REACHING FOR A CURE:
Alzheimer’s Disease and
Related Dementias Research
at NIH

BYPASS BUDGET PROPOSAL
FOR FISCAL YEAR 2017
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INVESTING IN RESEARCH, INVESTING IN HOPE

July 27, 2015

On behalf of the National Institutes of Health (NIH), I am pleased to present our first Professional Judgment Budget, commonly referred to as a Bypass Budget, for Alzheimer’s disease and related dementias. This plan for Fiscal Year (FY) 2017 outlines the optimal approach NIH would take in an ideal world unconstrained by fiscal limitations to make real and lasting progress against this devastating group of disorders.

As all of us are only too well aware, Alzheimer’s disease is exacting a steep physical, emotional, and financial toll on our Nation. Millions of Americans are affected by Alzheimer’s and related conditions; millions more are at risk. Yet there currently is no cure for this disease, and no treatments have been conclusively proven to prevent or delay its course. If tangible progress is not made in the coming years, the human and economic costs will be staggering.

But through this plan, NIH is proposing an investment in hope—hope grounded in biomedical research. We believe that if we expand and build upon our base of scientific knowledge, we can identify and implement the strategies for combating Alzheimer’s disease that are so desperately needed.

We are already starting to see this happen. In recent years, NIH-funded research has yielded new insights into the mechanisms of Alzheimer’s disease, from identification of genes that influence risk, to discovery of detailed information about the amyloid and tau proteins that form aggregates in the Alzheimer’s brain, to development of new models of disease pathogenesis using revolutionary new stem cell strategies. These and many other advances are suggesting new pathways for treatment and prevention.

For example, innovative compounds that target the disease’s underlying pathology early—before symptoms appear—are in the pipeline. Meanwhile, other drugs, already tested in humans for other conditions, are being repurposed with the aim of preventing and treating the disease’s most troublesome symptoms. Researchers are also exploring the extent to which modifiable lifestyle factors, such as exercise and diet, may protect the brain against dementia.

Clearly, there is great reason for hope. But we must do more.

The U.S. Congress has agreed and asked NIH to prepare this Bypass Budget. This plan concludes that NIH could significantly accelerate progress against Alzheimer’s disease with an additional investment of $323 million in FY 2017 above the agency’s base appropriation. The Bypass Budget will be updated annually through FY 2025, which is the target date set by the National Plan to Address Alzheimer’s Disease for developing effective modes of treatment and prevention.
Importantly, what we present here is more than simply a list of cold, hard numbers. Informed by input from a wide range of stakeholders in the public and private sectors, including participants at a February 2015 workshop, NIH’s National Institute on Aging and National Institute of Neurological Disorders and Stroke have charted a roadmap for success in our Nation’s ongoing battle against Alzheimer’s disease. This comprehensive research plan includes a set of specific, targeted milestones, as well as a list of areas poised for future discoveries. Utilizing this information, NIH has gone on to identify which areas of research stand to benefit the most from intensified investment in FY 2017.

Alzheimer’s disease and related dementias pose a formidable challenge to our Nation’s health and economic well-being. With science at our side, NIH stands ready and willing to take on that challenge.

Francis S. Collins, MD, PhD
Director, National Institutes of Health
INTRODUCTION

Today, more than 5 million Americans live with Alzheimer’s disease. Because there are currently no treatments that change the course of this progressive brain disorder, they will gradually lose their ability to remember, think, learn, and live independently. And because we do not yet know how to prevent Alzheimer’s, as the U.S. population grows older, the future impact of this age-related disorder looms large for our Nation.

But we have every reason to hope. With increased public attention and resources, the trajectory of Alzheimer’s disease and related dementias can change. Under the leadership of the National Institutes of Health (NIH), the Alzheimer’s research community is intensifying its efforts, seeking to identify effective ways to treat or prevent Alzheimer’s disease as soon as possible.

The challenges are great, and we still have much to learn about this complex disease. But NIH and the wider research community are determined to end the devastation of memories and lives lost to Alzheimer’s and related dementias. We are supported and motivated in this effort by the American public, far too many of whom face the challenges of living with or caring for a loved one with the disease.

