



**Testimony before the
Subcommittee on Health
Committee on Energy and Commerce
United States House of Representatives**

Alzheimer's Disease: Ongoing Challenges

Statement of
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Good morning, Chairman Pallone and Distinguished Members of the Subcommittee:

Thank you for inviting me to appear before you today to discuss Alzheimer's disease, a devastating disorder with a profound impact on individuals, families, the health care system, and society as a whole. I am Dr. Marcelle Morrison-Bogorad, and for fourteen years I have been Director of the Division of Neuroscience at the National Institute on Aging (NIA), a part of the National Institutes of Health and the lead federal agency for Alzheimer's disease research. I am delighted to be here today to tell you about the progress we are making, in partnership with the research and advocacy communities, regulatory bodies and industry, toward understanding, treating, and preventing Alzheimer's disease.

We humans have created our complex societies not because we have bigger hearts or hands, but because we have bigger and more complex brains. Our intelligence has allowed us to create conditions that enable most of us to live longer lives. These added years bring enormous opportunity and richness to our lives. But at the same time, advancing age brings us face to face with a growing burden of chronic, age-related diseases, including Alzheimer's disease.

Alzheimer's disease is a major public health issue for the United States. Today, it is estimated that 2.4 million¹ to 5.1 million² people in the United States have Alzheimer's disease. While estimates vary, depending on how dementia is measured, scientists agree that without breakthroughs in prevention or early treatment, the number of people with Alzheimer's will increase significantly as society ages. Studies suggest that the number of people with the disease doubles for every 5-year age interval beyond age 65, and the U.S. Census Bureau estimates that the 65-and older population will double to about 72 million during the next 20 years, starting with the oldest "baby boomers" who will turn 65 in 2011. The ranks of the very elderly, those 85 years old and older and at the highest risk of developing Alzheimer's disease, will increase even

¹ Plassman BL, Langa KM, Fischer GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Willis RJ, Wallace RB. Prevalence of dementia in the United States: the Aging, Demographics, and Memory Study. *Neuroepidemiology* 2007;29(1-2):125-132.

² Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Archives of Neurology* 2003;60(8):1119-1122.

more rapidly, potentially tripling their numbers by 2050. At the same time, the relatively small size of the “Generation X” cohort that follows the baby boomers may lead to a decrease in the number of potential caregivers by 2050, indicating that a higher share of the caregiving burden may need to be assumed by the health care system.

The staggering complexity of the brain and our incomplete understanding of fundamental aging mechanisms have made seeking a cure for Alzheimer’s disease in our older population a difficult task indeed. We know vastly more than we did even five years ago, but, if we have learned one thing, it is just how complex a disease Alzheimer’s is. I can report to you today, however, even amid such challenges, that we have made and are continuing to make dramatic gains in our ability to understand, diagnose, and treat Alzheimer’s disease, progress that offers us the hope of reversing current trends.

What has brought us to this point is a sustained research program employing different approaches to the research challenge. This can involve the support of individual investigators who have a particular research theory or larger scale studies employing the newest technologies to mine extensive data sets to find genes or risk factors related to Alzheimer’s disease. Some research questions, for example, are straightforward and can be pursued with relatively small grants. One recent finding, as a case in point, suggests that a genetic mutation may be involved in impairing the ability of neurons to break down and re-use helpful proteins, as well as compromising efforts to clear away harmful waste proteins and other debris; the insight helps tell us what may underlie the pathology of one of the mutations responsible for early onset Alzheimer’s, and that perhaps also may contribute to late onset disease. Ultimately, this information will allow us to design interventions that may prevent or reverse the processes that underlie disease.

NIA also encourages and engages in partnerships to create synergy and leverage resources within and among scientists, institutions and organizations. NIH-supported investigators often combine their expertise through Program Project Grants, in which a number of collaborators with different skills work together on a common problem. Investigators on one NIA-supported Program Project have worked together to show that around 20 percent of older

adults who are functioning normally have Alzheimer's characteristic amyloid plaques in their brains, and that many have subtle cognitive and brain changes typical of a person with the disease. Today, we are supporting long-term follow up studies of these individuals: How many of them will develop Alzheimer's disease? And when? And how are they able to function with levels of amyloid plaques in their brains that correlate with diagnosis of the disease in other individuals?

