH-supported researchers, including ADC researchers, established a method and standard for testing levels of two candidate biomarkers for AD—tau and beta amyloid proteins, which are potential biomarkers for AD in the brain and the CSF. The researchers now have correlated levels of these proteins in CSF with changes in cognition over time and determined that changes in these two protein levels in CSF may signal the onset of mild AD. This is a significant step forward in developing a test to help diagnose the early stages of AD sooner and more accurately to begin treatment that could delay the development of more severe AD symptoms. In fact, this effort may open the door to the discovery of an entire panel of CSF biomarkers that will not only identify people at risk of developing AD, but also assess how the disease responds to therapies. Importantly, these data are available online to qualified researchers worldwide.

Researchers have correlated levels of two proteins in cerebrospinal fluid with changes in cognition over time and determined that changes in these two protein levels may signal the onset of mild AD.

- **Measuring the Effects of AD Treatment.**[7] Recently, ADC investigators used a new method of stable isotope labeling in which they "tagged" molecules in a compound with a radioactive tracer to assess the effects of an experimental drug on the production and clearance rates of proteins that are implicated in the development of AD and other central nervous system (CNS) disorders. The results from this approach might help investigators make decisions about drug effectiveness and dosing in designing larger and longer clinical trials for diseases such as AD and may accelerate effective drug validation. Notably, this is the first time that investigators have been able to measure directly over time the reduction of beta amyloid in CSF by a drug that typically inhibits its production. This approach provides a means for testing the relative effects of dose and drug in current and novel therapeutic agents.

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 multicenter initiatives have begun. In 2008, the National Advisory Council on Aging, an external advisory committee, reviewed the program's progress in achieving recommendations made in 2002. The council suggested that NIH examine the need to revise clinical diagnostic criteria for AD for identifying people with AD at an earlier stage in its development so that clinicians can prescribe strategies for delaying the onset of AD. That initiative is currently underway.

Evaluation Plans

The National Advisory Council on Aging evaluates and makes recommendations for the ADC program every 4 years. The next evaluation will be in 2012.

Future Directions

NIH plans for the ADCs to continue to place less emphasis on late-stage AD and will concentrate instead on the transition from normal aging to mild cognitive impairment and to full-blown AD, as well as on studies of the overlap between AD and other neurodegenerative diseases. In addition, the ADCs will continue to search for biomarkers that predict cognitive decline and diagnose cognitive impairment and dementia. NIH will continue to support existing ADCs, which must recompete for funding after each grant cycle (typically every 5 years) and award new grants to institutions that the NIH peer-review process deems to be qualified.

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

Alzheimer's Disease Centers

Institution and Location	Year Established
University of California, San Francisco, CA	2004
Emory University, Atlanta, GA	2005
Florida Alzheimer's Center, Tampa, FL	2005
University of Wisconsin, Madison, WI	2009

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[3] Hebert LE, et al. *Arch Neurol* 2003;60:1119-22. PMID: 12925369.
[4] Aizenstein HJ, et al. *Arch Neurol* 2008;65(11):1509-17. PMID: 19001171. PMCID: PMC2636844.
[5] Aizenstein HJ, et al. *Arch Neurol* 2008;65:1509-17. PMID: 19001171. PMCID: PMC2636844.
[6] Shaw LM, et al, *Ann Neurol* 2009;65(4):403-13, PMID: 19296504. PMCID: PMC2696350.
[7] Bateman RJ, et al. *Ann Neurol* 2009;66(1):48-54, PMID: 19360898. PMCID: PMC2730994.

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 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 Geriatric Research and Training Centers 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. Section 445A of the Public Health Service Act (42 U.S.C. 285e-3) authorizes the OAICs, which NIH funds for 5-year periods, 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

NIH funding for the OAICs comes from NIA through a center grant mechanism (P30). The ultimate goal of the OAIC program is to translate research on aging to applications and interventions that increase or maintain independence for older persons. NIH currently funds 30 ADCs (see Table 4-1).

As Centers of Excellence in geriatrics research and training, the OAICs provide intellectual leadership in geriatrics research, encouraging and facilitating multidisciplinary and interdisciplinary collaborations in basic, translational, and clinical research relevant to the health and independence of older persons. In addition, each OAIC includes a Research Career Development Core to provide research training and career development opportunities 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—and 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.

By 2030, the number of individuals age 65 or older is likely to double to 70.3 million, and this group will comprise 20 percent of the entire U.S. population, in contrast to 13 percent today.

Burden of Illness

Currently, 35 million Americans are older than 65 years. Of these, more than 4 million are older than 85, and approximately 65,000 have reached their 100th birthday. By 2030, the number of individuals age 65 or older is likely to double to 70.3 million, and this group will comprise 20 percent of the entire U.S. population, in contrast to 13 percent today. The number of the "oldest old"—people age 85 or older—is expected to grow to at least 20.9 million by 2050.[8]

Today, half of all Americans older than age 65 show evidence of osteoarthritis in at least one joint.[9] More than half of Americans older than age 50 have osteoporosis or low bone mass.[10] Cardiovascular disease, cancer, and diabetes remain common among older Americans.

The ratio of older people to other age groups is important to society because older people, particularly the oldest old, sometimes depend on family members, the government, or both for financial, physical, and emotional support. In addition, a large part of older people's well-being depends on programs such as Social Security and Medicare, which are financed through the contributions of working-age individuals. When the entire population of baby boomers enters older age,

around 2030, the challenge to meet their needs through social, governmental, and other health care services will expand markedly.[11]

As life expectancy increases, the health care system will need new ways to minimize disease and disability during the additional years of life.

In 2006, U.S. health care expenditures totaled approximately $2.1 trillion, more than in any other industrialized country.[12] Researchers predict that increased longevity is likely to require more financing from Federal health care systems, including Medicare and Medicaid.[13] As life expectancy increases, the health care system will need new ways to minimize disease and disability during the additional years of life.

Scope of NIH Activities: Research and Programmatic

OAICs are designed to develop or strengthen each awardee institution's programs 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. The program's ultimate goal is to enhance translation of basic and developmental research on aging to applications and interventions that increase or maintain independence for older persons.

NIH expects each OAIC, in its selected area of focus, to:

- Provide intellectual leadership and innovation in geriatrics
- Stimulate translation of basic and clinical research in aging
- Facilitate and develop novel multidisciplinary and interdisciplinary research strategies to address current issues in geriatrics care
- Stimulate incorporation of emerging technologies, methods, and scientific advances into research designs
- Serve as a source of advice and collaboration to other institutions regarding technology, methodology, analysis, or other expertise relevant to research in aging
- Provide research training and career development for future leaders in geriatrics research

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the OAICs was $14.0 million in FY 2008 and $14.3 million in FY 2009, including $0.4 million from ARRA funds.

FY 2008 and FY 2009 Progress Report

Programmatic and Research Activities and Outcome

- The **University of Florida OAIC** focuses its aging research on sarcopenia (age-related muscle loss), including biological mechanisms and contributing factors, as well as the prevention and rehabilitation of disability resulting from sarcopenia. University of Florida researchers examine these issues from interdisciplinary perspectives across the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral and social sciences, and epidemiology. One ongoing project is evaluating interventions that change fat concentrations in aged rats to assess their effects on physical function, inflammation, damage to cells from free radicals (destructive molecules), cell death, and sarcopenia. This study could lead to testing of other interventions to lower fat concentrations in animals and to study the effect of reduced fat on age-related outcomes. Another project could help in the development of a novel, safe, and practical intervention to reduce muscle loss among older people by improving muscle function without high-intensity exercise.
- The **Boston Medical Center at Boston University** recently received a grant to establish an OAIC in collaboration with Tufts University, the Joslin Clinic, and the New England Research Institute. The central research theme of the new OAIC is to develop therapies that improve muscle function. Currently, few if any drugs or therapies are available

to improve muscle strength, mobility, and physical function for frail older people. The OAIC at Boston University will foster collaborations among the university's multidisciplinary team of investigators to improve physical mobility by covering the entire spectrum of drug discovery, from target identification to clinical trials and function-promoting therapies. For example, one project will recruit frail, elderly, vitamin D-deficient women to determine whether vitamin D supplements improve outcomes.

- The **University of Pittsburgh OAIC** provides support and resources for investigators to study balance disorders in the elderly. This OAIC provides an integrated, multidisciplinary approach by pulling resources from five schools at the University of Pittsburgh. The center's long-range goals are to incorporate into clinical care and wellness programs in diverse settings effective interventions to maintain or improve balance and reduce the negative consequences of balance disorders. In addition, the center aims to further define an approach to identify factors that contribute to balance disorders for use in prevention and treatment.

Growing evidence indicates that aging and functional decline might involve changes in the body's physical and chemical processing of lipids, or fatty substances, but scientists do not yet understand these changes. One current project is enhancing the ability to analyze lipid processing in body fluids and tissue samples from animals and people.

- The theme of the **Duke University OAIC** is to understand and modify different causes of decline in physical functioning. The Duke OAIC develops and evaluates interventions designed to help older Americans prepare for, cope with, and recover from disability arising from late-life disease and aging. Growing evidence indicates that aging and functional decline might involve changes in the body's physical and chemical processing of lipids, or fatty substances, but scientists do not yet understand these changes. One current project is enhancing the ability to analyze lipid processing in body fluids and tissue samples from animals and people.
- The **Johns Hopkins University OAIC** supports research to determine the causes of and potential interventions to reduce frailty in older adults. To support frailty intervention studies, the university created a clinical translation unit and a registry of older adults who might be willing to participate in research. The Johns Hopkins OAIC has established state-of-the-art infrastructure to generate genetic data and analyses related to frailty and has assembled a multidisciplinary team of experienced investigators. The center also has identified new markers of frailty, identified critical biological causes of frailty, and developed a strain of frail mice that investigators can use for research.
- The **University of California, Los Angeles OAIC** supports the development and testing of interventions to prevent disability. The center emphasizes research that builds bridges between basic biomedical science and clinical science. Current projects are addressing the underlying causes of bone loss in osteoporosis and the effects of stroke on nerve-repair genes in the aged brain.
- The **University of Maryland, Baltimore OAIC** is studying rehabilitation approaches involving exercise and motor learning. The goal is to improve the recovery of older adults who have suffered a stroke, hip fracture, or other chronic debilitating disease. The center plans to translate these findings into effective community-based rehabilitation programs. A current study is determining the functional, physiological, and metabolic changes in men and women who fracture a hip.
- The **University of Texas OAIC's** 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 have identified protein changes in upper leg muscles associated with hemiparetic stroke (affecting one side of the body). Other studies are assessing the effects of bed rest on muscle function. New technologies under development at the University of Texas OAIC will make it easier to identify damaged proteins in aged tissues, which will help scientists understand the effects of aging on muscle function.
- The **Wake Forest University OAIC's** mission is to assess the risk factors of physical disability in older adults and to develop and test effective prevention therapies. The Cooperative Lifestyle Intervention Program is an 18-month randomized, controlled trial to assess the effectiveness of physical activity, with and without weight loss, in the treatment of mobility disability. The 288 participants are older, overweight, or obese men and women who have cardiovascular disease or metabolic syndrome (a group of medical problems that increase heart disease and diabetes risk).
- The **Yale University Center OAIC's** research theme is the investigation of geriatric health conditions that have several causes. This focus includes single conditions resulting from several contributing factors or affecting several outcomes, and multiple conditions occurring at the same time. One study area is falls among the elderly. The Yale

Precipitating Events Project includes monthly assessments of participants' functional status over 10 years. In a landmark clinical trial, investigators from the Yale OAIC demonstrated that functional decline among frail older persons can be prevented through a prehabilitation program targeting underlying impairments in physical capabilities. Future research by this group will develop and test two strategies to restore the ability of older persons living in the community to bathe themselves as well as develop approaches to preventing mobility disability.

