Statement of Richard J. Hodes, M.D.
Director, National Institute on Aging
Senate Special Committee on Aging

Good afternoon, Chairman Collins, Ranking Member McCaskill, and distinguished members of the Committee. I am Richard J. Hodes, M.D., Director of the National Institute on Aging (NIA), which is one of the 27 Institutes and Centers of the National Institutes of Health (NIH). 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, Chairman Collins, as well as your colleagues on the Committee, for your unflagging championship of research on Alzheimer's disease. I would particularly like to acknowledge the significant increase in funding that the Congress has provided to NIH for both FY14 and FY15 to bolster our support for research on Alzheimer's. These additional funds are being used for large-scale research for identification of new risk and protective genes; development of new cellular models of the disease to enable rapid screens of hundreds of thousands of molecules for potential as therapeutic agents; establishment of translational centers that will develop and apply cutting-edge approaches to drug discovery and development; population studies of trends in the incidence and prevalence of dementia; development of novel interventions to support dementia caregivers; and trials of therapies in people at the highest risk of disease. With the resources requested for NIH in the FY 2016 President's Budget, NIH estimates it could further expand Alzheimer's research activities by another $51 million to a total of $638 million, a 55 percent increase since 2008. I am happy to update you on some of these activities and to share with you some exciting recent scientific discoveries and new initiatives.

An Issue of Mounting Concern

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, although a much smaller subset of patients see onset at earlier ages. Although treatment can help manage symptoms in some people, there is currently

no cure for this devastating disease. While my focus today will be on Alzheimer's disease, other forms of dementia, including frontotemporal degeneration and vascular, Lewy body, and mixed dementias, are also important topics of research at the NIH, and I will be sharing some of our activities in these areas with you as well.

Results of a recent meta-analysis[1] indicate 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. In the United States alone, as many as 5.1 million people age 65 and older suffer from Alzheimer's disease. Although several large epidemiological studies suggest that age-specific prevalence rates of dementia, including Alzheimer's disease, are declining,[2] it is nevertheless also true that risk for the disease is greatest in the "oldest old" – those over 85. Because this age group is projected to grow substantially in the coming decades – from approximately 5.8 million in 2010 to some 19 million in 2050[3] – it is certain that unless we identify a way to prevent or effectively treat Alzheimer's, the number of affected Americans will rise exponentially within the lifetime of many of us here today.[4]

This disease is not just a challenge to our health; it also has an impact 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.[5] Even if favorable trends in disease prevalence continue, costs are expected to rise dramatically in the coming decades – and this increase will be significantly magnified if unfavorable trends, such as the current epidemic of diabetes (associated with an increased risk of Alzheimer's), continue on their present course.

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[1] Prince M et al., The Global Prevalence of Dementia: A Systematic Review and Metaanalysis. Alzheimer's and Dementia 9: 63-75, 2013.

[2] Larson EB, Yaffe K, and Langa KM. New Insights into the Dementia Epidemic. *New England Journal of Medicine* 369: 22-25-2277, 2013.

[3] Vincent, Grayson K. and Victoria A. Velkoff. The Next Four Decades, The Older Population in the United States, 2010-2050. Current Population Reports, P25-1138. U.S. Census Bureau, Washington, D.C., 2010.

[4] Hebert LE et al. Alzheimer disease in the United States (2010-2050) estimated using 2010 census. *American Academy of Neurology* 80: 1778-1783, (2013).

[5] Hurd MD et al. Monetary Costs of Dementia in the United States. *New England Journal of Medicine* 368: 1321334, 2013. See also http://www.nia.nih.gov/newsroom/2013/04/nih-supported-study-finds-us-dementia-care-costs-high-215-billion-2010

In 2011, President Obama signed the National Alzheimer's Project Act which called for the creation of a National Plan to Address Alzheimer's Disease. In 2012, the Administration announced the plan at NIH, along with the announcement of new investments in two major Alzheimer's clinical trials. As the Federal lead on Goal 1 of the National Action Plan to Address Alzheimer's Disease – *Prevent and Effectively Treat Alzheimer's Disease by 2025* – NIH continues to move forward on a number of fronts, informed by input including that provided from the February 2015 Alzheimer's Disease Research Summit; the 2013 Summit on Alzheimer's-Related Dementias; and a meeting held in April 2013 to set a research agenda aimed at speeding the development of possible therapies to treat Alzheimer's in people with Down syndrome – a population at very high risk of developing the disease.

