

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Taking a Toll on Families and the Economy: The Rising Cost of Alzheimer's in America

Witness appearing before the
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Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

Accompanied by:

Richard J. Hodes, M.D.
Director, National Institute on Aging

Story C. Landis, Ph.D.
Director, National Institute of Neurological Disorders and Stroke

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Good afternoon, Mr. Chairman and distinguished members of the Committee. I am Francis S. Collins, M.D., Ph.D., the Director of the National Institutes of Health (NIH). I have with me Story C. Landis, Ph.D., Director of the National Institute of Neurological Disorders and Stroke (NINDS), and Richard J. Hodes, M.D., Director of the National Institute on Aging (NIA). It is an honor to be here today to discuss NIH's efforts to stem the rising tide of Alzheimer's disease, a devastating condition and a public health issue of increasing relevance and urgency, both in the United States and globally.

First, however, I would like to thank you, Mr. Chairman, and Ranking Member Moran, as well as your colleagues on the Committee, for your unflagging championship of NIH's research mission, especially our research on Alzheimer's disease. I would particularly like to acknowledge the significant increase in funding that you have provided to NIH for FY14, in order to bolster our support for research on aging. I am happy to share with you some of our plans for these additional funds, as well as some exciting recent scientific discoveries and new initiatives.

The Growing Public Health Crisis

As all of us are only too well aware, Alzheimer's disease is a currently irreversible, progressive brain disease that slowly destroys memory and thinking skills and eventually even the ability to carry out the simplest tasks of daily living. In most people with Alzheimer's, symptoms first appear after age 60. While Alzheimer's disease is the most common cause of dementia among older people, other forms exist, including frontotemporal dementia, Lewy body dementia, and mixed and vascular dementias. Although treatment can help manage symptoms in some people, there is currently no cure for these devastating diseases.

As many as five million people age 65 and older suffer from Alzheimer's disease in the United States alone, and we expect these numbers to increase exponentially as the U.S. population continues to age. Globally, the statistics are truly dire: results of a recent meta-analysis suggest that 35.6 million people lived with dementia worldwide in 2010, with numbers expected to double almost every 20 years, to 65.7 million in 2030 and 115.4 million in 2050.

This disease is not just a burden on our health; it is also a burden on our economy. Recently, NIH-supported economists calculated that the costs in 2010 to the U.S. health care and long-term care systems for caring for people with Alzheimer's disease were between \$159 billion and \$215 billion, depending on how caregiver costs were assessed. The researchers estimated direct costs of dementia care purchased in the market in 2010 at \$109 billion. To place that figure in context, that same year, direct health costs for heart disease and cancer were estimated at \$102 billion and \$77 billion, respectively. And again, unless effective interventions are developed, those costs will rise dramatically with the increase in the numbers of senior citizens in coming decades.

An Explosion of Knowledge

The good news, in the face of these grim statistics, is that we have made tremendous strides in our understanding of the basic mechanisms of Alzheimer's disease within the last five years, and this new understanding has led to entirely new research paradigms: both for studying the disease in the laboratory and managing it in the clinic.

The first set of discoveries I'd like to discuss have to do with the genetics of Alzheimer's disease. Until 2009, only one genetic variant, APOE ϵ 4, had been shown to increase the risk of late-onset Alzheimer's disease. However, with the advent of genome wide association studies (GWAS) and other high throughput technologies, the list of known gene risk factors grew substantially over the next few years, and in 2013, the largest GWAS ever conducted identified a total of 11 genetic risk factors. The research conducted by the International Genomic Alzheimer's Project--a collaborative, international study supported in part by the NIH--strengthens evidence about the involvement of particular pathways in the disease, such as inflammation, lipid metabolism, and amyloid deposition, and also points to entirely new molecular pathways that were not known to be involved.