In a landmark clinical trial, investigators from the Yale OAIC demonstrated that functional decline among frail older persons can be prevented through a prehabilitation program targeting underlying impairments in physical capabilities.

- The **University of Michigan Center OAIC,** the first OAIC funded by NIH, advances research on health care problems of older adults. One of the Michigan OAIC's projects is determining whether deficiencies of dopamine (a chemical brain messenger) in older people contribute to gait imbalance and falls. The study investigators hope to demonstrate that L-DOPA, an agent that is converted to dopamine in the brain, could be an effective treatment for older adults who are experiencing problems with walking and falls.

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

The OAIC Coordinating Center at Wake Forest University facilitates information exchange and research collaborations among OAICs. The Coordinating Center helps develop and implement projects in shared areas of interest. The Coordinating Center's major activities are coordinating and enhancing OAIC training programs and organizing seminars and other activities for trainees at the OAIC Annual Scientific Meeting.

Evaluation Plans

NIH program staff review the progress of each OAIC at the end of each award cycle, typically every 5 years. In addition, a panel of experts external to the OAICs conducts a formal mid-cycle review 2 to 3 years into the funding cycle of each center. This review assesses the OAIC's progress in meeting the goals in its application and identifies areas of concern to address prior to the next competing renewal. NIH staff provides a written summary of the review to each OAIC principal investigator for use in directing the center.

Future Directions

NIH plans to continue to fund new and existing Claude D. Pepper OAICs. Because the number of qualified applicants for OAIC sites continues to grow, a new OAIC site is planned by FY 2010, bringing the total number of OAIC sites to 12.

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

Institution and Location	Year Established
Duke University, Durham, NC	1955[14]
University of Michigan, Ann Arbor, MI	1989
University of California, Los Angeles, CA	1991
Wake Forest University, Winston-Salem, NC	1991[15]
Yale University, New Haven, CT	1992
University of Maryland, Baltimore, MD	1994

Claude D. Pepper Older Americans Independence Centers

Institution and Location	Year Established
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
Boston University, Boston, MA	2008

[8] Federal Interagency Forum on Aging Related Statistics. Older Americans 2008: Key Indicators of Well-Being. Washington, DC: Federal Interagency on Aging-Related Statistics; 2008.
[9] For more information, see *MMWR Morb Mortal Wkly Rep* 2006;55(40):1089-92. PMID: 17035926.
[10] For more information, see http://www.nof.org/advocacy/prevalence/index.htm.
[11] 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.
[12] For more information, see http://www.cdc.gov/nchs/products/pubs/pubd/hus/healthexpenditures.htm.
[13] 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.
[14] The only remaining Geriatric Research and Training Center.
[15] NIH added a Coordinating Center 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.

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) included provisions for expanding and intensifying research on muscular dystrophy and mandated that NIH establish Centers of Excellence for muscular dystrophy research. Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs) in the Omnibus Appropriations for FY 2004 (Public Law 108-199) in honor of the former Minnesota senator who was a driving force behind the MD-CARE Act. The MD-CARE Act of 2008 officially renamed the centers.

How the Wellstone MDCRCs Function within the NIH Framework

NIAMS, NINDS, and NICHD fund the Wellstone MDCRCs through the U54 Specialized Centers Cooperative Agreement award mechanism (see Table 4-3). NHLBI also has co-sponsored the two most recent competitions for Wellstone MDCRCs and plans to support projects within future Wellstone MDCRCs if NIH receives fundable applications that address NHLBI's mission.

A Steering Committee, consisting of directors and co-directors of each center and NIH science officers, coordinates the Wellstone MDCRCs' scientific program. Through annual meetings and regular conference calls, the Steering Committee promotes collaborations among center investigators and makes strategic decisions about Wellstone MDCRC goals and activities, including standardization of operating procedures.

Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of skeletal muscles. Many dystrophies also affect other organ systems such as the heart, blood vessels, and gastrointestinal tract (stomach and intestines). Some forms occur in infancy or childhood, whereas others usually do not appear until middle age or later. The Wellstone MDCRCs address, but are not limited to, the following conditions.

- **Duchenne and Becker Muscular Dystrophies**. Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy. An X-linked recessive disease (related to genes carried on the X chromosome), it primarily affects males who inherit a genetic mutation from their mothers. Boys who have DMD lack the protein dystrophin, which muscle cells need to function properly. DMD 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 20s. Becker muscular dystrophy (BMD), a less severe disease, occurs when the body produces a form of dystrophin that does not work properly.
- **Myotonic Dystrophy**. Myotonic dystrophy is the most common adult form of muscular dystrophy, although forms of this disease can affect newborns and other children. It is marked by myotonia (an inability to relax muscles after they contract) and muscle wasting and weakness. Myotonic dystrophy varies in severity and symptoms. It can affect body systems in addition to skeletal muscles, including the heart, endocrine organs (organs that release hormones, or substances that affect cell function in another part of the body, into the bloodstream), eyes, and gastrointestinal tract.
- **Facioscapulohumeral Muscular Dystrophy (FSHD).** FSHD initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humeral). Symptoms usually develop in the teenage years. Some affected individuals become severely disabled. Wasting of muscles of the trunk can lead to life-threatening breathing complications.

- **Limb-Girdle Muscular Dystrophies (LGMDs).** All LGMDs show a similar distribution of muscle weakness, affecting both upper arms and legs. Scientists have identified many forms of LGMDs; some affect children, whereas others affect adults.
- **Miyoshi Myopathy.** Miyoshi myopathy causes initial weakness in the calf muscles. It is caused by defects in the same gene that is responsible for one form of LGMD, suggesting that research progress against one form of muscular dystrophy could 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. Treatments such as physical therapy, use of appliances for support, corrective orthopedic surgery, and drugs can reduce symptoms and improve quality of life for some individuals. Some drugs, such as corticosteroids, can slow the progression of DMD to some extent but have adverse effects. Several treatments, including gene therapy, cell-based treatments, and strategies to reduce muscle wasting have shown promise in experiments using cells and animals. Clinical trials of some therapies have begun, including the use of drugs to reduce muscle damage, approaches to increase muscle mass by stopping the activity of other proteins that inhibit muscle growth, and strategies to bypass mutations that cause disease.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy.

Burden of Illness

DMD and BMD affect 1 in 3,500 to 1 in 5,000 boys. With more than 4 million annual births in the United States, about 400 to 600 boys are born with DMD or BMD every year.[16] Myotonic dystrophy affects approximately 1 in 8,000 people worldwide,[17] whereas FSHD affects approximately 1 in 20,000 people and affects men and women equally.[18]

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. Recently published results from the project described the delay between the start of symptoms and definitive diagnosis of DMD.[19]

Scope of NIH Activities: Research and Programmatic

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDCRCs promote communication and collaboration, develop and share research resources, and help train new muscular dystrophy researchers. Each center can conduct a mixture of basic research to understand the diseases, translational research to turn basic research findings into interventions for patients, and clinical studies to test interventions in people. The overall focus of the Wellstone MDCRCs is to integrate activities to develop therapies for muscular dystrophies. In 2008, NIH funded two new Wellstone MDCRCs and renewed one that had received funds from the original competition in FY 2003.

Collectively, the Wellstone MDCRCs conduct research on various forms of muscular dystrophy, including some not listed above. Examples of research topics addressed by the Wellstone MDCRCs in FY 2008 and FY 2009 follow.

- The **University of Pittsburgh** center, for which funding ended in FY 2009, focused on developing gene therapy techniques, as well as research on muscle stem cells as potential therapies for DMD.
- At the **University of Rochester** center, researchers are examining cellular and molecular factors that contribute to myotonic dystrophy and testing potential treatments.
- The **University of Washington** center, for which funding ended in 2009, focused on developing gene therapy techniques for DMD and studying the processes that lead to FSHD.
- Ongoing research at the **Children's National Medical Center** focuses on genetic and cellular factors that contribute to DMD's progression and patient responses to treatment.
- Research at the **University of Iowa** center focuses on gene and stem cell treatments for DMD, LGMDs, and other muscular dystrophies.

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- Ongoing research at the **University of Pennsylvania** and **Johns Hopkins University** center focuses on improving muscle growth or slowing muscle deterioration. In the future, researchers may be able to use these approaches to treat several kinds of muscular dystrophies and other disorders.
- Established in FY 2008, the **Boston Biomedical Research Institute** center seeks to identify biomarkers and is conducting a clinical trial of a potential FSHD therapy. In FY 2009, the center received funding through the American Recovery and Reinvestment Act of 2009 (ARRA) to accelerate collection and study of multiple biopsies.
- Established in FY 2008, the **University of North Carolina at Chapel Hill** center is developing and testing gene therapies for DMD and other muscle disorders.

Each Wellstone MDCRC has core facilities that provide unique resources or services for the muscular dystrophy research community. Cores include repositories of research data and biologic resources from patients with different types of muscular dystrophy, assistance with gene therapy development and production, and a data-coordinating site for clinical trials conducted by the Cooperative International Neuromuscular Research Group (CINRG). The Wellstone MDCRC program also contributes to therapy development by supporting the National Center for Canine Models of Duchenne Muscular Dystrophy and a facility at the University of Pennsylvania that tests mice for muscular dystrophy investigators.

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the Wellstone MDCRC program was $9.9 million in FY 2008 and $9.3 million in FY 2009, including $406,000 from ARRA funds.

FY 2008 and FY 2009 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments in FY 2008 and FY 2009 include establishing new Wellstone MDCRCs at the Boston Biomedical Research Institute and the University of North Carolina at Chapel Hill in FY 2008. In addition, the Wellstone MDCRC at the University of Rochester competed successfully for renewal through FY 2013. The two other centers funded under the first Wellstone competition (University of Pittsburgh and University of Washington) ended their formal center programs in FY 2009. However, many of these centers' investigators continue to conduct muscular dystrophy research with support from other grants. Moreover, these universities still are eligible to compete for future Wellstone MDCRC grants.

In 2005 and 2006, NIH invited junior investigators from the Wellstone MDCRCs to apply for Wellstone fellowships, which support salary and some research expenses.[20] In FY 2008 and FY 2009, fellowship recipients published articles in high-quality journals; one left the center to establish a muscular dystrophy research program at a new institution; and another received an independent NIH research grant. Because training and career development is an important component of the Wellstone MDCRC program, all centers funded under the Wellstone MDCRC FY 2008 or FY 2010 competition will have formal training and education core facilities. These facilities will provide stipends to predoctoral and postdoctoral researchers and enhance the programs' educational environments.

Because training and career development is an important component of the Wellstone MDCRC program, all centers funded under the Wellstone MDCRC FY 2008 or FY 2010 competition will have formal training and education core facilities.