In further support of collaborative research, NIA facilitates and participates in a number of strategic partnerships. The largest public-private partnership in Alzheimer's research is the Alzheimer's Disease Neuroimaging Initiative (ADNI), testing whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI), often a precursor condition to Alzheimer's disease, and early onset of the disease, as well as to measure more accurately the effectiveness of potential therapies. NIA's partners in this groundbreaking endeavor include a number of other NIH Institutes (National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, National Institute of Nursing Research, National Institute on Drug Abuse, National Institute for Research Resources, and the National Institute of Biomedical Imaging and Bioengineering), pharmaceutical and diagnostic companies, and manufacturers of imaging equipment, as well as non-profit organizations and foundations, with important participation from the U.S. Food and Drug Administration. The partnership with private sector is managed by the Foundation for NIH, which Congress authorized several years ago to encourage and facilitate such projects.

Using imaging techniques and biomarker measures in blood and cerebrospinal fluid (CSF), ADNI investigators have already established a method and standards for testing the levels of AD's characteristic *tau* and beta-amyloid proteins in the CSF, have correlated levels of these proteins with changes in cognition over time, and have determined that changes in these two protein levels in the CSF may signal the onset of mild Alzheimer's. Last year, funding under the American Recovery and Reinvestment Act expanded the scope of the original ADNI research by allowing enrollment of participants at an even earlier stage of MCI, when symptoms are less severe, and this year the ADNI 2 was funded to enroll a new cohort of participants and expand

on the collection of biological measures. ADNI data are freely available on line, and over 170 papers worldwide have been published using ADNI data. ADNI's success has fueled similar studies in a number of other countries.

A high priority for the NIH is the identification of possible risk and protective factors for cognitive impairment and dementia. One approach encourages and supports use of national surveys of health and well-being to learn more about not only disease risk, but effects on families, use of health care services, and more. For example, investigators with the long-running Health and Retirement Study, the nation's leading source of combined data on health and financial circumstances of Americans over age 50, collect data on the cognitive health of older Americans. NIA also works with the U.S. Census Bureau and the Federal Forum on Aging Related Statistics to coordinate data collection in the area of cognitive impairment and dementia.

In recent years, there has been an explosion of knowledge from large-scale efforts, particularly in providing new clues about risk factor genes and possible environmental and lifestyle factors involved in Alzheimer's disease and cognitive impairment. Identifying risk factor genes pinpoints the brain pathways that are involved in the initiation of disease pathologies, and provides novel avenues for drug targeting. Until recently only one risk factor gene for late-onset Alzheimer's – the $\epsilon 4$ allele of the APOE gene – had been validated. The advent of new technologies to find risk factor genes necessitated the identification of thousands of patients and controls for testing – far too many for any one investigator to assemble – so we asked researchers in the genetics community to form a consortium and pool resources to find the remaining genes. The Alzheimer's Disease Genetics Consortium was funded last year, and in just one year, affiliated researchers have identified and confirmed an astonishing four additional risk factor genes. These investigators have gone on to form an international consortium with members of the European Union, an interaction facilitated by funding from the Alzheimer's Association, which will expand the pool of participants even further and facilitate even more rapid discovery of the remaining Alzheimer's genes. As with all our large studies, the data will be made broadly available to the scientific community.

A related area in which extensive scientific collaboration has been invaluable has been the study of families who are genetically predisposed to develop Alzheimer's disease in early to middle age. Such early-onset disease is rare, and individual investigators usually cannot identify enough individuals to study by themselves. NIA therefore established the Dominantly Inherited Alzheimer's Network (DIAN), a consortium of scientific investigators to identify, recruit, evaluate, and follow up individuals from families beset by early onset dominantly inherited Alzheimer's disease. The scientists involved in this study hope to identify the sequence of brain changes in early-onset Alzheimer's before symptoms appear. Understanding this process could provide insight as well into the more common late-onset form of the disease. Eventually, the investigators intend to conduct a clinical trial in this group. DIAN includes a number of sites in the United States as well as in England, and Australia.