A Nation United Against Alzheimer’s

Fighting Alzheimer’s disease and related dementias is a priority not just at NIH and other Federal agencies, but across the Nation and much of the world. In January 2011, President Obama signed the National Alzheimer’s Project Act (NAPA), which called for an aggressive and coordinated national plan to accelerate Alzheimer’s disease research, provide better clinical care, and improve services for people with the disease and their families.

The law also established an Advisory Council on Alzheimer’s Research, Care, and Services, consisting of some of the Nation’s foremost experts. The Advisory Council’s first National Plan to Address Alzheimer’s Disease in 2012 outlined objectives and set milestones to achieve the ultimate research goal: to find effective interventions to treat and prevent Alzheimer’s and related dementias by 2025.

Updated annually, most recently in July 2015, the research component of the National Plan is a collaborative, constantly evolving framework. It outlines the basic, translational, and clinical research needed to understand and conquer Alzheimer’s disease and related dementias.

As the world’s leading funder of Alzheimer’s research, NIH plays a vital leadership role in this inclusive and collaborative effort that involves private, public, and academic sectors, along with clinicians and advocacy groups. The National Plan encourages the American public, which is increasingly aware of the devastation wrought by this disease, to be fully engaged in this critical effort.

Funding Research Opportunities

The passage of NAPA has spurred a national effort to end the devastation, emotional trauma, and financial burden brought on by Alzheimer’s disease and related dementias. For its part, NIH over the past few years has directed additional funds
to support promising areas of science. In addition, a boost in Federal appropriations to the National Institute on Aging (NIA) of $100 million in fiscal year (FY) 2014 and $25 million in FY 2015 carried the expectation that a significant portion of these funds would go toward Alzheimer’s research. Overall, NIH spending on Alzheimer’s disease research increased 25 percent from FY 2011 to FY 2014.

The FY 2014 and FY 2015 increases enabled new and innovative projects, such as:

- Large-scale research to identify new risk and protective genes
- Development of new human cellular models of Alzheimer’s that may enable rapid screening of hundreds of thousands of molecules as potential 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
- Clinical trials of therapies in people at the highest risk of dementia

Despite these developments, the current level of Alzheimer’s disease funding at NIH is insufficient to achieve our national target of finding effective interventions by 2025. After 10 years of essentially flat budgets eroded by the biomedical inflation rate and such measures as the 2013 sequester (an automatic, across-the-board 5 percent cut in NIH support), NIH’s purchasing power has been cut by 22 percent since FY 2003. Increasing NIH funding for Alzheimer’s and related dementias research would allow the Nation to realize a fuller range of promising scientific opportunities and to move more quickly toward a cure.

### Alzheimer’s Disease Research Funding at NIH, FY 2011-FY 2016

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<thead>
<tr>
<th>Fiscal Year</th>
<th>NIA Alzheimer’s Funds</th>
<th>NIH Alzheimer’s Funds</th>
<th>NIH Budget</th>
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Changes in Alzheimer's Disease Research Funding at NIH

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<th>Fiscal Year</th>
<th>NIA Alzheimer's Funds</th>
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Budgeting for a Cure

Reflecting the Nation’s determination to end the scourge of Alzheimer’s, NIH for the first time has prepared this professional judgment budget proposal for FY 2017. This budget proposal estimates the additional funding needed to reach the ultimate research goal of the National Plan—to effectively treat and prevent Alzheimer’s and related dementias by 2025—and will be updated annually. It focuses on funding for investigator-initiated research grants and NIH initiatives that would spur research beyond NIH’s base budget allocated in the previous year.

As mandated in Section 230, Division G of the Consolidated and Further Continuing Appropriations Act of 2015, NIH will prepare and submit to the President, for review and transmittal to Congress, this annual professional judgment budget through 2025. Only two other areas of biomedical research—cancer and HIV/AIDS—have been the subject of such special budget development aimed at speeding discovery. This approach is often referred to as a “bypass budget” because of its direct transmission to the President and then to Congress without modification through the traditional Federal budget process.

NIH welcomes this new opportunity to develop a budget for expanding research on Alzheimer’s and related dementias. It is built on a rigorous, extensive planning process that gauged progress in research, assessed emerging and new scientific opportunities to build on that progress, and calculated the additional funds necessary to capitalize on those opportunities and move more quickly in the most promising directions. We have also taken into account the heavy and growing public health and financial burden of Alzheimer's and related dementias on individuals, families, caregivers, services, and society.