New Frontiers in Treatment for Dementia

Recent years have brought a paradigm shift in Alzheimer's treatment from an emphasis on treatment of individuals with symptomatic disease to include a focus on prevention among individuals at risk. Importantly, we also continue to support research aimed at helping those patients whose disease has advanced; NIH currently supports clinical trials of both pharmacologic and non-pharmacologic interventions for agitation, disruption, depression, and other troubling symptoms of Alzheimer's in affected individuals. For example, investigators with the NIH-supported Citalopram for Agitation in Alzheimer's Disease Study (CitAD) trial recently reported that the commonly-prescribed antidepressant citalopram, especially in lower doses, may be a more effective and safer alternative to treating agitation in Alzheimer's patients than the antipsychotic drugs with which they are currently often treated.

However, many of our newest clinical trials focus on presymptomatic, at-risk individuals. Ongoing and upcoming clinical trials include:

- The **A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer's)** trial 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. Recruitment began in July 2014.

- The **Study of Nasal Insulin to Fight Forgetfulness (SNIFF)** will test an insulin nasal spray to see if it improves or preserves memory in adults with memory-related mild cognitive impairment or mild Alzheimer's disease. This trial is ongoing.

- The **Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU)** trial will assess the safety, tolerability, and biomarker efficacy of two experimental drugs, gantenerumab and solanezumab, in people who are genetically at high risk for the disease. Recruitment recently began for this trial.

- The **Alzheimer's Prevention Initiative APOE4 (API APOE4)** trial will test two anti-amyloid drugs, an active vaccine and a beta-secretase inhibitor, in cognitively normal older volunteers who are at increased risk of developing late-onset Alzheimer's because they have two copies of the APOE4 gene. We anticipate beginning recruitment for this study later this year.

- The **Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease (API ADAD)** study is 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. This study is ongoing.

In addition, NIH supports over 70 projects aiming to discover and develop new therapeutics for Alzheimer's, including a major ongoing initiative supporting studies that lead to the submission of an Investigational New Drug (IND) application to the Food and Drug Administration, a prerequisite for beginning human trials of potential new therapies. NIH also supports over 35 clinical trials, including both pilot and large scale trials, of a wide range of interventions to prevent, slow, or treat Alzheimer's, mild cognitive impairment (MCI), and/or cognitive decline.

As we move toward identifying at-risk individuals earlier in the disease course, we are also identifying more effective ways to gauge treatment efficacy more quickly and efficiently. For example, although we have made tremendous strides in the development of measures that can alert physicians and researchers to subtle cognitive declines in healthy older people, the best way to detect changes in people's everyday function is less clear. Researchers with the NIA-supported

Alzheimer's Disease Cooperative Study (ADCS) have developed a new tool known as the Cognitive Function Instrument (CFI), which tracks functional decline over time in people who start out cognitively normal and may serve as a useful outcome measure in prevention trials.[6]

Increasing enrollment in clinical trials and studies is critical to reaching a primary goal of the National Plan to Address Alzheimer's Disease: To prevent and effectively treat Alzheimer's by 2025. Tens of thousands of participants of all kinds will be needed for trials focused on delaying, treating, or preventing this significant public health problem. With the National Plan as a catalyst and aided by a small award from an HHS program encouraging innovation, a cross-agency team from NIA, the Administration for Community Living (ACL), and the Centers for Disease Control and Prevention approached the challenge of increasing participation in clinical trials by bringing their aging, public health, research networks, and resources together. The effort, dubbed "Recruiting Older Adults into Research," or ROAR, seeks to raise research awareness and engagement among older adults, connect them with easy and actionable opportunities to participate and, ultimately, expand the pool of older adults willing to participate in clinical studies and trials for Alzheimer's and other health conditions. Although other health conditions will be covered under this initiative, Alzheimer's is currently the primary focus.