As basic knowledge accumulates, it is critical to apply what we have learned, as quickly as possible, to the ultimate goal – the development of interventions and therapies to treat or prevent Alzheimer's disease. NIA has a longstanding interest and commitment to translational research, and efforts shifted into high gear in 2004 when NIA launched a set of initiatives focused on supporting early drug discovery and preclinical drug development of novel compounds for Alzheimer's therapy. The goal of this translational program is to increase the number of investigational new drugs that can be then clinically developed either by the pharmaceutical industry or through publicly-supported clinical trials. In addition, the program supports the repurposing and reformulation of existing drugs, already approved for other disease conditions such as antihypertensive drugs, as well as the preclinical development of naturally occurring compounds. To date, these translational initiatives have supported more than 60 projects aimed at discovering and developing novel compounds for more than a dozen different therapeutic targets such as amyloid, tau, various neurotransmitter and growth factor receptors, inflammation, ApoE, and more. NIA also co-funds a number of aspects of preclinical development for Alzheimer's disease through the trans-NIH Rapid Access to Interventional Development (NIH-RAID) Program (<http://nihroadmap.nih.gov/raid/>).

To support the extensive research efforts needed to understand the disease process and to test possible interventions, the NIA has organized institutions and studies to facilitate research

and collaboration. The 29 NIA-supported Alzheimer's Disease Centers (ADCs) across the U.S., are an invaluable resource and the source of many fundamental discoveries about Alzheimer's. These Centers combine the expertise of clinicians, pathologists, and many other scientists for studies across the research spectrum, from the longitudinal study of cognitively normal individuals and those in the early stages of disease to the clinicopathological study of their brains after death. The ADCs have provided essential resource and infrastructure support to efforts as diverse as clinical trials and ADNI. To maximize the combined efforts of the ADCs, NIA supports the National Alzheimer's Coordinating Center, which has made possible many new studies incorporating data from tens of thousands of participants seen annually from across the country, and additionally has provided essential infrastructure for DNA collection from Center participants for the Alzheimer's Disease Genetics Initiative. Data and biological samples are shared with scientists not in the Center network.

Many clinical studies collect data on aspects of neurological and behavioral function, but the fact that different studies may not employ the same tests or agree on methodologies can make it difficult to compile data across the full range of normal neurological function, and to compare data across studies. Through the support of the NIH Blueprint for Neuroscience and the NIH Opportunity Network for Research in the Basic Behavioral and Social Sciences, a brief yet comprehensive measurement tool for assessment of cognitive, emotional, sensory and motor function is being developed. Known as the NIH Toolbox for Assessment of Neurological and Behavioral Function, these measures can be used to uniformly assess cognitive performance and to track changes in performance across the lifespan. In addition, NIA is currently partnering with the Alzheimer's Association to update the diagnostic criteria for Alzheimer's disease for the first time in 25 years. The new criteria, to be applied primarily in a research setting where they can be validated, will incorporate knowledge gained over a quarter-century of research, including the role of biomarkers in Alzheimer's dementia diagnosis.

To assess the state of knowledge in developing interventions to prevent Alzheimer's disease the NIH last April convened the collaborative State of the Science Conference on Preventing Alzheimer's Disease and Cognitive Decline . The expert panel – not experts in Alzheimer's research but experts in other aspects of biomedical research and caregiving – noted

that research is providing some important clues, but concluded that no interventions to prevent or delay the onset of age-related cognitive decline or Alzheimer's disease have been scientifically validated. The conference was convened by NIH in collaboration with HHS's Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, and the Centers for Medicare and Medicaid Services.

NIA already has studies underway in a number of areas highlighted by the panel as areas in need of additional research. Several seek to determine whether behavioral interventions such as exercise or cognitive training might stem the development or progression of age-related cognitive decline or Alzheimer's disease. We know that exercise for example is good for healthy aging in a variety of ways, and observational studies and some short-term clinical trials have suggested that it might be beneficial in delaying the symptoms or preventing dementia or cognitive decline. Testing whether it may have an effect on Alzheimer's is very important. One very large clinical trial, the Lifestyle Interventions and Independence for Elders (LIFE), aims to determine whether a specific regimen of exercise reduces disability in the elderly, and a cognitive component to that study has been designed to determine whether exercise affects cognitive decline or development of Alzheimer's.