Assessing Research Opportunities

Development of this budget was led by NIA, which is designated as the lead institute on Alzheimer’s research at NIH.

A number of NIH Institutes and Centers contributed to the scientific milestones that were used as a basis for developing this budget, in particular the National Institute of Neurological Disorders and Stroke, which has the second largest portfolio in Alzheimer’s disease and a particular focus on Alzheimer’s disease-related dementias.
The following NIH Institutes and Centers helped refine the milestones by providing feedback and identifying scientific gaps and opportunities to consider: the National Institute of Mental Health; National Institute of Nursing Research; National Institute of Biomedical Imaging and Bioengineering; National Institute of Child Health and Human Development; National Institute of Environmental Health Sciences; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Dental and Craniofacial Research; National Heart, Lung, and Blood Institute; Fogarty International Center; and National Center for Advancing Translational Sciences.

In setting the research and funding priorities reflected in this budget, NIH received expert input from a variety of sources and perspectives. Central to this process was a series of research summits hosted by NIH and attended by dementia experts from academia, industry, and advocacy groups. Planning under NAPA began with the Alzheimer’s Disease Research Summit 2012: Path to Treatment and Prevention, followed by the Alzheimer’s Disease-Related Dementias (ADRD): Research Challenges and Opportunities 2013 Summit and Advancing Treatment for Alzheimer Disease in Individuals with Down Syndrome in 2013.

Our planning was revised and updated most recently as a result of the Alzheimer’s Disease Research Summit 2015: Path to Treatment and Prevention, which drew hundreds of experts in Alzheimer’s and other chronic diseases. Among a number of topics, they examined critical knowledge gaps and what kinds of new resources, infrastructure, and multi-stakeholder partnerships were needed to fully realize emerging research opportunities.

**Recommendations** developed at this meeting provided a framework for setting priorities for a bold and transformative Alzheimer’s disease research agenda over the next few years. This agenda has guided the milestones presented in this FY 2017 budget proposal and will inform the milestones developed over the next decade as we work to achieve our 2025 goals. The 2015 Summit recommendations include:

- Focus on emerging scientific opportunities in basic, translational, and clinical research.
- Outline new scientific approaches to address critical knowledge gaps and propose ways to harness emerging technologies to accelerate treatments for people at all stages of the disease.
- Call for new and expanded partnerships among Alzheimer’s researchers in academia, industry, and government that generate, share, and use knowledge to propel the development of critically needed therapies.
- Identify infrastructure and partnerships necessary to successfully implement the new research agenda.
- Advocate for strategies to empower patients and engage citizens.
How NIH Determines Research Investment

NIH funds and conducts a diverse and productive research program in the basic biology of Alzheimer’s disease, factors that influence its development and progression, genetic and environmental risk and protective factors, diagnosis, possible treatment and prevention strategies, and care of individuals with Alzheimer’s disease and their caregivers. This research involves a broad array of scientific disciplines and seeks to answer complex questions such as: What causes Alzheimer’s disease? How can it be diagnosed early and accurately? How might it be treated, delayed, or prevented?

The bulk of Alzheimer’s and related dementias research funding at NIH goes to investigator-initiated applications. Applications for such funding reflect the creativity and innovation of both established scientists and new investigators, who seek to build on progress being made or who offer wholly new ways of thinking about the disorders.

NIH also guides the direction of research by announcing funding opportunities that target specific, particularly promising avenues of research. These announcements are open for a set period of time and can be reissued or allowed to lapse as scientific priorities change.

All applications are selected for funding through a rigorous peer-review process in which experts in the field carefully review applications for scientific merit, potential impact, innovation, and likelihood of success. Competition for available funding is intense. In addition to research initiatives in specific high-priority areas, NIH would direct much of the additional funding that might be allocated as a result of this budget proposal to investigator-initiated research addressing Summit recommendations and milestones. Increased appropriations in FY 2017 will greatly enhance the ability of NIH to support promising research focused on finding interventions for Alzheimer’s and related dementias by 2025.
Alzheimer's Disease and Related Dementias

Dr. Alois Alzheimer first described what is now recognized as Alzheimer's disease more than 100 years ago. It was not until the 1970s, however, that researchers first began to understand that the Alzheimer’s type of dementia—then known as senility—was not a normal part of aging. Since then, scientists have greatly expanded our understanding of this complex disease and related dementias.