The Wellstone MDCRC program has enhanced public-private partnerships in muscular dystrophy. Projects have involved collaborations with, and additional support from, companies such as PTC Therapeutics, Acceleron Pharma, and Insmed. The centers also have strong ties with patient advocacy groups, including the Muscular Dystrophy Association, Parent Project MD, the FSH Society, Inc., the Jain Foundation, and the Foundation to Eradicate Duchenne, Inc. These organizations provide additional support for center research projects. The synergy created by NIH resources and the involvement of industry and advocacy groups is accelerating progress toward muscular dystrophy treatments.

In FY 2008, the NIH Wellstone MDCRC program, the NIH Office of Rare Diseases, the Foundation to Eradicate Duchenne, Inc., and the European organization TREAT-NMD hosted two workshops.[21] The goal of these workshops was to develop standard protocols for DMD treatment studies in mice and dogs. By adopting standardized protocols, investigators will be better able to compare results from different studies. Moreover, the outcomes will greatly accelerate treatment testing in animals.

The Wellstone MDCRC core facilities are national resources for the muscular dystrophy community. These facilities have been publicized at national meetings and through center websites and the Wellstone MDCRC website. These shared research tools foster collaborations across departments or schools within institutions and among investigators and health care providers nationwide. Examples of these facilities follow.

- The University of Rochester established the **Repository and National Registry of Myotonic Dystrophy Patients and Family Members** when NIH renewed the center's funding in FY 2008. The facility, a combination of the center's existing Tissue Repository Core and the NIH-funded Registry of Myotonic Dystrophy Patients and Family Members, provides researchers with cell or tissue samples and clinical information about the donors of these samples. This resource has facilitated two publications in 2008, advancing understanding of sleep disturbances[22] and chronic pain[23] in these patients.
- The University of Iowa's **Muscle Tissue/Cell Culture/Diagnostics Core** maintains a muscle tissue repository of well-characterized samples from a spectrum of muscular dystrophy types. The core continues to expand its repertoire of diagnostic services that are not readily available through clinical laboratories. Accomplishments in 2009 include contributions to a genetic test for a mutation associated with congenital muscular dystrophy in the Ashkenazi Jewish population.[24]
- The MDCRC at the University of North Carolina at Chapel Hill launched the **National Vector Muscular Dystrophy Core** in FY 2008. The Core is producing and testing gene therapy materials for researchers.[25] As tests are completed successfully, the facility will supply investigators with materials that they can use for clinical research. The core also will help investigators submit documents to regulatory agencies (such as the U.S. Food and Drug Administration) and comply with all relevant regulations. In FY 2009, the center successfully competed for supplemental ARRA funding to purchase additional laboratory equipment.
- The **Physiological Assessment Core** at the University of Pennsylvania evaluates muscle integrity and function for center investigators and other academic and industrial researchers. The facility's experienced staff conduct measurements that now are the standard for showing whether a new treatment is effective in animals. Accomplishments in FY 2008 and 2009 include contributions to papers on muscle function in models of FSHD[26] and DMD.[27]

Research Activities and Outcomes

The Wellstone MDCRCs conduct basic, translational, and clinical studies related to a variety of muscular dystrophies. Examples of accomplishments in FYs 2008 and 2009 are provided below.

- Investigators at the Nationwide Children's Hospital (Columbus, Ohio), funded through a subcontract from the University of Pittsburgh Wellstone MDCRC, developed a gene-therapy technique for making alpha-sarcoglycan protein (which is essential for muscle function) without triggering a destructive response by the body's immune system. The three-person clinical trial builds on findings from the University of Iowa and elsewhere showing that restoring alpha-sarcoglycan gene expression can halt the advance of a type of limb-girdle muscular dystrophy in mice.[28] The Nationwide Children's Hospital study demonstrated that the gene-delivery strategy was safe and that a single injection produced gene expression for at least 12 weeks.[29] Although the study was designed to test safety (not improvements in muscle function), findings from one patient suggest that the delivered gene might be useful for restoring muscle function.
- Animal study findings from Wellstone MDCRCs have suggested strategies for people who have various muscular dystrophies. For example, mouse studies at the University of Pennsylvania and Johns Hopkins University Wellstone MDCRC showed that a drug being studied for hepatitis C treatment slowed progression of congenital muscular dystrophy, DMD, and LGMDs by blocking damage caused by calcium to mitochondria (the main energy sources of

cells).[30] Although the drug might not be appropriate for people because of its potential side effects, the study shows that protecting cells from calcium damage could be beneficial.

- Researchers at the Children's National Medical Center increased the amounts of modified dystrophin protein in dogs with DMD, a disease caused by the body's inability to make dystrophin protein. They used artificial molecules (morpholino oligonucleotides) that cause the cell's protein-generating machinery to skip over the damaged segment of the dystrophin gene and produce shortened, but functional, dystrophin. If researchers can refine this strategy so that it can safely be studied in people, this approach could benefit nearly 90 percent of patients with DMD.[31]

Some researchers are exploring the role of neuronal nitric oxide synthase in controlling blood flow in skeletal muscle and thus in minimizing the fatigue associated with exercise that many people with a nerve or muscle disease experience.

- Wellstone MDCRC researchers are using animals to find treatments that could be effective for several different types of muscular dystrophies. Some researchers are exploring the role of neuronal nitric oxide synthase (nNOS) in controlling blood flow in skeletal muscle and thus in minimizing the fatigue associated with exercise that many people with a nerve or muscle disease experience.[32] University of Iowa scientists used mice with DMD to show that a drug that allows blood vessels to dilate prevents the severe fatigue that the mice experienced after brief exercise periods. Other studies by researchers at the University of Missouri in collaboration with an investigator at the Seattle Wellstone Center restored functioning of diseased mice to nearly normal levels by using a gene therapy strategy involving nNOS.[33]

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

In response to research advances and Steering Committee recommendations, NIH changed the requirements for FY 2008[34] applicants to improve the program's overall effectiveness, efficiency, and outcomes. The FY 2008 solicitation emphasized multidisciplinary teams and patient-oriented research. Details about the recommendations' rationale and implementation follow.

- NIH removed the requirement that all centers conduct basic research on disease mechanisms because the number of findings that are ready to be studied in animals or humans has increased dramatically since the last competitions.[35, 36] This change allows the Wellstone MDCRCs to focus more on translating basic findings to human studies and conducting studies in humans. Meanwhile, NIH continues to encourage basic muscular dystrophy research through other funding mechanisms, such as traditional research project grants.
- By reducing the required number of projects from three to one, NIH allowed FY 2008 applicants to propose collaborative studies involving animal models of disease or human subjects that were larger, more expensive, and more in-depth than were possible under the original structure.
- NIH urged FY 2008 applicants to propose collaborative studies that address at least one gap in muscular dystrophy treatment research and overcome obstacles in the development of therapies.
- In FY 2008, all applicants had to provide letters from other researchers to show how one of their proposed cores would fill a high-priority need beyond their individual institutions. This change was designed to increase the Wellstone MDCRC program's ability to serve the entire muscular dystrophy research community.
- NIH enhanced the program's training activities in FY 2008 by requiring all centers to create Research Training and Education Cores that support predoctoral students and postdoctoral fellows. The addition of a formal career-development program at each site enhances the Wellstone MDCRCs' contributions to the pipeline of new muscular dystrophy researchers.
- Engaging patients throughout the research process can improve a program's impact by ensuring that researchers are developing and testing treatments that are acceptable to patients (and the parents of pediatric patients). To this end, the new Wellstone MDCRC at the Boston Biomedical Research Institute has been working closely with the FSH Society to jointly set and achieve research objectives with the patient community.
- NIH is organizing a broader collaborative network of muscular dystrophy researchers. To make communication more seamless among everyone who cares about people with muscular dystrophy and to increase the exchange of

knowledge for treatment development, NIH invited major advocacy groups and grantees who have other center awards to participate in a 2009 meeting of the Wellstone MDCRCs. Investigators presented examples of collaborations among the centers and other researchers. New opportunities for interactions and multi-laboratory projects were identified.

Evaluation Plans

Major review criteria for the Wellstone MDCRCs include the degree to which an institution shows that it can foster substantive collaborations among its researchers and with scientists elsewhere that address key issues in muscular dystrophy and its potential to serve as a national infrastructure and training resource.

NIH responded to the burgeoning number of basic research findings in muscular dystrophy by changing the focus of the FY 2008 Wellstone MDCRC competition to encourage research that translates basic findings about the disease to human studies and applications in the clinic.

NIH responded to the burgeoning number of basic research findings in muscular dystrophy by changing the focus of the FY 2008 Wellstone MDCRC competition to encourage research that translates basic findings about the disease to human studies and applications in the clinic. Informal comments about the change in focus from reviewers, grantees, and advocacy groups were positive. Discussions about the centers' structure among NIH program staff and IC directors led to a decision to retain the structure adopted for the FY 2008 competition. NIH will continue to monitor the program's coordination and productivity as staff review the progress of each center at the time of noncompeting renewal and through regular contact with Wellstone MDCRC leaders through the Steering Committee.

Future Directions

NIH is committed to supporting six outstanding Wellstone MDCRCs. The agency issued 3 5-year awards to the Wellstone MDCRC program in FY 2008. In FY 2010, NIH is holding an open competition and intends to fund up to three other center sites.[37] Grantees will join the network of Wellstone MDCRCs to translate scientific findings and technological developments into treatments for muscular dystrophies.

NIH supports multi-project grants and core centers for muscular dystrophy research at academic institutions in addition to the Wellstone Centers. The agency also is promoting interactions among investigators at the Wellstone Centers and these other institutions to expand the scope and strength of the Wellstone Network. For example, the Wellstone Center meeting in June 2009 included participants from two NIAMS-funded core centers, two NINDS-supported program project grants, the NINDS- and NIAMS-supported National Center for Canine Models of DMD, and representatives from patient advocacy groups.

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

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Institution and Location	Year Established
University of Pennsylvania, Philadelphia, PA, and Johns Hopkins University, Baltimore, MD	2005
Boston Biomedical Research Institute, Boston, MA	2008
University of North Carolina, Chapel Hill, NC	2008

[16] For more information, see www.cdc.gov/ncbddd/duchenne/who.htm.
[17] For more information, see http://ghr.nlm.nih.gov/condition=myotonicdystrophy.
[18] For more information, see www.nlm.nih.gov/medlineplus/ency/article/000707.htm.
[19] Ciafaloni E, et al. *J Pediatr* 2009;155(3):380-5. PMID: 19394035.
[20] For more information, see http://grants2.nih.gov/grants/guide/notice-files/NOT-AR-05-001.html.
[21] Nagaraju K, et al. *Neuromuscul Disord* 2009;19(7):502-6. PMID: 19560356. PMCID: PMC2766092.
[22] Ciafaloni E, et al. *Neurology* 2008;70(3):226-30. PMID: 18195268.
[23] Jensen MP, et al. *Arch Phys Med Rehabil* 2008;89(2):320-8. PMID: 18226657.
[24] Chung W, et al. *Prenat Diagn* 2009;29(6):560-9. PMID: 19266496. PMCID: PMC2735827.
[25] Li C, et al. *J Virol* 2009;83(13):6817-24. PMID: 19369348. PMCID: PMC2698563.
[26] Daniels DW, et al. *Arch Oral Biol* 2008;53(2):187-92. PMID: 18028868. PMCID: PMC2262833.
[27] Millay DP, et al. *Nat Med* 2008;14(4):442-7. PMID: 18345011. PMCID: PMC2655270.
[28] Pacak CA, et al. *Mol Ther* 2007;15(10):1775-81. PMID: 17653106.
[29] Mendell JR, et al. *Ann Neurol* 2009; 66(3):267-70. PMID: 19798725.
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[32] Yokota T, et al. *Ann Neurol* 2008;456(7221):511-5. PMID: 18953332. PMCID: PMC2588643.
[33] Lai Y, et al. *Clin Invest* 2009;119(3):624-35. PMID: 19229108. PMCID: PMC2648692.
[34] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-08-002.html.
[35] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-03-001.html.
[36] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-04-008.html.
[37] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-027.html.