In the clinical arena, researchers – supported by a compelling body of NIH-supported research – have realized that the most effective way to treat and prevent Alzheimer's disease is to attack it early, before symptoms begin. Investigators discovered that higher amounts of brain beta-amyloid, the toxic protein that clogs the brains of Alzheimer's patients and is associated with memory loss and other symptoms, is related to an increased risk of developing dementia over time and to loss of brain volume and subtle declines in cognitive abilities. These findings suggest that brain beta-amyloid may in fact be a preclinical sign of disease even among individuals who appear cognitively normal.

In parallel, NIH-supported investigators with the Alzheimer's Disease Neuroimaging Initiative (ADNI) established a method and standards for testing levels of beta-amyloid and tau, another known biomarker for Alzheimer's disease, in the cerebrospinal fluid (CSF). They correlated levels of these proteins in the CSF with changes in cognition over time and determined that changes in these two protein levels in the CSF may precede the onset of the disease.

In 2011, these findings made possible the first revision of the clinical diagnostic criteria for Alzheimer's disease in 27 years through a joint effort of the NIA and the Alzheimer's Association. Unlike the previous criteria, the updated criteria cover the disease as it gradually progresses over many years, from the earliest preclinical, pre-symptomatic phase through mild cognitive impairment (MCI) to advanced dementia. The new guidelines also address the use of imaging and biomarkers to determine whether changes in the brain and body fluids are due to Alzheimer's. A separate update addresses diagnosis at autopsy, to help neuropathologists

characterize Alzheimer's-related brain changes at death in people who have been diagnosed with dementia and those who have not yet shown clinical symptoms, taking into account that the disease process may begin a decade or two before outward signs like memory loss appear.

Recognizing the devastating impact of Alzheimer's disease and Alzheimer's Disease-Related Dementias, or ADRDs, on patients and families, and also recognizing that the time is right – from both a scientific and a public health standpoint – to move aggressively toward the development of new and effective treatments for Alzheimer's and ADRDs, President Obama signed the National Alzheimer's Project Act (NAPA) into law on January 4, 2011. NAPA requires the HHS Secretary to:

- Create and maintain an integrated national plan to overcome Alzheimer's disease and related dementias
- Coordinate research and services across all federal agencies
- Accelerate the development of treatments that prevent, halt, or reverse the disease
- Improve early diagnosis and coordination of care and treatment of the disease
- Improve outcomes for ethnic and racial minority populations at higher risk
- Create an Advisory Council to review and comment on the national plan and its implementation
- Coordinate with international bodies to fight Alzheimer's disease globally

Under NAPA, the first National Plan to Address Alzheimer's Disease (National Plan) was released on May 15, 2012, was subsequently updated in June 2013, and will continue to be updated annually.

In response to guidance from NAPA and the National Plan, NIA convened the Alzheimer's Research Summit 2012: Path to Treatment and Prevention. An international group of some 500 researchers, clinicians and members of the broader Alzheimer's community contributed actively to the Summit process through extensive input and discussion during the course of the meeting. As a result of recommendations from the Summit, NIH issued several solicitations for research on topics including the discovery of basic molecular processes underlying Alzheimer's disease and drug development and testing. Seven groundbreaking studies, ranging from research on the most basic underpinnings of the disease to early-stage clinical trials of promising agents, are now underway.

In addition, in May 2013, as part of the National Plan, NINDS together with NIA held the workshop "Alzheimer's Disease-Related Dementias: Research Challenges and Opportunities."

An international group of experts developed prioritized research recommendations to address ADRDs, including frontotemporal, Lewy body, mixed, and vascular dementias, as well as clinical diagnosis and health disparities in ADRDs. These recommendations were revised based upon public discussion during the lively two-day conference, and in February, the Advisory Council on Alzheimer's Research, Care, and Services created under NAPA recommended that they be added to the National Plan. NINDS has already begun implementing these recommendations by using a high program priority funding process to support investigator-initiated grants on frontotemporal dementia and the vascular contributions to dementia.