Over time, people with Alzheimer’s disease lose their ability to remember, think, learn, and carry out even the simplest tasks. Signs and symptoms of dementia result when once-healthy neurons (nerve cells) in the brain stop working, lose connections with other brain cells, and die. While everyone loses some neurons as they age, people with dementia experience far greater loss.

The first symptoms of Alzheimer’s disease typically include memory loss or other cognitive problems, such as trouble with language or decisionmaking. As cognition declines, people with Alzheimer’s sometimes experience disturbing personality and behavior changes. In the final stage of Alzheimer’s dementia, people lose the ability to recognize family and friends and become completely dependent on others for daily care. Ultimately, Alzheimer’s disease is fatal.

While Alzheimer’s is the most common form of dementia in older people, it is only one of many dementia disorders. An estimated 20 percent to 40 percent of older people with dementia have another form of dementia, such as vascular dementia, Lewy body dementia, or frontotemporal dementia. Many people diagnosed with Alzheimer’s disease may actually have “mixed dementia,” a combination of two or more disorders, at least one of which is dementia. For example, some people have both Alzheimer’s changes plus another pathology, most commonly cerebrovascular disease.

It can be difficult for doctors to distinguish among Alzheimer’s and other dementias, as they often share similar symptoms. It is sometimes difficult to separate the role of changes due to Alzheimer’s from those due to cerebrovascular disease in contributing to dementia in an elderly person. But all forms of dementia have one thing in common: they exact a terrible physical, emotional, and financial toll on those with the disorder and their loved ones.
A Growing Public Health Crisis
In most people with Alzheimer’s, symptoms first appear in their mid-60s. Although treatment can help manage symptoms for a limited period of time in some people, no intervention is currently available to slow or prevent the underlying disease process. This budget is aimed at developing disease-modifying therapies and prevention strategies, as well as continuing to provide relief for dementia symptoms.

Results of a recent meta-analysis indicated that 35.6 million people lived with dementia worldwide in 2010, with numbers expected to double almost every 20 years—to 65.7 million people in 2030 and 115.4 million in 2050. Recently, several large studies suggested that dementia rates in the United States and parts of Europe may be declining, at least for now, possibly due to such factors as improved education and treatment of risk factors for stroke and heart attack. That said, the greatest risk factor for Alzheimer’s is age, and the American and, indeed, the world population is aging.

In the United States alone, as many as 5.1 million people age 65 and older suffer from Alzheimer’s disease. Many others are living with the rare, inherited types of Alzheimer’s disease and frontotemporal dementia that can occur in people in their 30s, 40s, and 50s, or related forms of dementia, such as Lewy body dementia and vascular dementia. Unless we identify ways to prevent or effectively treat Alzheimer’s and related dementias, the number of affected Americans will rise exponentially as the population ages.

The Economic Impact of Alzheimer’s
Alzheimer’s disease has a major impact on the U.S. economy. Recently, NIH-supported economists calculated that caring for people with Alzheimer’s disease in 2010 cost the U.S. health care and long-term care systems 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 at $109 billion in 2010. To place that figure in context, that same year, direct health care costs for heart disease and cancer were estimated at $102 billion and $77 billion, respectively. Even if favorable trends in disease prevalence continue, costs are expected to rise dramatically in the coming decades with the aging of the population. This increase may be magnified by the current epidemic of diabetes, a known risk factor for Alzheimer’s disease.

Ramping Up Research
Our Nation faces many challenges as we work together to find effective therapies to prevent and treat Alzheimer’s disease and related dementias by 2025. But, we are optimistic. With the generous support of study volunteers and their families, dedicated researchers are advancing our understanding of this complex disease day by day. NIH, with the participation of all who search for answers, has set our sights on a cure for Alzheimer’s.

This bypass budget proposal outlines what it will take to get us there. The following narrative covers specific areas of research that describe the approach, important recent progress—including specific research highlights for calendar years 2014 and
early 2015—and how NIH intends to build on that progress with research and initiatives in FY 2017. NIH proposes that an additional investment of $323 million will be needed in FY 2017.