The major clinical trial programs sponsored by NIA are the Alzheimer's Disease Cooperative Study (ADCS) and the pilot clinical trials initiative. These programs are in addition to continued support of investigator initiated clinical trials for Alzheimer's, MCI and age-related cognitive decline. The ADCS, a large clinical trials consortium with sites throughout the US and Canada, is a major initiative for Alzheimer's disease clinical trials in the Federal Government, addressing treatments for both cognitive and behavioral symptoms. The ADCS mission is to advance research in the development of clinical trial designs, instruments, and interventions that might be useful for treating patients with Alzheimer's disease, particularly interventions that might not be developed by industry.

NIA currently supports over 60 clinical trials targeting aspects of Alzheimer's disease and cognitive decline, including those being conducted by the ADCS. Both pilot and large scale trials are being undertaken, addressing a wide range of interventions to prevent, slow, or treat

Alzheimer's and/or cognitive decline or to address behavioral problems in person with the disease. Experts in the field are coming to believe it likely that any treatment will be more effective if started before the disease takes hold, and so there is a particular emphasis on prevention trials in presymptomatic individuals using biomarkers identified through ADNI (or elsewhere, as appropriate). However, prevention clinical trials are very expensive. To optimize efficiency and pool resources, we collaborate with other NIH Institutes to incorporate cognitive endpoints into relevant existing and planned trials. One such study is the National Heart, Lung, and Blood Institute's (NHLBI's) Systolic Blood Pressure Intervention Trial (SPRINT), which will evaluate the health effects of lowering systolic blood pressure either to a target level of 140 or to a target level of 120. The add-on study, SPRINT-MIND, is funded by NIA and the National Institute of Neurological Disorders and Stroke (NINDS) and will assess the effect of lowering systolic blood pressure on cognitive decline and development of MCI and Alzheimer's disease. The study will also include brain imaging to measure treatment effects on brain structure, including white matter lesions typical of vascular disease. In partnership with the Food and Drug Administration, NIA also maintains the Alzheimer's Disease Clinical Trials Database, which provides information about Alzheimer's disease clinical trials at sites throughout the U.S.

Finally, a number of studies have demonstrated that the chronic stresses of caring for a family member with dementia can cause lasting psychological and even physical consequences, and NIA works extensively with other agencies on interventions to meet the needs of Alzheimer's caregivers. An initiative with the National Institute of Nursing Research, Resources for Enhancing Alzheimer's Caregiver Health (REACH), has shown that a personalized intervention consisting of home visits, structured telephone support sessions, and telephone "check-ins" can significantly improve the quality of life for caregivers of people with Alzheimer's disease. The REACH intervention is currently being translated more broadly through a partnership between the Veterans Health Administration Geriatrics and Extended Care Unit and the Memphis VA Medical Center, with participating centers in 15 states. The Administration on Aging is also implementing the REACH intervention at centers in Georgia, North Carolina, and Florida.

A core part of NIA's mission is to disseminate information about research, aging and health to a variety of audiences. The NIA-sponsored Alzheimer's Disease Education and Referral Center (ADEAR) is the Federal government's leading source of evidence-based information about Alzheimer's disease and age-related cognitive change, providing resources to older people and their families, health professionals, and the general public. The Institute offers free publications and online materials about the disease and caregiving, a toll free telephone number for seniors and others without web access, details about clinical trials on Alzheimer's disease and a library for experts working with Alzheimer's patients. (ADEAR is located at www.nia.nih.gov/alzheimers and at 1-800-438-4380.)

It is difficult to predict the pace of science or to know with certainty what the future will bring. However, the progress we have already made will help us speed the pace of discovery, unravel the mysteries of Alzheimer's disease's pathology, and develop safe, effective preventions and treatments, to the benefit of older Americans.

Thank you for giving me this opportunity to share with you the challenges and accelerating progress regarding Alzheimer's disease research. I would be happy to answer any questions you may have.