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

Overview

NIH defines health disparities as differences in the incidence, prevalence, morbidity, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups.[38] These population groups are African Americans, American Indians, Alaska Natives, Asian Americans, Hispanic Americans, Native Hawaiians, and Pacific Islanders, subpopulations of all of these racial/ethnic groups, socioeconomically disadvantaged individuals, and medically underserved populations including individuals residing in rural and urban areas.

The National Center on Minority Health and Health Disparities (NCMHD) Centers of Excellence (COE) program is one of several programs that are central to NIH's scientific investment strategy for addressing and ultimately eliminating health disparities (see Table 4-4). That strategy encompasses:

- Conducting and supporting basic, clinical, social sciences, and behavioral research
- Promoting research infrastructure and training
- Fostering emerging programs
- Disseminating information
- Reaching out to racial and ethnic minority and other communities that experience health disparities

Why the NCMHD Centers of Excellence Were Established

The Minority Health and Health Disparities Research and Education Act of 2000 (Pub. L. No. 106-525) included provisions for the creation of NCMHD to conduct and support research, training, and dissemination of information with respect to minority health conditions and other populations with health disparities. Section 485F specifically mandated that NCMHD establish Centers of Excellence in research institutions for the purpose of conducting biomedical and behavioral health disparities research and training.

How the NCMHD Centers of Excellence Function within the NIH Framework

NCMHD established COEs to create a comprehensive platform in academic institutions to address health disparities in priority diseases and conditions through the fundamental strategies of research, training a diverse scientific workforce, and engagement of the community. NCMHD also designed the COE program to support Department of Health and Human Services initiatives for eliminating health disparities.

Since 2002, NCMHD has established Centers of Excellence (COEs) in 32 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. NCMHD supported 49 COEs in FY 2008 and 51 COEs in FY 2009.

Since 2002, NCMHD has established COEs in 32 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. Initially, the program used three different funding mechanisms for Resource-Related Centers (R-24), Exploratory Centers (P20), and Comprehensive Centers (P60). The use of these different funding mechanisms allowed NCMHD to support institutions with varying levels in biomedical research expertise and capacity. This approach also enabled NCMHD to leverage resources to support the capabilities of the Nation's geographically and culturally diverse institutions that have longstanding partnerships with local and regional health disparity organizations and communities. The Resource-Related Centers mechanism, which NCMHD no longer uses, enabled institutions with emerging or modest research infrastructures to begin building research capacity to address health disparities. Several institutions that received these R24 awards have since successfully established an NCMHD COE using the Exploratory Centers mechanism.

Similar to other COEs that NIH supports through these mechanisms, a typical project period is 4 to 5 years. All NCMHD COEs (P20 and P60) established since FY 2005 have had project periods of 5 years.

Currently, the types of institutions funded directly by the NCMHD COE program or through partnerships with NCMHD COEs are broad. These institutions include research-intensive institutions, medical schools, historically black colleges and universities, Hispanic-serving institutions, tribal colleges/universities, and liberal arts colleges. NCMHD supported 49 COEs in FY 2008 and 51 COEs in FY 2009.

As a hub for health disparities research, NCMHD COEs provide opportunities for the development of novel partnerships between different types of institutions, such as community-based organizations or foundations, to partner in the conduct of rigorous basic scientific research, human subjects and vertebrate animal research, and applied population and community-based research.

One example of an NCMHD COE is the partnership funded in FY 2009 that established the University of South Florida and Moffitt Transdisciplinary Center to Address Cancer Health Disparities. Florida has the second highest estimated number of new cancer cases and cancer deaths. This COE seeks to reduce racial and ethnic cancer disparities through research, education, training, and community engagement. Significantly, this partnership will engage three different communities by conducting community cancer discussion groups, health and science fairs, and workshops, and by using social marketing approaches to disseminate information through radio talk shows, an interactive website, a Facebook page, and podcasts. The Florida program also provides opportunities for increasing the pool of investigators from populations that experience health disparities through research training, faculty development, programs and activities to interest K-12 students in science, health information dissemination, and approaches to increasing the participation of these populations in clinical trials.

Description of Disease or Condition

The research and other COE activities that NCMHD supports are not limited to or focused on a single disease, illness, or condition. As described in various solicitations published in the *NIH Guide for Grants and Contracts*, the NCMHD COEs conduct research on health disparities associated with the following priority diseases and conditions: cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity. The NCMHD COE program also supports research on lung disease, liver disease, psoriasis, scleroderma, and glomerular (kidney) injury; all of these diseases and conditions disproportionately affect racial and ethnic minorities.

NCMHD Centers of Excellence conduct research on health disparities associated with the following priority diseases and conditions: cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity. The program also supports research on lung disease, liver disease, psoriasis, scleroderma, and glomerular (kidney) injury; all of these diseases and conditions disproportionately affect racial and ethnic minorities.

Burden of Illness

The diversity of the contemporary American population is one of the Nation's greatest assets. However, the richness of this diversity is diminished by the disproportionate burden of disease and illness and the reduced access to quality health care that racial and ethnic minority populations and the rural and urban poor experience. Compelling evidence of the disparate health status of America's racial and ethnic minority and economically disadvantaged populations includes their shorter life expectancies and higher rates of cancer, birth defects, infant mortality, asthma, diabetes, obesity, cardiovascular disease, and stroke. Racial and ethnic minorities and the medically underserved also suffer a disproportionate burden of morbidity and mortality associated with HIV/AIDS; autoimmune diseases, such as lupus and scleroderma; oral health; sexually transmitted diseases; mental disorders; violence; and substance abuse.

Recent statistics on disparities for select diseases and conditions are provided in the following tables.

Ischemic Stroke Death Rates[39]	
Race/Ethnicity	***Rate (per 100,000)***
White	73.7
African American	95.8
American Indian/Alaska Native	48.6
Asian/Pacific Islander	45.8
Hispanic	39.7

Intracerebral Stroke Death Rates[40]	
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, 2002—2006[41]	
Race/Ethnicity	***Rate (per 100,000 Women)***
All Races	24.5
White	23.9
African American	33.0
Asian/Pacific Islander	12.5
American Indian/Alaska Native	17.6
Hispanic	15.5

Prostate Cancer Rates by Race/Ethnicity, 2002—2006[42]	
Race/Ethnicity	***Rate (per 100,000 Men)***
All Races	25.6
White	23.6
African American	56.3
Asian/Pacific Islander	10.6
American Indian/Alaska Native	20.0
Hispanic	19.6

Obesity in Men, 2003—2006[43]	
Group	***Percent***
All	33.1
White	33.0
African American	36.3
Mexican	30.4

Obesity in Women, 2003—2006[44]	
Group	***Percent***
All	35.2
White	32.5
African American	54.3
Mexican	42.6

Scope of NIH Activities: Research and Programmatic

The scope of activities at NCMHD COEs are guided by the Research, Infrastructure, and Outreach (RIO) framework used in developing the NIH Health Disparities Strategic Plan. Implementing the RIO framework within the NCMHD COE program provides a flexible structure that allows considerable freedom in designing and implementing the multi- and transdisciplinary strategies, studies, interventions, and activities required for reducing and ultimately eliminating health disparities.

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

The NCMHD COE program requires all COEs to establish mandatory cores:

- An Administrative Core for carrying out and overseeing administrative matters and functions
- A Research Core for conducting, coordinating, generating, and advancing research on health disparities
- A Research Training and Education Core for conducting and advancing research training
- A Community Engagement Core for engaging communities and others as partners in eliminating health disparities through community participation in research and the joint development and dissemination of effective health information messages and research findings

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the NCMHD COE program was $56.8 million in FY 2008, and $72.5 million in FY 2009,[45] including $5.6 million from ARRA funds.

FY 2008 and FY 2009 Progress Report

Significant programmatic accomplishments include establishing seven new COEs and one competing renewal (see Table 4-4). The number of active NCMHD COEs was 49 in FY 2008 and 51 in FY 2009.

The COE at the University of Southern California received one of three telehealth/telemedicine supplements to develop technology and tools for use with mobile devices to prevent pediatric obesity among Hispanic and African American youth in Los Angeles.

Administrative supplements were made in FY 2008 to NCMHD COEs to support the following:

- The use of telehealth and telemedicine. NCMHD considers the use of telehealth and telemedicine to be innovative strategies to reduce and eliminate health disparities in hard-to-reach rural, Alaska Native, American Indian, Native Hawaiian, Pacific Islander, African American, Hispanic American, or Asian American populations.
- Regional seminar series on health disparities to share and disseminate minority health and health disparities research findings and increase the participation of health professionals and community stakeholders in the effort to eliminate health disparities.
- The development and implementation of science education programs for grades K–12 to promote careers in biomedical, behavioral, and biosocial research for populations that are underrepresented in the health science fields.

Research Activities and Outcomes

Funding for the NCMHD COEs has resulted in several FY 2008 and FY 2009 research accomplishments. The centers conduct research on minority health and the biologic and non-biologic factors contributing to health disparities. As shown by the following examples, NCMHD researchers are exploring the role of social and cultural factors in the prevalence of priority diseases and conditions.

The Carolina-Shaw Partnership for the Elimination of Health Disparities completed a pilot study to qualitatively explore cultural attitudes and perceptions toward body image, food, and physical activity among a sample of overweight African American girls.[46] The investigators found that weight and body size preferences were determined primarily by the individual and her immediate social circle and were less influenced by opinions of those outside of the social circle. The findings also showed that the girls' food choices depended on texture, taste, appearance, and context more than nutritional value; engagement in recreational physical activity was influenced by time constraints from school and extracurricular activities and by neighborhood safety; participation in structured exercise was limited because of the cost and time required to maintain personal aesthetics (hair and nails); and the girls did not perceive celebrities as role models for diet and physical activity habits.

The University of Oklahoma Center for American Indian Diabetes Health Disparities seeks to reduce and eventually eliminate the excess mortality, morbidity, and loss of quality of life and culture due to diabetes.

The University of Oklahoma Center for American Indian Diabetes Health Disparities seeks to reduce and eventually eliminate the excess mortality, morbidity, and quality of life and culture lost due to diabetes. The center also focuses on maternal health, infant mortality, and obesity. Current studies include Early Markers of Pre-eclampsia in American Indians with Type 2 Diabetes, Insulin Resistance and Glucocorticoid Treatment of Inflammatory Diseases of High Prevalence among American Indians, and American Indian Diabetes Beliefs and Practices: Maternal Care, Infant Mortality, and Adherence. In addition, the center is providing instruction and support for conducting practical research to address diabetes within their health care settings to a cadre of nurses from American Indian clinics and hospitals in Oklahoma and Kansas. The Community Engagement/Outreach Core supports the Native Youth Preventing Diabetes summer camp that is open to all Oklahoma American Indians ages 8 to 12 years.