An Explosion of Knowledge

Several of the clinical trials I just discussed are only possible thanks to the deeper understanding of the basic mechanisms of Alzheimer's disease gained within the last several years.

One area that has shown explosive growth over the past decade is the genetics of Alzheimer's disease. Until 2009, only one genetic variant, APOE ε4, had been shown to increase the risk of late-onset Alzheimer's, the most common form of the 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. By 2013, the largest GWAS ever conducted had identified a total of 11 genetic risk factors. This research was conducted by the International Genomic Alzheimer's Project (IGAP) – a collaborative,

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[6] Amariglio RE et al. Tracking Early Decline in Cognitive Function in Older Individuals at Risk for Alzheimer's Disease Dementia: The Alzheimer's Disease Cooperative Study Cognitive Function Instrument. *JAMA Neurol* . Published on line February 23, 2015. http://archneur.jamanetwork.com/article.aspx?articleid=2110225.

international study supported in part by the NIH. As of today there are 35 identified regions in the Alzheimer's genome that strengthen evidence about the involvement of particular pathways in the disease, such as inflammation, lipid metabolism, and amyloid deposition, and also point to entirely new molecular pathways for us to explore.

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, both known biomarkers 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. This groundbreaking finding raised the possibility of using fluid and imaging biomarkers to track disease progression, as well as to rapidly assess the efficacy of interventions in clinical trials, and enabled a working group led by the NIA and the Alzheimer's Association to develop the first revisions to the clinical and neuropathological guidelines for Alzheimer's disease diagnosis in over 25 years.

Identification and characterization of biomarkers and targets for intervention are the primary goals of the year-old Accelerating Medicines Partnership (AMP), an innovative public-private partnership involving the NIH, biopharmaceutical companies, and several nonprofit organizations. AMP-supported investigators are currently incorporating an expanded set of biomarkers into three ongoing trials – the DIAN-TU, A4, and API APOE4 studies – designed to delay or prevent disease, and then evaluate which biomarkers are most effective as measures of disease progression and response to treatment. Screening and recruitment are well underway for the DIAN-TU and A4 studies, and we anticipate enrolling the first participants in the API APOE4 trial later this year.

AMP resources are also supporting large-scale, systems biology analyses of brain tissue samples from people with Alzheimer's disease and controls to identify and 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. In March, AMP launched its Alzheimer's Big Data Portal and concomitantly released the first wave of data through this new resource. This will enable sharing and analyses of large and complex biomedical datasets with appropriate privacy protections. This approach will enable the development of predictive models of Alzheimer's disease and the selection of novel targets that

drive the changes in molecular networks leading to the clinical signs and symptoms of the disease.

The next frontier in research involves the integration of genetic, biomarker, and clinical information. Even as genetic studies such as the previously-discussed IGAP study may be of considerable utility in identifying potential pathways of interest and biomarkers of disease, biomarkers can also guide genetic studies in both early- and late-onset forms of the disease.[7] For example, using neuroimaging and cerebrospinal biomarkers as *endophenotypes* – markers that are associated with, but not direct symptoms of, a condition – investigators have identified several novel Alzheimer's-related genetic variants.

We hope to expand our knowledge of the gene/biomarker interface through a major new initiative supported by the NIA and the National Human Genome Research Institute which was announced in July 2014. Five newly-awarded projects will analyze how genome sequences—the order of chemical letters in a cell's DNA—may contribute to increased risk or protect against Alzheimer's disease. The NIH awarded grants for using innovative new technologies and computational methods for the analyses. The scientists also will seek insights into why some people with known risks do not develop the disease. The investigators will analyze the genome sequencing data generated during the first phase of the ongoing Alzheimer's Disease Sequencing Project (ADSP), and will use the data to identify rare genetic variants that protect against, or contribute to, Alzheimer's disease, explore differences in data from different racial/ethnic groups, and examine how brain images and other biomarkers are associated with genome sequences. This work may lead to the development of personalized approaches to treatment for Alzheimer's disease, in the spirit of the newly-announced President's Precision Medicine Initiative.