Revving Up Research

Research in Alzheimer's disease at NIH today runs the gamut from very basic neuroscience research to cutting-edge clinical trials designed to prevent or treat the disease. In the basic science arena, a major new program that has just begun this year is the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative – referred to by President Obama as the “next Great American Project”. NIH is a leading member of this pioneering new venture, and has issued several research solicitations in the past two months that will enable us to develop a deeper understanding of brain function through the creation of new tools capable of examining the activity of millions of nerve cells, networks, and pathways in real time. By measuring activity at the scale of circuits and networks in living organisms, we can begin to translate data into models that will decode sensory experience, motor planning, and, potentially, even memory, emotion, and thought. We believe that successful completion of the BRAIN Initiative will revolutionize the field of neuroscience, providing a foundational platform for major advances in Alzheimer's and other brain diseases.

Another major current opportunity lies in the work of the Alzheimer's Disease Sequencing Project (ADSP), a program supporting large scale DNA analysis for the Alzheimer's disease research community. The ADSP is a collaboration between NIA-funded geneticists and the National Human Genome Research Institute Large-Scale Sequencing Program. Goals of the program are to identify new genes contributing to increased risk of and protection from the disease; to provide insight as to why individuals with known genetic risk factors escape the disease; and to identify potential avenues for therapeutic and preventive approaches. Last December, NIH announced the availability of the first batch of genome sequence data from the ADSP, including whole genome sequence (WGS) data from 410 individuals in 89 families. Researchers can access the sequence data at dbGaP (<http://www.ncbi.nlm.nih.gov/gap>) or the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS), <https://www.niagads.org/>.

Still another example of how NIH-supported research is accelerating scientific discovery, with the potential for tremendous gains in the area of Alzheimer's disease, is in the area of stem cells. Induced pluripotent stem (iPS) cell technology is revolutionizing the way we study disease, and holds the promise of dramatic advances in treatment. iPS cells are patient-derived cells, typically from skin or blood, that scientists can reprogram back to an embryonic stem cell-like state. These cells can then be induced to turn on specific sets of genes to differentiate into a variety of cell types, including neurons. For Alzheimer's disease, it has been possible to show abnormalities in amyloid metabolism in this "disease in a dish" model, opening the door to a new method to screen drug compounds for possible efficacy.

A seminal finding that has recently generated a lot of excitement is the discovery that the protein, tau, which appears to be in part responsible for the cognitive decline in Alzheimer's patients, may spread from neuron to neuron. This means that if researchers could find a way to prevent cell-to-cell transmission, perhaps by blocking tau with an antibody, the disease process could be halted. The problem was that until recently we had no way of visualizing what was happening with tau inside the living brain, making it difficult to assess the efficacy of treatment on that particular molecule. However, last fall researchers reported that they had developed a new class of imaging agents, termed PBBs, that bind to tau deposits in transgenic mice and in human subjects with normal cognition, Alzheimer's disease, or a corticobasal syndrome. The ability to visualize both beta-amyloid and tau in the living organism will enable us to evaluate the effect of new treatments more rapidly and efficiently than ever before.

With respect to new treatments for Alzheimer's disease, as I noted before, the paradigm has really shifted in recent years, from an emphasis on treatment of individuals with symptomatic disease to primary prevention among individuals at risk. This is not to say that we have forgotten those patients whose disease has advanced; NIH currently supports clinical trials of interventions for agitation, disruption, depression, and other troubling symptoms of Alzheimer's in affected individuals.

Vascular contributions to dementia are especially common and highlight the complex relationships among various types of dementia. The 7 million U.S. stroke survivors and 13 million people who have had "silent strokes" have an increased likelihood of cognitive problems. Brain vascular problems that cause stroke are associated with Alzheimer's disease in multiple ways. For example, signs that a stroke has occurred are often found in the brains of Alzheimer's patients, and beta-amyloid, a key protein in Alzheimer's pathology, may stimulate the formation of blood clots, which can cause stroke. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, which is following more than 30,000 people, is one of several epidemiological studies that demonstrate that high blood pressure and other known risk factors for stroke increase the risk of cognitive problems, even among people who have never had a stroke. Because reducing blood pressure and other cardiovascular risk factors might have an

immediate impact on dementia, NINDS and NIA are funding a study to test whether an aggressive treatment program to reduce systolic blood pressure lower than the currently recommended goal also reduces age-related cognitive decline. This is part of a large, multi-center trial funded by NHLBI and NIDDK on the effects of this treatment on cardiovascular and kidney disease.