This bypass budget presentation is organized in categories determined by the Common Alzheimer Disease Research Ontology (CADRO) of the International Alzheimer’s Disease Research Portfolio (IADRP). The NIA-supported IADRP database, developed in collaboration with the Alzheimer’s Association, captures a wide spectrum of current Alzheimer’s disease and related dementias research investments and resources in the United States and internationally. IADRP enables the global research community to coordinate planning, leverage resources, avoid duplication of funding efforts, and identify gaps in research. The CADRO categories, which have informed the goals and objectives set forth in the National Plan to Address Alzheimer’s Disease, have proven useful in tracking spending in specific areas of research, making the categories an ideal structure for organizing this proposed budget.

Distribution of Professional Judgment Budget Funding Across CADRO Categories (FY 2017)
CATEGORY A. MOLECULAR PATHOGENESIS AND PHYSIOLOGY OF ALZHEIMER’S DISEASE

This category of research focuses on the molecular and physiological processes underlying Alzheimer’s disease pathogenesis and the genetic and epigenetic determinants of Alzheimer’s disease. Topics under this category include amyloid, tau, presenilins, ApoE and lipids, brain circuits and synapses, cell death, immunity and inflammation, bioenergetics, vascular/metabolic factors, hormones, and genetics.

Scientists funded by the National Institutes of Health (NIH) are exploring the complex cellular, molecular, and genetic brain changes that play a role in Alzheimer’s and related dementias.

The abnormal buildup of specific proteins in the brain is thought to play a key role in the loss of communication between neurons and the eventual death of brain cells. Researchers continue to gain new insights into how the abnormal buildup of beta-amyloid and tau proteins influences disease onset and progression.

Beyond these hallmarks of Alzheimer’s disease, NIH-supported scientists and clinicians are examining a wide range of brain functions and factors that may also play a role in Alzheimer’s and related dementias, including immune response and inflammatory, metabolic, and vascular factors. Our growing understanding of these basic mechanisms and disease pathways—and how they may interact with one another—is vital to identifying therapeutic targets and developing effective interventions.

Researchers are also working to identify the genetic factors that may contribute to overall risk for—or protection against—developing Alzheimer’s and related dementias, as well as how these genes may affect disease progression. This knowledge may then suggest specific disease pathways that can be targeted to develop new treatments.

Genetics

In addition to age and vascular risk factors, many of the best defined risk factors for Alzheimer’s disease are genetic. Several genetic mutations are known to cause the rare early-onset form of the disease, and evidence is mounting for a number of genetic risk factors for late-onset Alzheimer’s. In addition to directly influencing disease risk, genes may interact with environmental and lifestyle factors to contribute to the risk of developing late-onset Alzheimer’s.

By identifying genetic factors that may confer risk or protection, we gain insights into the molecular mechanisms and disease pathways that influence disease onset and progression. In some cases, knowledge of these mechanisms and pathways can suggest targets for treatment and prevention, and even influence the development of new interventions.

Apolipoprotein E (APOE) ε4, one form of the APOE gene, was the only known genetic risk factor for late-onset Alzheimer’s until 2009. Since then, thanks to rapidly changing technologies in genetics, researchers have detected and confirmed a growing list of others (see figure on page 14). These newly discovered genetic risk factors have
strengthened evidence about the involvement in Alzheimer’s disease of certain biological pathways, including amyloid metabolism and immune responses. The results also pointed to new candidate pathways, including those involved in cellular function.

Researchers are working collaboratively on genome-wide association studies to identify additional genes that may play a role in Alzheimer’s disease. Technological advances enabling the scanning of thousands of DNA samples from volunteers both with and without the disease have revolutionized the detection of gene variants involved in a number of diseases and conditions, including Alzheimer’s. NIH also supports research using cutting-edge technology to analyze how genome sequences—the order of chemical letters in a cell’s DNA—may contribute to increased risk or protection. In 2014, NIH directed $24 million over 4 years toward innovative new technologies and computational methods at eight academic medical centers at the forefront of Alzheimer’s genetics research.