Expanded Funding, Expanded Discovery

The funding increases in FY14 and FY15 to our base appropriations to support new research on aging, including Alzheimer's disease, will enable us to plan carefully for their use, consistent with funding the best peer-reviewed science and the priorities established at the

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[7] Guerreiro R et al. Genetic Variants and Related Biomarkers in Sporadic Alzheimer's Disease. *Current Genetic Medicine Reports* 3: 19-25, 2015.

Alzheimer's Summit and 2013 Alzheimer's Disease Related Dementias Summit.   We look forward to your support of the President's FY 2016 budget.

New Alzheimer's-related initiatives that will begin this year include:

- **Biomarkers of Alzheimer's Disease in Down Syndrome**. Adults with Down syndrome are at extremely high risk for developing Alzheimer's disease. Most individuals with Down syndrome develop the disease's characteristic amyloid plaques and tau tangles in the brain by their 30s and 40s, with clinical symptoms of dementia often beginning when they are in their 50s or 60s. Recently, NIA and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development partnered on an initiative to enable the identification of the longitudinal progression of Alzheimer's disease in adults with Down Syndrome using clinical, cognitive, imaging, genetic, and biochemical biomarkers. One or two projects will be awarded later in FY15.

- **Interdisciplinary Research to Understand the Vascular Contribution to Alzheimer's Disease**. Most Alzheimer's patients have a variety of cerebrovascular lesions (largely due to small vessel disease) in addition to amyloid and tau pathology. Midlife vascular risk factors are associated with significantly elevated risk for late life Alzheimer's and dementia. Evidence also exists that vascular health may be critical to delaying the onset of vascular cognitive impairment/vascular dementia as well as Alzheimer's and Lewy Body Dementia. Research to date suggests a very complex and not well understood interaction among vascular risk factors, cerebrovascular disease and the pathogenesis of Alzheimer's and related dementias. NIA and the National Institute of Neurological Disorders and Stroke (NINDS) are collaborating on an initiative soliciting interdisciplinary research on the mechanisms by which vascular factors contribute to Alzheimer's and related dementias. Awards will be made later in FY15.

- **Immune and Inflammatory Mechanisms in Alzheimer's Disease**. Brain immune and inflammatory processes have been implicated as key contributors to Alzheimer's pathophysiology, yet we still lack a comprehensive understanding of the network of immune cells, inflammatory mediators, and cellular pathways that cause or contribute to the disease. The goal of this initiative is to establish the immune and inflammatory mechanisms contributing to or mediating the development and progression of

Alzheimer's disease. NIA anticipates funding six to eight projects under this initiative later in FY15.

- **AD Translational Centers for Predictive Drug Development**. NIA plans to establish up to two translational centers that will develop/apply quantitative systems pharmacology (QSP) approaches to AD drug discovery and development. QSP is an emerging, data-driven, model-based approach to drug development that integrates systems biology with pharmacology and breaks decisively with a "one-gene, one-receptor, one-mechanism" approach in favor of a network-centric view of drug targets and drug action. Awards will be made in FY16.

Progress in Alzheimer's-Related Dementias

While Alzheimer's disease is the most common cause of dementia among older people, many may be affected by a mix of Alzheimer's and vascular pathology. Stroke and diffuse white matter disease are linked to cognitive decline with aging and can co-occur with Alzheimer's, likely contributing to some clinical manifestations. Control of vascular risk factors is one explanation offered in the reports of declining dementia incidence in recent years. Other forms of dementia include frontotemporal dementia (FTD), diffuse Lewy body disease (dLBD), and Parkinson's disease (PD). These forms of dementia are included in the National Plan to Address Alzheimer's disease.