However, many of our newest clinical trials focus on presymptomatic, at-risk patients. New studies include:

- A five-year clinical trial to determine if an antibody treatment, crenezumab, designed to bind to and possibly clear away abnormal amounts of amyloid protein in the brains of people with Alzheimer's, can prevent decline in cognitive function. Crenezumab will be tested among members of a unique and large family population in Colombia sharing a genetic mutation known to cause observable signs of Alzheimer's disease at around age 45, along with a smaller number of U.S. participants ages 30 and older.
- The A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer's) Trial which will test the drug solanezumab in 1,000 cognitively normal volunteers, age 65 to 85, who have enough of the amyloid protein in the brain to put them at risk for developing Alzheimer's, but do not show clinical symptoms of the disease.
- The Dominantly Inherited Alzheimer's Network Therapeutic Trials Unit, which will study the effects of different treatments among individuals who are at high genetic risk for developing the disease. In 2014, the first DIAN-TU trial, a comparison of two monoclonal antibodies – gantenerumab and solanezumab – with placebo will begin.

Each of these studies will rely on the availability of validated biomarkers of disease.

Identification and characterization of biomarkers and targets for intervention are the primary goals of the Accelerating Medicines Partnership (AMP), just announced in February 2014. With project management by the Foundation for NIH (FNIH), ten pharmaceutical companies will collaborate with NIH. All data will be made publicly available, and NIH and industry will share in the \$230 million cost over five years for the first projects: Alzheimer's disease, type 2 diabetes, and the autoimmune disorders rheumatoid arthritis and systemic lupus erythematosus. For Alzheimer's disease, AMP resources will be used to incorporate an expanded set of biomarkers into four ongoing trials designed to delay or prevent disease, and then evaluate which ones are most effective. AMP resources will also support large-scale, systems biology analyses of brain tissue samples from people with Alzheimer's disease to validate biological targets that play key roles in disease progression, in order to increase understanding of molecular networks involved in the disease and identify new potential therapeutic targets. AMP represents an unprecedented model for pre-competitive collaboration that should substantially accelerate the ability to identify the next generation of drug targets and biomarkers.

Expanded Funding, Expanded Discovery

On behalf the biomedical research community, whose scientists have been under stress as NIH purchasing power over the last decade has declined due to inflationary effects, I would like to acknowledge the FY14 funding increase with which NIH has been entrusted for supporting new research on aging, including Alzheimer's disease. The addition of these new funds to our base appropriation will enable us to plan carefully for their use, consistent with funding the best peer-reviewed science and the priorities established at the Alzheimer's Summit and 2013 ADRD Workshop.

Several FY 2014 initiatives can be mentioned that we plan to support with this increased base. First, these funds will facilitate analysis of the DNA sequences generated through the ADSP. Second, we are soliciting research on the use of iPS and other reprogrammed human cells specifically for aging and Alzheimer's disease. Also, researchers will study the function and activity of individual cells in the brain in animal models by turning functions of those cells on and off using – simply – light. Remarkably, the technology has advanced to the point where we can safely introduce tiny lasers and light-sensitive proteins into the brains of mice and rats. When the laser is remotely activated, the proteins respond by turning cells on and off, enabling us to track the cell's function. This technology – known as *optogenetics* – is being used in animal models of Alzheimer's disease to provide information that will help us to understand functions of the normal as well as the Alzheimer's brain.

This concludes my testimony. I am happy to respond to your questions.