The Uniform Services University Center for Health Disparities Research, a partnership between the Uniform Services University of the Health Sciences and the University of Maryland, Eastern Shore, is conducting research on long-term behavioral modification to reduce and prevent obesity among African American women. The center is using the results of this research to build a program on cardiovascular disease and metabolic syndrome, which disproportionately affect minority populations. The center's research addresses issues related to lifestyle and health, health care access, health status, and health disparities. The Healthy Lifestyles among African American Women through Weight Loss and Exercise project is exploring ways for women in faith-based communities to sustain weight reduction and maintenance efforts using different exercise regimes and behavioral therapies. The project's long-term goal is to decrease the risk and incidence of obesity and associated conditions.

The Uniform Services University Center for Health Disparities Research is using the results of its research on long-term behavioral modification to reduce and prevent obesity to build a program on cardiovascular disease and metabolic syndrome, which disproportionately affect minority populations.

Researchers at the Center for Research on Minority Health of the University of Texas M.D. Anderson Cancer Center and Prairie View A&M University are defining the biological relevance of susceptibility gene polymorphisms (different forms of these genes) as risk factors for cancer and other adverse health effects. Specifically, the researchers are developing and validating a food frequency questionnaire to assess the folate and vitamin B12 intake of Mexican American children in Texas. The study's short-term goal is to estimate the prevalence of the social, environmental, and genetic factors associated with stomach cancer risk among Mexican American children; the long-term goal is to prevent stomach cancer in Mexican Americans. The findings from this study could reduce stomach cancer health disparities in the United States and around the world.

To address the disproportionate burden and impact of HIV/AIDS on women of color, the University of Miami COE is evaluating the efficacy of an HIV risk reduction intervention delivered by Hispanic women. The intervention is culturally tailored to meet the needs of Hispanic women, who are disproportionally affected by HIV/AIDS. The intervention is designed to increase HIV prevention behaviors in inner-city Hispanic women. The study also is exploring the role of acculturation, family, stress, and family functioning as risk factors, protective factors, or both in the prevention of HIV/AIDS among Hispanic women.[47]

To address the disproportionate burden and impact of HIV/AIDS on women of color, the University of Miami COE is evaluating the efficacy of an HIV risk reduction intervention delivered by Hispanic women and designed for Hispanic women in the United States.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the NCMHD COEs

Since their inception in year 2002, NCMHD COEs made progress toward the elimination of health disparities. However, much more needs to be done in designing and taking the critical steps needed to translate research findings to meaningful actions that will improve the quality of life experienced by those overburdened by health disparities. Efforts need to be more targeted toward interventions that work. Specifically, guidance will be provided to COEs to:

- Establish partnerships with other NIH-funded centers and programs, other Federal agencies, and others committed to eliminating health disparities as a way to maximize resources.
- Increase the diversity of the scientific workforce, especially the number of women and biomedical and behavioral scientists from racial/ethnic and other health disparity populations. Focused efforts are especially needed to increase the number of women scientists and researchers who: a) remain in the sciences beyond the terminal research or professional degree and beyond the postdoctoral or residency stage and who pursue basic or clinical research as a career; and b) serve in leadership and decision-making roles as members of scientific review panels or members of national advisory councils.
- Create opportunities for biomedical and behavioral scientists to work with social scientists, health services researchers, and other public health researchers to address more effectively the transdisciplinary challenges in health disparities elimination and prevention research.
- Enhance the Nation's research capacity to conduct health disparities research by expanding the research and training opportunities available.

NCMHD and its COEs cannot act alone—NCMHD actively seeks new partners and also encourages each NCMHD COE to establish partnerships with other NIH-funded centers and programs, other Federal agencies, and others committed to eliminating health disparities.

Evaluation Plans

NCMHD program staff evaluate the COEs' annual progress by examining each COE's published peer-reviewed articles, books, and book chapters; conferences sponsored and presentations given on health disparities; community engagement activities, such as health fairs and other forums for disseminating health-promotion materials; community participation in research and clinical trials (if applicable); training of junior faculty from health disparity populations, postdoctoral fellows, and graduate and undergraduate students; and K–12 educational efforts. This review ascertains the COE's progress in meeting the aims and objectives of the grant and may identify areas of concern that need to be addressed.

Future Directions

The NCMHD COE program will continue to intensify research efforts to reduce and eliminate health disparities, with an emphasis on sustaining current partnerships and establishing new ones. NCMHD expects that its COEs will discover new biomedical and behavioral knowledge for improving minority health and 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 in lung and liver diseases, psoriasis, scleroderma, and glomerular injury. An important emphasis area is reducing co-morbidities in populations that experience health disparities.

The NIH Science of Eliminating Health Disparities Summit, held in December 2008, provided significant recommendations for future research themes for COEs. These include, but are not limited to:

- Support for infrastructure that involves community leaders in the design and conduct of clinical trials. Since infrastructures can cover a wide range of diseases, investigators should take advantage of already established systems to maximize resources.
- Support studies using multi-level and/or ecological approaches that take into consideration the interactions between variables that represent individual, family, community, and neighborhood characteristics.

- Support research on the broad social and political processes that lead to or ameliorate social disparities in health. In the same way as the genome has been mapped, the fundamental social determinants of health must be mapped in order to understand the social and political processes that must inform the development of effective interventions.
- Promote greater interdisciplinary training opportunities to evolve a new scientific approach that includes disseminating information, communicating, and capacity-building.

The COEs also will continue to develop new technologies for measuring the interactions between these various factors and new paradigms. The resulting new knowledge and technologies will lead to the development of bio-psychosocial and other interventions and strategies for improving minority health and eliminating health disparities.

Conducting population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the United States—especially the Mississippi Delta, Appalachia, the U.S.-Mexico border region, and tribal communities—will continue to be important.

The success of these and future research efforts by the NCMHD COEs will continue to 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, behavioral, and social factors, and health policies and practices. Conducting population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the United States—especially the Mississippi Delta, Appalachia, the U.S.-Mexico border region, and tribal communities—will continue to be important. NCMHD will continue to support 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 these regions.

Table 4-4. NCMHD Centers of Excellence Active in FY 2008 and FY 2009

Institution and Location	Year Established
Charles R. Drew University of Medicine & Science, Los Angeles, CA	2002
Howard University, Washington, DC	2002
Johns Hopkins University, Baltimore, MD	2002
Morehouse School of Medicine, Atlanta, GA*	2002
Mount Sinai School of Medicine of NYU, New York, NY	2002
North Carolina Central University, Durham, NC	2002
San Diego State University, San Diego, CA	2002
Tuskegee University, Tuskegee, AL*	2002
University of California, San Diego, CA	2002
University of Hawaii, Manoa, HI	2002
University of North Carolina, Chapel Hill, NC	2002
University of Pennsylvania, Philadelphia, PA*	2002
University of Pittsburgh, Pittsburgh, PA	2002

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

Institution and Location	Year Established
Columbia University Health Sciences, New York, NY	2003
Meharry Medical College, Nashville, TN	2003
New York University School of Medicine, New York, NY	2003
Texas A&M University System, College Station, TX	2003
Uniformed Services University of the Health Sciences, Bethesda, MD	2003
University of Alabama, Birmingham, AL	2003
University of Arizona, Tucson, AZ*	2003
University of California, Davis, CA	2003
University of Colorado Denver and Health Sciences Center, Aurora, CO	2003
University of Maryland, Baltimore, MD*	2003
University of Oklahoma Health Sciences Center, Oklahoma City, OK	2003
University of Puerto Rico Medical Sciences, San Juan, PR	2003
University of Texas Health Sciences Center, Houston, TX	2003
University of Texas M.D. Anderson Cancer Center, Houston, TX	2003
Yeshiva University, New York, NY	2003
University of South Alabama, Mobile, AL	2004
University of the Virgin Islands, St. Thomas, VI	2004
Loma Linda University, Loma Linda, CA	2005
University of Connecticut, Storrs, CT	2005
University of North Texas Health Sciences Center, Fort Worth, TX	2005
University of South Carolina, Columbia, SC	2005
University of South Dakota, Vermillion, SD	2005
Arizona State University, Tempe, AZ	2007
Case Western Reserve University, Cleveland, OH	2007
Clark Atlanta University, Atlanta, GA	2007
Florida International University, Miami, FL	2007
Montana State University, Bozeman, MT	2007

Institution and Location	Year Established
University of Arkansas Medical Sciences, Little Rock, AR	2007
University of Massachusetts, Boston, MA	2007
University of Miami, Coral Gables, FL	2007
University of Michigan, Ann Arbor, MI	2007
University of North Carolina, Greensboro, NC	2007
University of Southern California, Los Angeles, CA	2007
University of Texas, El Paso, TX	2007
Virginia Commonwealth University, Richmond, VA	2007
Winston-Salem State University, Winston-Salem, NC	2007
Medical College of Georgia, Augusta, GA	2009
State University of Albany, Albany, NY	2009
University of Illinois, Chicago, IL	2009
University of Minnesota, Twin Cities, MN	2009
University of South Florida, Tampa, FL	2009
University of Wisconsin, Madison, WI	2009
Weill Medical College, Ithaca, NY	2009

*Center was active in FY 2008 but not FY 2009

[38] For more information, see http://www.ncmhd.nih.gov/our_programs/strategic/pubs/VolumeI_031003EDrev.pdf, p. 7.
[39] Ayala C, et al. *Am J Epidemiol* 2001;154:1057-63. PMID: 11724723.
[40] Ibid.
[41] For more information, see http://seer.cancer.gov/statfacts/html/breast.html?statfacts_page=breast.html&x=16&y=16.
[42] For more information, see http://seer.cancer.gov/statfacts/html/prost.html?statfacts_page=prost.html&x=18&y=17.
[43] For more information, see Table 75 at http://www.cdc.gov/nchs/data/hus/hus08.pdf.
[44] Ibid.
[45] The funding increase from FY 2008 to FY 2009 is due to the addition of seven new NCMHD COEs and one competing renewal.
[46] Boyington JE, et al. *Prev Chronic Dis* 2008;5(2):A36. PMID: 18341772. PMCID: PMC2396970.
[47] For more information, see http://elcentro.sonhs.miami.edu/research/full_research_studies.html.

Rare Diseases Clinical Research Network

Overview

Why the RDCRN Was Established

The need for centers of excellence for rare diseases research has been voiced for more than 20 years. A disease is defined as rare if fewer than 200,000 persons in the United States have it. Scientists have identified approximately 6,500 rare diseases and believe that approximately 80 percent have a genetic origin.

In 1989, the National Commission on Orphan 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 had to wait 5 years or more to obtain a correct diagnosis. An additional 30 percent of patients waited 1 to 5 years before obtaining a diagnosis.