Investigators at these centers are analyzing genome sequencing data generated during the first phase of the Alzheimer’s Disease Sequencing Project, a collaboration between the National Institute on Aging (NIA) and the National Human Genome Research Institute begun in 2012. The first phase of the project determined the order of all 3 billion letters in the individual genomes of 580 participants. It also generated whole exome sequencing data (focused on the portion of the genome that directly encodes—or guides production of—proteins that influence risk for or protection against the disorder) of an additional 11,000 volunteers, including 6,000 with Alzheimer’s and 5,000 controls.

In a groundbreaking effort, research teams today are using these data to identify rare genetic variants, explore differences in data from different racial/ethnic groups, and examine how changes in brain structure or function (assessed from brain images and other biomarkers) are associated with genome sequences.

Such approaches in genetics are allowing NIH to move forward with a Precision Medicine Initiative. One goal of the Precision Medicine Initiative is to launch a national cohort study of a million or more Americans to propel understanding of many diseases, including Alzheimer’s and related dementias. Each participant will share his/her genomic information and biological specimens. This information, along with important clinical data from electronic health records (such as laboratory test results and MRI scans) and other data on lifestyle and environmental exposures, will help researchers understand how genomic variations and other health factors affect the development of disease.

**Progress in Understanding Alzheimer’s Genetics**

Recent discoveries have not only identified more genes involved in Alzheimer’s, but also have helped us figure out what they may do. Discovering the mechanisms involved in Alzheimer’s onset and progression, as well as disease-related brain changes, directs us to pathways that might be targeted to help stop disease or protect against it.
Genetic Regions of Interest in Alzheimer’s Disease

By year of discovery

NOTE: Color indicates mechanism of action in the body. See key below.

KEY
- Early-onset genes
- Innate immune/brain inflammatory response genes
- Endocytosis and cellular protein trafficking, including APP trafficking and Aβ processing
- Lipid transport/metabolism
- Synaptic transmission
- Cytoskeletal function, including tau
Recent examples illustrate how such discoveries are moving this area of research forward:

**Longevity gene may boost cognition**

Scientists had previously shown that people who have a variant of the longevity gene KLOTHO have improved brain skills such as thinking, learning, and memory. The gene activates production of a protein found in both the kidney and the brain.

Researchers looked at the impact of a variant of the KLOTHO gene, called KL-VS, on cognitive performance in more than 700 cognitively normal volunteers age 52 to 85 (Dubal et al., 2014). Compared with participants who carried no copies of the KL-VS form, those with one copy had higher blood levels of the klotho protein and performed better on tests of multiple brain functions, including attention, problem solving, visuospatial ability, learning, and memory.

To better understand why, the scientists studied mice genetically engineered to overproduce the klotho protein. Not only did these mice live up to 30 percent longer, they outperformed control mice on tests of learning and memory. The modified mice showed higher-than-normal brain levels of a receptor for the neurotransmitter glutamate, which enhances cognitive function. When this action was blocked in the mice, cognitive function returned to control levels.

This study suggests that drugs targeting the klotho protein could improve cognition in people at risk for Alzheimer's disease. The FY 2017 research agenda calls for increased efforts to incorporate and build on new advances in human biology in the study of the Alzheimer's brain.

**Genetically reprogrammed cells offer new insights into Alzheimer's**

While animal models have provided important information about the basic biology of Alzheimer's, scientists are working hard to develop better human models of the disease. The recent development of induced pluripotent stem cells (iPSCs) is a major step forward in biomedical research. iPSCs are adult human skin cells that have been genetically reprogrammed to resemble embryonic stem cells, and they can be manipulated in tissue culture to produce any type of cell desired.

In Alzheimer's research, iPSCs have advanced our understanding of how gene mutations influence early-onset Alzheimer’s, a rare form that occurs in people in their 30s, 40s, and 50s. These insights inform our basic knowledge of both early- and late-onset disease. Two recent studies are cases in point.

In one study, scientists studied iPSCs donated by people carrying the so-called London mutation in the gene for amyloid precursor protein (APP) (Muratore et al., 2014). Named for the home city of the family in which it was discovered, the London mutation is the most common APP mutation associated with early-onset Alzheimer's disease.