Informed by the 2013 Summit *Alzheimer's Disease-Related Dementias: Research Challenges and Opportunities*, the NIH continues to support research in this critical area. As part of a large international collaboration to understand the genetic causes of AD-related dementias, NIH intramural researchers are sequencing DNA samples from over 1,500 people with FTD and 1,300 people with dLBD to characterize chromosomal regions that are associated with a risk of developing these diseases. A consortium of NIH-funded investigators is developing induced pluripotent stem cells, a type of stem cell derived from skin cells, as a model system for understanding the cellular basis of FTD. Within the Rare Disease Clinical Research Network, a clinical research consortium is improving clinical trial design and bringing together a variety of techniques and methods to generate new types of treatments for FTD. In addition, NIH is funding a longitudinal study of people with a familial form of FTD to identify biomarkers that

will be useful for determining the efficacy of new therapies, as well as a program project to further understand the cellular disease processes by which certain genetic mutations lead to FTD.

Through an interdisciplinary workshop, NIH recently brought together diverse groups of researchers to address issues related to research on small blood vessels in the brain and other organ systems, which will inform research on the underlying causes of vascular contribution to cognitive decline and dementia. Finally, as mentioned earlier, NIH has released an initiative to encourage interdisciplinary research to understand the interaction of vascular disease and Alzheimer biology. These are just a few examples of the many NIH-supported studies, initiatives, and workshops aimed at understanding the causes of and finding treatments for these devastating diseases.

Supporting Caregivers of Patients with Dementia

Finally, NIH-supported research on interventions and strategies to support individuals who face the often overwhelming challenge of caring for a loved one with dementia has produced some welcome results. We now know that some of these interventions, many of them developed and tested by NIH-supported researchers, can reduce caregiver depression and anxiety, improve the caregiver's knowledge about dementia and how to cope with it, reduce overall burden on the caregiver, and delay time to institutionalization of the patient.[8] For example, REACH II (Resources for Enhancing Alzheimer's Caregiver Health), an NIH-funded study, developed the first intensive caregiver support intervention to be proven effective, through rigorous testing, in an ethnically diverse population. The REACH II intervention is currently being translated more broadly through the U.S Department of Veterans Affairs (VA), with participating centers in fifteen states at 114 different sites. Called REACH VA, the system is consulting with previously NIA-supported REACH II investigators. The VA is also beginning to test the intervention with caregivers of patients with other chronic conditions, and is partnering with ACL, the Indian Health Service, and a private foundation to adapt and implement REACH in Tribal communities. This program will partner with tribal public health nursing, community

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[8] Gitlin L and Hodgson, in press. Caregivers as Therapeutic Agents in Dementia Care: The Evidence-base for Interventions Supporting Their Role.   J. Gaugler and R. Kane (Eds.), *Family Caregiving in the New Normal.* San Diego, CA. Elsevier, Inc.

health representatives and ACL's Native American Family Caregiver programs to train and support caregivers of frail elders.

At the same time, a significant gap continues to exist between our knowledge of effective caregiver interventions and their real-world implementation. Since 2008, ACL, in collaboration with NIH, has translated and implemented evidence-based interventions and other innovative programs for caregivers of persons with Alzheimer's and related dementias. Nearly 49 thousand dementia caregivers have been served through the ACL-sponsored Alzheimer's Disease Supportive Services[9] program to date; however we encourage and support further translation of these crucial programs to support the more than15 million dementia caregivers in the United States.[10] [11]

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

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[9] Source: "Alzheimer's Disease Supportive Services Program (ADSSP) Grantee Data Collection Reporting," compiled by the National Alzheimer's and Dementia Resource Center, January 2015.

[10] Gitlin et al. Translating Evidence-based dementia caregiving interventions into Practice: State of the Science and Next Steps. *The Gerontologist Advance Access.* Published on line February 17, 2015.
http://gerontologist.oxfordjournals.org/content/early/2015/02/16/geront.gnu123.full

[11] Gitlin et al. Translating Evidence-based dementia caregiving interventions into Practice: State of the Science and Next Steps. *The Gerontologist Advance Access.* Published on line February 17, 2015.
http://gerontologist.oxfordjournals.org/content/early/2015/02/16/geront.gnu123.full