In 1989, the National Commission on Orphan Diseases found that 15 percent of patients with rare diseases had to wait 5 years or more to obtain a correct diagnosis. An additional 30 percent of patients waited 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 specialized centers for rare diseases. The panel recommended funding for specialized research and diagnostic centers for major categories of rare diseases. The panel recommended establishing rare diseases centers of excellence on a graduated basis, starting with 10 regional centers in the first year with incremental increases of 10 centers per year until NIH had established 40 regional centers. The panel also emphasized that centers should work closely with patient advocacy groups. Congress realized the panel's recommendations with the Rare Diseases Act of 2002, Pub. L. No. 107-280. In response to the Act, NIH established the Rare Diseases Clinical Research Network (RDCRN) in 2003. ORDR partnered with 6 NIH ICs to fund 10 RDCRN consortia that focused on rare disease groups at multiple academic institutions and shared a central Data and Technology Coordinating Center (DTCC).

In February 2008, ORDR, in collaboration with several NIH ICs, released two RFAs to recompete the network and establish Phase II of the RDCRN—Rare Diseases Clinical Research Consortia (RDCRC) for the Rare Disease Clinical Research Network [U54] (RFA-OD-08-001) and Data Management and Coordinating Center (DMCC) for the Rare Diseases Clinical Research Network [U54] (RFA-OD-08-002). Existing as well as potentially new consortia and data coordinating centers were invited to apply.

ORDR and 7 NIH Institutes funded and provided administrative support to 19 consortia and the DMCC (see Table 4-5) in FY 2009. These Phase II RDCRN awards are for 5 years.

How the RDCRN Functions within the NIH Framework

In 2009, the RDCRN grew from 10 to 19 consortia, 4 of which were funded through the American Recovery and Reinvestment Act (ARRA).

Originally, in Phase I, ORDR partnered with six NIH Institutes (NCRR, NICHD, NINDS, NIAMS, NIDDK, and NHLBI) in administering and funding the network. For Phase II of the network, ORDR is partnering with seven Institutes: NICHD, NIAMS, NINDS, NHLBI, the NIAID, NIDDK, and NIDCR.

Each consortium develops clinical protocols for a set of related rare diseases and includes several participating institutions. The network incorporates uniform data and methodological standards across all the consortia and their component sites. The original RDCRN contained more than 70 sites across the United States and in other countries. The current network

includes approximately 165 sites in at least 29 states. Twenty sites are in other countries. The total number of sites is expected to further facilitate enrollment of and access for patients.

The current Rare Diseases Clinical Research Network includes approximately 165 sites in at least 29 states. Twenty sites are in other countries.

A steering committee guides the network. The steering committee consists of the principal investigator of each consortium, NIH representatives, and a patient advocacy representative nominated by the 57 collaborating patient advocacy groups. The patient advocacy groups associated with each consortium have formed a coordinating committee that is instrumental in participating in the development of informed consent statements, informational materials about diseases and treatments, protocols, recruitment strategies, and other important activities. Other network committees and working groups facilitate communication and collaboration across and within consortia to ensure research efficiency and excellence.

In general, the current network's infrastructure and functions build on lessons learned and uses those approaches that have proven to be most efficacious.

Description of Diseases and Conditions under Study in Phase II of the RDCRN

With establishment of Phase II of the RCDRN, network researchers are poised to study 92 rare diseases, including:

Urea cycle disorders (UCD): UCDs are a group of genetic disorders caused by a deficiency of one of the enzymes in the urea cycle, which is responsible for removing ammonia from the blood stream. Because many cases of UCD remain undiagnosed, infants born with the disorders may die without a definitive diagnosis.

Vasculitides: Vasculitides are a heterogeneous group of diseases resulting in severe inflammation of blood vessels. Arteries and veins of any size in any organ may be affected, leading to damage to organs caused by a loss of the blood supply, known as ischemia.

Genetic Disorders of Mucociliary Clearance: Genetic disorders of mucociliary clearance include disorders such as primary ciliary dyskinesia (PCD), variant cystic fibrosis (CF), and pseudohypoaldosteronism (PHA). They reflect genetic defects in airway host-defense and impaired clearance of mucus, and typically result in severe chronic infection of the airways.

*Dystonias:*The dystonias are a group of neurological disorders characterized by involuntary twisting movements and unnatural posturing. Focal dystonias affect only one body part. Some of the most common forms of focal dystonia are cervical dystonia, affecting the neck; blepharospasm, affecting the eyelids; spasmodic (or laryngeal) dysphonia, affecting the voice box; craniofacial dystonia, affecting the lower face; and limb dystonias, affecting the hand or arm or foot or leg.

Brain vascular malformations: Brain vascular malformations are characterized by veins and blood vessels in the brain that are structurally malformed and can cause drainage of an area of the brain, resulting in repeated and debilitating bleeding, seizures, and hemorrhaging as a result of the formation of blood clots. Brain vascular malformations are resource-intensive to manage effectively, and have high probability of serious neurological morbidity. Specific medical therapies for these diseases are lacking.

*Immune-Mediated Disorders Post Transplant of Donor Bone Marrow:*Hematopoietic stem cell transplantation is the infusion of stem cells from the bone marrow of a donor into a patient to treat tumors, disorders of the blood, immunodeficiency syndromes, congenital enzyme deficiencies, and autoimmune disorders. Persons who receive grafts from donors (known as allogeneic or allografts) are at a substantially greater risk for graft-versus-host disease and delayed immune system recovery than are persons who receive grafts harvested from one location on their body and transplanted

to another site (autografts). Recipients of allografts also have greater rates of graft rejection, cytomegalovirus infection, invasive fungal infection, and Epstein-Barr virus-associated post-transplant lymphoproliferative disease, in which the body has too many white blood cells, which can overactivate the immune system.

Nephrotic Syndromes or Nephrosis: Nephrotic syndromes and nephrosis cause damage to the kidney, resulting in leakage of large amounts of protein into the urine. The loss of so much protein in the kidney causes other conditions, which are often characterized by excess body fluid.

Primary Immune Deficiencies: Primary immune deficiencies, also called primary immune disorders, weaken the immune system, allowing repeated infections to occur more easily. Many people with primary immunodeficiency are born without some of the body's immune defenses, which leaves them more susceptible to infections. In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular defenses against infection fail to work properly.

Lysosomal Storage Diseases: Lysosomal storage diseases are a large group of diseases, each characterized by a specific lysosomal enzyme deficiency in a variety of tissues. Consortium investigators study 11 lysosomal storage diseases—mucopolysaccharidoses (MPS), Batten disease, Niemann-Pick disease type C, mucolipidosis type IV, late infantile neuronal ceroid lipofuscinosis, glycoproteinoses, Wolman disease, Pompe disease, bone disease in the MPS, and Fabry disease. These conditions involve severe central nervous system disease, which is difficult to treat. They are devastating to quality of life and can lead to dementia and death.

Autonomic Rare Diseases: The autonomic nervous system controls vital involuntary body functions, such as blood pressure; heart and breathing rates; body temperature; digestion; metabolism; the balance of water and electrolytes; the production of saliva, sweat, and tears; urination; defecation; and sexual response. Disorders of the autonomic nervous system can affect any body part and may be reversible or progressive.

Charcot Marie Tooth Disease (CMT): CMT is an inherited disease involving damage to the nervous system. Even patients with this progressive disease who come from the same family show a wide range of symptoms. For example, progressive muscle wasting leads to problems with walking, running, and balance. Later in the course of the disease, hand function may become affected. Loss of nerve function in the extremities also can result in sensory loss. People can be unaware of having developed ulcers of the feet or of cuts or burns on the hands. Sensory loss can lead to gradual hearing impairment and, sometimes, deafness. Some people with CMT also have tremors, usually of the hands. Weakness of the respiratory muscles can cause life-threatening problems. Scoliosis of the spine also is associated with this disease. No effective therapies are available for any form of CMT.

Hereditary Nephrolithiasis and Kidney Failure: Hereditary causes of nephrolithiasis and kidney failure are inborn errors of metabolism that lead to high concentrations of insoluble mineral salts in the urine and severe, recurrent kidney stones. Patients with primary hyperoxaluria (PH), cystinuria, adenine phosphoribosyltransferase deficiency (dihydroxyadeninuria [DMA]), and Dent disease experience stones beginning in childhood. All patients with hereditary nephrolithiasis and kidney failure experience deposition of crystals in kidney tissue and loss of kidney function. Disease expression varies widely. Some PH patients progress to end-stage renal failure during infancy. Progress toward effective treatment has been slow.

Porphyrias: Porphyrias are a group of inherited metabolic disorders that arise as a result of a malfunction in one of the eight steps in the body's synthesis of a complex molecule called "heme," which is essential for the transport of oxygen to cells in the body. A common feature of all porphyrias is the accumulation in the body of porphyrins, chemicals that are normally present in the body but do not normally accumulate, or porphyrin precursors. The type of porphyria depends on which of these chemicals builds up. Symptoms include effects on the nervous system and burning, blistering, and scarring of sun-exposed areas of the skin.

Angelman, Rett, and Prader-Willi Syndromes: Angelman syndrome is a complex genetic disorder that primarily affects the nervous system and causes developmental delay, intellectual disabilities, severe speech impairment, seizures, small head size, and problems with movement and balance in young children. Rett syndromeis a childhood neurodevelopmental disorder characterized by normal early development followed by loss of purposeful use of the hands, distinctive hand movements, slowed brain and head growth, gait abnormalities, seizures, and intellectual disabilities. Prader-Willi Syndrome (PWS) is a rare genetic disorder that causes poor muscle tone, low levels of sex hormones, and a constant feeling of hunger.

Sterol and Isoprenoid Disease: Sterol and isoprenoid diseases are a group of rare diseases bound by common biochemistry and severe impact on health: cerebrotendinous xanthomatosis (CTX), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), Niemann-Pick disease type C (NPC), sitosterolemia, Sjogren-Larsson syndrome (SLS), and Smith-Lemli-Opitz syndrome (SLOS).

Salivary Gland Carcinomas: Salivary gland carcinomas are comprised of widely varied subtypes with different clinical behaviors and can result in disfigurement, death, or both. In general, salivary gland carcinomas afflict individuals later in life. The cause of salivary gland tumors remains unknown. Of the risk factors investigated, exposure to radiation has been the only known factor associated with salivary gland tumors. Individual differences in sensitivity to radiation have been implicated as an underlying cause for the development of these tumors.

Inherited Spinocerebellar Ataxias: Inherited forms of spinocerebellar ataxias 1, 2, 3, and 6 are a heterogeneous group of disorders characterized by degenerative symptoms in the cerebellum, spinal cord, and brain stem. Ataxia means “loss of the ability to coordinate muscular movement.” Degenerative ataxias show continuous worsening of the disease, leading to severe disability or death. Currently, there are no treatments for these disorders.

Neurologic Channelopathies: Nervous system channelopathies include episodic ataxias, non-dystrophic myotonic disorders, and Andersen-Tawil syndrome. The episodic ataxias are characterized by attacks of clumsiness and imbalance triggered by factors such as stress or fatigue. Episodic ataxia type 1 is characterized by episodes of imbalance with fine twitching or rippling of muscles, which is difficult to see except in small muscles of the hands and face. Episodic ataxia type 2 is characterized by episodes of slurring of speech, gait imbalance, and dysfunction of eye movements. The non-dystrophic myotonias are a very rare group of muscle disorders caused by abnormalities in different muscle cell membrane proteins. Patients experience impaired muscle relaxation that causes impaired physical activity, pain, and weakness. There are no proven therapies, and it is not known if treatment should differ for different disease subtypes. Andersen-Tawil syndrome is a rare form of periodic paralysis that affects the function of skeletal and heart muscles. Periodic paralysis is characterized by episodes of muscle weakness.