The scientists stimulated mutant and control iPSCs to develop into brain cells and then compared their APP-processing pathways. The mutant cells increased production of beta-amyloid 42, a toxic form of the protein involved in forming amyloid plaques, and higher levels of tau. The findings suggest a direct link between
the biochemical pathways responsible for generating beta-amyloid and tau and revealed the effects of the most common form of the APP mutation.

A second research team used iPSCs to study how mutations in a different gene—presenilin-1 (PSEN1), the most common cause of early onset Alzheimer’s—might wreak havoc (Sproul et al., 2014). They generated neurons from skin cells donated by volunteers from two families carrying PSEN1 mutations. The cells in tissue culture resembled those in the brains of humans with the PSEN1 mutation in that they produced a higher-than-normal ratio of beta-amyloid 42.

The researchers also discovered 14 genes that were activated at significantly higher or lower levels in mutant iPSCs brain cells and identified three genes, NLRP2, ASB9, and NDP, involved in inflammation, energy production, and the generation of new neurons.

These and other intriguing studies show the promise of iPSC technology for unraveling the molecular mechanisms of both early- and late-onset Alzheimer’s disease. Ultimately, these findings could point to new and more precise therapeutic targets. Additional funding in FY 2017 would accelerate such novel explorations into Alzheimer’s disease pathways.

**Alzheimer’s in a dish**

It is extraordinarily difficult to mimic the brain’s complexity in standard laboratory models. Now, NIH-funded researchers have developed a new model that for the first time contains the two proteins that are hallmarks of Alzheimer’s disease. Using genetic engineering to spur the growth of neural stem cells in a gel, the cells formed into three-dimensional networks with the amyloid plaques and tau tangles found in the human brain (Choi et al., 2014). This process took just 6 weeks, compared with the year it takes for plaque alone to form in a mouse model.

The researchers then used this new model, called “Alzheimer’s in a dish,” to show that blocking the formation of amyloid plaques with certain drugs prevents tau tangles from forming inside neurons. This finding lends support to the hypothesis that amyloid triggers the cascade of events that leads to Alzheimer’s dementia. It also provides new encouragement that a category of drugs called beta-secretase and gamma-secretase inhibitors might ultimately benefit patients if given early enough in the course of the disease.

This new model should inform our FY 2017 efforts to test existing and novel drugs as potential therapies, and it may be used to develop models of other neurodegenerative diseases.

**Epigenetics**

The epigenome—chemical modifications, or marks, on DNA that turn gene activity on and off—may influence Alzheimer’s disease. The epigenome can be modified by lifestyle and environmental influences, and studies such as the one described here are fueling scientists’ speculation that epigenomic changes might contribute to Alzheimer’s disease.
**Epigenome changes linked to Alzheimer’s disease**

Scientists looked at samples from 708 donated brains from the NIA-supported Religious Orders Study and Rush Memory and Aging Project (De Jager et al., 2014). About 60 percent of the brains displayed Alzheimer’s disease pathology. They analyzed DNA sequences from the brains for a specific chemical change—methylation, a process that can control how a gene is turned on or off—and correlated that change with amyloid plaque burden, a hallmark of Alzheimer’s disease.

The researchers found greater methylation levels correlated with Alzheimer’s disease pathology in 71 of the 400,000-plus chemical modifications analyzed. These 71 markers were found in gene variants already associated with Alzheimer’s and others suspected to be. These include genes thought to be involved in regulating processing of beta-amyloid and several others that have been linked to cell function.

They estimated that those methylation-related epigenomic changes accounted for about 29 percent of the plaque burden in the participants. This compares to the effect of all known Alzheimer’s genes, which accounted for just 14 percent of the plaque burden in this group. This intriguing new avenue of research exploring how the epigenome influences a person’s risk for developing Alzheimer’s—and ways to target related toxic changes—is a focus of the FY 2017 research agenda.

**Vascular System**

Scientists for some time have been interested in how the body’s vast network of small and large blood vessels—the vascular system—may be involved in the development of dementia and the clinical symptoms of Alzheimer’s disease. Some scientists are focusing on what happens to the brain’s blood vessels in aging and Alzheimer’s. Others are zeroing in on the relationship between Alzheimer’s and vascular problems in other parts of the body, such as cardiovascular disease, stroke, and diabetes.