Respiratory Chain Mitochondrial Diseases: Mitochondrial diseases due to defects of the respiratory chain are clinically and genetically diverse; occur most often in infants, children, and young adults; and can be fatal. (Mitochondria are units within cells that generate its energy. The “respiratory chain” is the process by which mitochondria generate potential energy). Diagnosis of respiratory chain mitochondrial disease is difficult because of the broad variability in symptoms. Many of these diseases progress rapidly, and no treatments currently exist. The common link that these diseases share is the inability of the mitochondria to completely burn food and oxygen, a critical function for the mitochondria to generate the energy needed by cells to function properly. Mitochondrial impairment results in a host of devastating conditions, including respiratory chain diseases with complex clinical features, such as neurological and muscular dysfunction often accompanied by kidney dysfunction, hormone, cardiac, and liver complications.

More information on these rare diseases is available in the NIH Rare Diseases and Related Terms glossary at http://rarediseases.info.nih.gov/RareDiseaseList.aspx?PageID=1.

Burden of Illness

The burden of illness for all rare diseases is difficult to assess because of the large number of disorders, the complexity of each disease, and the limited availability of prevalence and incidence data. The National Organization for Rare Disorders (NORD) estimates that 25-30 million people in the United States have a rare disease.

Overall, rare diseases are devastating and costly. This is due partly because of their severity and partly because diagnosis can take a long time, often occurring well after symptoms have appeared. In addition, often treatment is not available once a disease is diagnosed. Moreover, scientists cannot assess the pain, suffering, and lost opportunities experienced by patients and their families.

The National Organization for Rare Disorders estimates that 25-30 million people in the United States have a rare disease.

Scope of NIH Activities: Research and Programmatic

The RDCRN brings together experts who are skilled in studying, diagnosing, and treating particular groups of rare diseases and who are eager to train junior faculty and postgraduate fellows. In addition, the network enables each consortium to gather groups of patients with similar or related disorders, fosters basic scientific investigation and longitudinal natural history and epidemiological studies, encourages synergy in translational research, and enhances opportunities for collaborative clinical investigation. The 2003-2008 DTCC and the current DMCC enable sharing of study results nationally and internationally in a timely and uniform way. Although the DMCC has primary responsibility for the coordination and management of data, participating RDCRN institutions, NIH program officers, and patient advocacy group representatives provide input and participate actively in overall data coordination.

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the RDCRN in FY 2008 was $10.2 million for 10 consortia and the DTCC. In FY 2009, actual funding for the 19 consortia and the DMCC was $23.4 million, including $2.1 million from ARRA funds. The total cost over 5 years for the RDCRN's Phase II is estimated to be $117 million.

FY 2008 and FY 2009 Progress Report

Programmatic and Research Activities and Outcomes

Throughout its first funding cycle, the RDCRN cumulatively enrolled more than 5,500 patients in 37 clinical studies. Patient recruitment for clinical studies is a fundamental challenge in rare diseases research because typically there are few affected patients in any one geographic area. The RDCRN is designed to address this problem by fostering collaboration among scientists and sites and shared access to geographically distributed research resources.

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The Coalition of Patient Advocacy Groups included representatives of 57 patient advocacy groups by late 2009. The coalition assists in many aspects of network research and publications. The protocols ranged from natural history studies to research on biomarkers, treatment efficacy, and genotype-phenotype correlations; genetic analyses; Phase I and II clinical trials; and pilot projects.

The Rare Diseases Clinical Research Network benefits from a coalition of patient advocacy groups that grew to 57 in 2009. The coalition assists in many aspects of network research and the development of educational materials.

The RDCRN is unique in its approach to addressing rare diseases as a group. Previously, the NIH ICs funded research on individual rare diseases in their respective disease-type or organ domain. The network established a comprehensive training program for clinical investigators and developed a network-wide website to inform the public, physicians, patients, and investigators about the rare diseases under study. The network's aims continue to include training a cadre of young investigators in the clinical, pathophysiologic (physiological process associated with disease), and pharmacologic aspects of specific rare diseases. The network's training includes instruction on and experience with methodologies for patient-oriented clinical research in rare diseases, including biostatistics and epidemiology; and the conceptualization, ethics, design, implementation, analysis, and reporting of controlled clinical trials. An integrated training program provides supervision by clinicians and biostatisticians with extensive experience in investigating rare diseases and developing novel therapies. The training program also provides an integrated statistics, epidemiology, and computer science curriculum; seminars on clinical trial design; courses in the basic sciences underlying experimental therapeutics and in ethics; career development support; participation and collaboration with network faculty with expertise in designing rare diseases studies; clinical experience in intensively investigating disease states; and mentoring to achieve an independent academic career in rare diseases.

The Data and Technology Coordinating Center created a central public website, developed as a portal for the rare diseases community, including patients and their families and health care professionals. The website provides information on rare diseases research, consortium activities, approved protocols, disease information, and practice guidelines. The website had more than 3.4 million visits in 2008.

The RDCRN is the first program that aims to create a specialized infrastructure to support rare diseases research. The DTCC developed and enabled new technologies, tools, and services for the network. These tools and services included electronic data entry, remote direct laboratory transfer, vocabulary and laboratory standards, statistical support, website development and maintenance, and database-querying tools. The DTCC, in collaboration with each consortium, also implemented an effective patient contact registry that allows individuals to register to receive information about new or ongoing clinical studies in addition to periodic educational updates and to consider participating in clinical studies. To facilitate patients' transportation to RDCRN sites, Angelflight NIH links patients with volunteer pilots who donate their time, planes, fuel, and operating expenses to transport patients and family members free of charge. By accepting donated frequent flyer miles, Angelflight also provides free tickets from select commercial airlines. The goal of the program is to ensure that no patient is denied access to medical evaluation or ongoing research projects because of a lack of air transportation.

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

In 2008, ORDR and participating NIH program staff reviewed the RDCRN's progress before publishing two RFAs. As a result of this review, ORDR staff decided to open the RFAs to the incumbent consortia and the DTCC as well as to new applicants. Some consortia were not renewed and many new consortia were added to the network.

ORDR and NCRR convened a workshop on July 16, 2009, titled "Advancing Rare Diseases Research through Networks and Collaboration." The workshop featured several speakers from the RDCRN and addressed the advantages and occasional disadvantages of multicenter collaborations in rare diseases research, trainee experiences, patient recruitment, outreach and dissemination, strategies for forming effective teams and networks, the interplay of basic and clinical research in the translation process, and the application of clinical research findings to clinical practice. Suggestions for improvements from workshop speakers included further increasing the number of sites in each consortium, even if this increase could result in fewer participants per site, and including more biostatisticians with expertise in small patient

populations early in protocol development at participating institutions in addition to central technical support from the DMCC.

Evaluation Plans

Because the RDCRN has been in operation only since 2003, it has not yet been formally evaluated to assess the impact of its research and training activities. Until that is possible, NIH will continue to regularly review RDCRN performance via scrutiny of progress reports, site visits, and program reviews.

When the RDCRN's impact on research and its contribution to rare diseases treatment is more mature and measurable, the RDCRN's contribution to the health of the Nation will be determined using the following criteria:

- Study completion and outcomes
- Timely recruitment of adequate patient populations
- Number of trainees who complete their training programs
- Trainees' impact on the rare disease field
- Impact of scientific publications on future rare diseases research

Contribution of the DTCC and subsequent DMCC to research in the form of a coordinated data management system; the ability to capture and integrate many different types of data; and the development and broad acceptance of novel technological approaches to distributed computing, federated databases, and data mining within and across diseases.

Future Directions

ORDR and its partner Institutes will continue to work with the RDCRN and encourage the continued training of new rare diseases researchers. The current consortia and the DMCC will build on the experience and lessons learned in the program's previous years. ORDR hopes that in response to the recommendations of the 1999 NIH Special Emphasis Panel on the Coordination of Rare Diseases Research, the numbers of consortia, sites in each consortium, trainees, and patients served will continue to increase in the United States and in other countries. As a result, patients and their families will be able to look forward to better treatments and cures, improving the duration and quality of their lives.

Table 4-5. Rare Diseases Clinical Research Network

Institution and Location	Year Established
Boston University School of Medicine, Boston, MA	2003
Children's National Medical Center, Children's Research Institute, UCDC, Washington DC	2003
University of Alabama at Birmingham, AL (previously Baylor College of Medicine, Houston, TX)	2003
University of Rochester, NY	2003
University of South Florida, Tampa, FL (DMCC)	2003
University of North Carolina, Chapel Hill, NC	2004
Columbia University Medical Center, New York, NY	2009
Emory University, Atlanta, GA	2009
Fred Hutchinson Cancer Research Center, Seattle, WA	2009

Institution and Location	Year Established
Mayo Clinic College of Medicine, Rochester, MN	2009
Mount Sinai School of Medicine of NYU, New York, NY	2009
Oregon Health and Sciences University, Portland, OR	2009
University of California, San Francisco, CA	2009
University of Florida, Gainesville, FL	2009
University of Michigan at Ann Arbor, MI	2009
University of Minnesota Twin Cities, Minneapolis-St. Paul, MN	2009
University of Texas MD Anderson Cancer Center, Houston, TX	2009
Vanderbilt University Medical Center, Nashville, TN	2009
Wayne State University, Detroit, MI	2009

Autism Centers of Excellence

Overview

Why the Autism Centers of Excellence Were Established

Recent studies suggest that autism spectrum disorders (ASD) affect approximately 1 in 110 children in the United States.[48] 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. This Act emphasized the need to expand research and improve coordination among NIH Centers of Excellence focused on ASD. The new Autism Centers of Excellence (ACE) program, the funding of which began in FY 2007 and FY 2008, focuses on identifying the causes of ASD and developing new and improved treatments.

In response to the Combating Autism Act, the NIH Autism Coordinating Committee (ACC) formed the ACE program by consolidating the aims of two previous ASD research programs into a single research effort (see Table 4-6). The previous programs were the Collaborative Programs of Excellence in Autism (CPEA, established in 1997) and Studies to Advance Autism Research and Treatment (STAART, established in 2002 and completed in 2008). This report will focus mainly on the goals, activities, and accomplishments of the ACE program. The ACC itself also was formed at the request of Congress and comprises representatives from five ICs.

How the Autism Centers of Excellence Function within the NIH Framework

The Children's Health Act of 2000 established the Interagency Autism Coordinating Committee (IACC), which includes Federal agency representatives and members of the public appointed by the Secretary of HHS. At the request of Congress, the IACC developed an Autism Research Matrix. The matrix delineated goals and action items in epidemiology, the characterization of ASD, the role of the environment, neuroscience, screening, early intervention, specific treatments, and school and community interventions, to guide NIH-funded ASD research. ACE grantees are addressing the matrix goals, particularly the goals of identifying the causes of ASD and developing treatments.

The NIH ACC established the goals of the ACE program, and the NIH ICs share administrative and oversight responsibilities. The ACE program comprises centers and a network infrastructure. ACE centers foster multidisciplinary collaboration among teams of specialists at a single facility to address a particular research problem in depth. Each center conducts interdependent sub-projects. ACE networks unite researchers at many different facilities throughout the country; working as a unit, each network addresses a single research question. Because networks encompass multiple sites, they can recruit large numbers of participants with ASD, achieving optimal design for treatment trials. A program officer and grants management officer at the awarding NIH Institute administer each ACE award.

The Combating Autism Act of 2006 expanded the scope of the IACC. In accordance with the new law, the IACC develops and updates annually a strategic plan for ASD research and a summary of ASD research advances. The IACC also monitors and makes recommendations about Federal ASD-related activities. The priorities and progress of the ACE program will be an integral component of these annual activities.

In January 2009, the Interagency Autism Coordinating Committee released the first edition of its Strategic Plan for Autism Spectrum Disorder Research. Consistent with the Strategic Plan, the six ACE centers and five networks that comprise the ACE program have begun research on biomarkers, genetic susceptibility to ASD, pharmacological treatments, early intervention, and risk and protective factors for ASD.

In January 2009, the IACC released the first edition of its Strategic Plan for Autism Spectrum Disorder Research. The Strategic Plan advises Federal agencies and Congress on needs and opportunities in ASD research. The scientific

community, service providers, advocates, parents, and people with ASD contributed to the Plan. The Plan has six sections focused on six critical questions asked by people and families living with ASD:

- When should I be concerned?
- How can I understand what is happening?
- What caused this to happen and can this be prevented?
- Which treatments and interventions will help?
- Where can I turn for services?
- What does the future hold?

The NIH ACC plays an integral role in coordinating NIH activities inspired by and relevant to the Strategic Plan. Consistent with the Strategic Plan, the six ACE centers and five networks that comprise the ACE program have begun research on biomarkers, genetic susceptibility to ASD, pharmacological treatments, early intervention, and risk and protective factors for ASD.

Description of Disease or Condition

Leo Kanner first described autism in 1943 as a disorder "characterized by extreme aloneness and a desire for the preservation of sameness, with a variety of behavioral (cognitive, affective) symptoms derived from them."[49] Over time, growing recognition of a broader range of related disorders led to the use of the term autism spectrum disorders (ASD), which includes several complex neurodevelopmental disorders of early childhood that vary in severity, share common clinical features, and persist throughout the lifetime of the individual. Common features include social impairments; verbal and nonverbal communication difficulties; and restricted, repetitive, and stereotyped behavior patterns. "Classic" autistic disorder is the most disabling; other forms of ASD, such as Asperger's disorder, have fewer or milder symptoms. Intellectual disabilities, seizures, and self-abusive behaviors are common among children at the more severe end of the spectrum.

A child's primary caregivers often are the first to identify ASD symptoms. As early as infancy, a baby with ASD may be unresponsive to people or focus intently on one item to the exclusion of others for long periods. A child with ASD may appear to develop normally and then withdraw and become indifferent to social engagement. Clinicians can make a reliable ASD diagnosis for most children by age 3. The current ASD diagnostic criteria and classifications represent progress in identifying a core set of developmental symptoms that, in the past, clinicians might have 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, no coherent and comprehensive system of care is available for affected individuals. People with ASD might receive private and public services in special education settings, hospitals, university medical centers, or residential treatment facilities, among others.

Some scientists and economists have estimated that the combined direct and indirect costs of providing care for all Americans with ASD during their lifetimes exceed $34 billion. The estimated costs over a lifetime for each person total $3 million.

Some scientists and economists have estimated that the combined direct and indirect costs of providing care for all Americans with ASD during their lifetimes exceed $34 billion. The estimated costs over a lifetime for each person total $3 million.[50] Families often incur large debts for medical and education services that public programs or medical insurance do not cover. In addition, autism often leads to profound emotional hardships for patients and their families.

CDC currently estimates that as many as 9.0 per 1,000 children have an ASD.[51] The total number of individuals in the United States with an ASD diagnosis is unknown. However, CDC estimates that up to 730,000 individuals age 21 or younger have an ASD (assuming a prevalence rate of 1 in 110, a birth rate of 4 million children per year in the United States, and a constant prevalence rate over the past 20 years). Boys are approximately four times as likely as girls are to have an ASD.[52]

Prevalence estimates, or the number of affected individuals at a given point in time, have increased markedly since the early 1990s. However, it is unclear if incidence, the number of new cases across time in the same population, also has increased. It also is unclear whether the rise in prevalence is due to such factors as the use of different criteria to diagnose ASD or earlier and more accurate ASD diagnoses. A similar increase in ASD prevalence has occurred in other countries.

Scope of NIH Activities: Research and Programmatic

The six centers and five networks that compose the ACE program cover a broad range of ASD research areas, including early brain development and functioning, social interactions in infants, rare genetic variants and mutations, associations between autism-related genes and physical traits, possible environmental risk factors and biomarkers, and a potential new treatment.

In the past, ASD researchers collected clinical data using different formats and analysis methods and stored data in different locations. This approach made comparing data from different sites difficult. ASD researchers now can use the National Database for Autism Research to gather and analyze data.

In the past, ASD researchers collected clinical data using different formats and analysis methods and stored data in different locations. This approach made comparing data from different sites difficult. ASD researchers now can use the National Database for Autism Research (NDAR), a common bioinformatics system, to gather and analyze data from human subjects. The NDAR has built on the collaborative aspects of the STAART data coordinating center and makes gathering, evaluating, and sharing ASD research data from a variety of sources easier and faster for researchers. NDAR allows the seamless integration of data, research tools, and research projects from institutions across the United States and internationally.

All ACE centers and networks are contributing data to NDAR. In addition, efforts to add data from the STAART data coordinating center are underway. NDAR also will coordinate data access with other Federal databases, such as the NIMH Center for Collaborative Genetic Studies. The center is a national resource for researchers who study the genetics of complex mental disorders, including ASD, and stores human DNA, cell cultures, and clinical data.

NIH Funding for FY 2008 and FY 2009

Three NIH ICs fund the ACE program—NICHD, NINDS, and NIMH. Actual NIH funding for the ACE program, which includes centers (P50s), a cooperative agreement (U01), and networks (R01s), was $25.2 million in FY 2008 and $26.5 million in FY 2009, including $1.89 million from ARRA funds.

FY 2008 and FY 2009 Progress Report

Programmatic and Research Activities and Outcomes

Several accomplishments of the ACE program and one of the STAART centers (funded through 2008) are highlighted briefly below.

- Researchers at **Yale University** are searching for biomarkers of visual engagement and auditory perception in infants at risk for ASD.

- Researchers at the **University of Illinois at Chicago** are studying genetic factors as well as brain chemicals and brain functions that could account for repetitive behaviors in people with ASD. They also are testing whether genetic differences influence how individuals respond to certain medications intended to reduce the frequency of these behaviors.
- Researchers at the **University of Washington** are investigating genetic and other factors that might increase a person's risk of having an ASD and factors that might protect people from getting an ASD.
- Investigators involved in the **University of North Carolina at Chapel Hill** ACE network are studying abnormal processes in early brain development by examining brain images of very young children at risk for developing ASD.
- The **University of California, San Diego,** ACE is using brain imaging methods to track brain development in children believed to be at risk for ASD. The researchers aim to identify brain or other physical differences that might increase a child's risk of developing ASD.
- Researchers at the **University of California, Los Angeles,** are determining the causes and treatments of social communication problems in people with ASD.
- The **University of Pittsburgh** ACE is studying how people with ASD learn and understand information.
- Researchers at the **Drexel University** network sites are studying possible risk factors and biological indicators of ASD before and soon after birth. This project is part of the Early Autism Risk Longitudinal Investigation (EARLI).

Researchers at the Drexel University network sites are studying possible risk factors and biological indicators of ASD before and soon after birth. This project is part of the Early Autism Risk Longitudinal Investigation (EARLI).

- Researchers at the **University of California, Davis,** network sites are examining factors that might be useful for improving treatment outcomes in very young children with autism. They are comparing an intensive behavioral intervention to standard community-based treatment.
- Investigators at **Wayne State University** network sites will conduct a clinical trial to test the safety and efficacy of buspirone, a drug that increases the body's production of serotonin—one of several neurotransmitters that brain cells use to communicate with each other—as an early intervention in children younger than 6 years with ASD. A pilot study by the Wayne State researchers showed that buspirone improves social interaction and reduces repetitive behaviors, sensory dysfunction (extreme sensitivity or lack of sensitivity to light, noise, and touch), and anxiety in children with autism.

Investigators at Wayne State University network sites will conduct a clinical trial to test the safety and efficacy of buspirone, a drug that increases the body's production of serotonin—one of several neurotransmitters that brain cells use to communicate with each other—as an early intervention in children younger than 6 years with ASD.

- Researchers at the **University of California, Los Angeles,** network sites are studying the relationship between genes related to autism and physical features. They also are investigating rare genetic variations, mutations, and abnormalities that affect a person's risk for autism.
- In three separate studies of genetic risk factors linked to ASD, **STAART investigators, ACE investigators, and other collaborators** identified common and rare genetic factors that affect ASD risk. The results point to genes that are involved in forming and maintaining the connections between brain cells. These results confirm previous findings on the role of genes in ASD and abnormal brain wiring in people with ASD. The study findings are a significant step forward in a larger effort to understand the complex genetic architecture of ASD. The investigators recently published their findings in the journals *Nature*[53, 54] and *Annals of Human Genetics*.[55]
- **STAART investigators** collaborated in a multisite study to evaluate the efficacy of a drug, citalopram, to treat ASD symptoms. Citalopram selectively can inhibit the activity of serotonin, which might play a role in the repetitive behaviors associated with autism. The researchers recently published their results in the *Archives of General Psychiatry*.[56] After 12 weeks of treatment, roughly one out of three children in both the group that took citalopram and the group that took a placebo (medicine with no active ingredients) had fewer or less severe repetitive symptoms. However, the children in the citalopram group experienced more adverse side effects than the children in the placebo group. According to the researchers, the study results show that the drug is no better than placebo in treating ASD symptoms.

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

Evaluation Plans

The Combating Autism Act of 2006 and the NIH Reform Act of 2006 require NIH to evaluate the performance and research outcomes of the ACE program. In 2008, NIH established a trans-NIH evaluation team to conduct the first evaluation, which will gather baseline, descriptive data on the implementation of the program. The evaluation will use a two-part approach, focusing on process evaluation questions related to program implementation and determining the feasibility of future evaluation efforts to assess the outcomes of the ACE program.

In 2010, HHS will provide Congress with a progress report on activities related to ASD that will include results from the initial ACE program evaluation. The report also will discuss the incidence of ASD, average age at diagnosis, average age of intervention start, effectiveness and outcomes of interventions by subtype, and effectiveness and outcomes of newly developed intervention strategies.

Future Directions

In 2010, the NIH ACC plans to convene a 2-day meeting at which the investigators will present the goals of their ACE and exchange ideas for collaborations. Some sessions will address data sharing options through the NDAR, with time allotted for a question-and-answer period with NDAR staff. ACE principal investigators and project principal investigators, as well as core directors and data managers, will be invited to attend. Principal investigators will be encouraged to invite K award (career development grant) recipients, fellows, and postdoctoral students from their laboratories. Approximately 55 to 65 ACE investigators are expected to attend this meeting, which will take place annually thereafter.

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 (ACEs)

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
Yale University, New Haven, CT	2008
Wayne State University, Detroit, MI	2008
University of California, Los Angeles, CA	2008
Drexel University, Philadelphia, PA	2008

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