Recent NIA-funded studies including the following:

**Beta-amyloid impairs the function of the blood-brain barrier**

Researchers used transgenic mice to study how beta-amyloid protein interacts with pericytes, cells that are important for controlling the movement of molecules into and out of blood vessels in the brain (Sagare et al., 2013). They found that beta-amyloid deposits impaired the normal pericyte function of removing the protein from the brain, which then led to further accumulation of the protein. Pericyte deficiency also led to the development of tau pathology and an early loss of neurons that is not normally seen in these transgenic mice.

These findings suggest that pericytes may be a viable target for therapeutic intervention. In FY 2017, researchers hope to further such basic science discoveries.

**Lymphatic drainage system is discovered in the brain**

Scientists have long believed that although the brain maintains a functional immune system, it lacks the type of lymphatic vessels that drain cellular debris from other
tissues in the body. NIH-supported investigators recently made a significant discovery that overturns this scientific dogma (Louveau et al., 2015).

In mice, the investigators developed a new method to mount the membranes covering the brain on a single slide so they could be examined as a unit. While examining the membranes, the investigators noticed what appeared to be lymphatic vessels, and further testing confirmed this fact. The well-hidden vessels follow a major blood vessel into the sinus cavity, an area that is notoriously difficult to image.

The discovery of this remarkable “brain drain” raises a number of research possibilities. For one thing, the vessels appear different in older mice than in younger ones, so researchers are intrigued by the roles they may play in the aging process. In the case of Alzheimer’s disease, the investigators theorize that the vessels may not efficiently remove abnormal proteins.

More research is needed to determine whether the vessels are unable to remove large chunks of amyloid-beta and tau, or if they lose this ability over time. Further, this discovery may have major implications for an array of other brain diseases, including autoimmune diseases and autism. Expanded funding in FY 2017 may lead to such intriguing and unexpected new insights into the array of disease mechanisms involved in Alzheimer’s disease and aging.

Promising Research Opportunities
Our understanding of Alzheimer’s disease at the biological level is mounting rapidly, spurred by the creative thinking of researchers and an array of new technologies that allows them to explore uncharted territory at the genetic, molecular, and cellular levels. These studies were not possible just a few years ago. As translational and clinical studies build on what we have learned, it is critical that scientists accelerate basic science research leading to a new generation of Alzheimer’s treatments. The research milestones developed at the NIH-hosted Alzheimer’s Disease Research Summits in 2012 and 2015 and other input inform this course. Please see the list of milestones to which additional funding in FY 2017 would apply. Also see the full list of milestones aimed at prevention and treatment by 2025.

Moving ahead in basic research
Additional funding in FY 2017 would build on an exploding area of science by conducting:

• Cross-disciplinary, systems-based research that integrates findings on Alzheimer’s disease with research on the fundamental biology and neurobiology of aging
• Studies exploring the interaction between peripheral systems (for example, immunity, metabolism, and the microbiome) and the brain, and the impact of this interaction on brain aging and neurodegeneration
• Epigenetics research on the interaction of genetic and environmental factors across the lifespan, and how this influences brain aging and disease risk, with the goal of identifying potential targets for treatment and prevention
• Projects exploring the impact of sex differences on brain aging and disease
• In-depth studies of the risk-factor gene APOE, including how APOE genotype influences response to drug and nondrug interventions
• Research on how the disruption of circadian rhythms and sleep influence brain aging and risk of Alzheimer’s and related dementias
• Studies of the molecular networks linked to cognitive resilience as potential therapeutic targets for disease prevention
CATEGORY B. DIAGNOSIS, ASSESSMENT, AND DISEASE MONITORING

This category includes research focused on the development, testing, and validation of tools and methods for diagnosing and monitoring patients with Alzheimer’s disease, from the preclinical phase through advanced dementia. These methods and tools include all types of novel and established biomarkers. Topics under this category include fluid biomarkers; imaging biomarkers; cognitive, behavioral, and functional assessment; multimodal biomarkers; novel biomarkers; and novel methodologies and techniques.

In the last decade, science has provided us the ability to diagnose Alzheimer’s disease and monitor its progression, particularly in the research setting. Growing evidence suggests that cellular and brain changes associated with the disease begin years—even decades—before people first show clinical symptoms of memory loss or cognitive difficulties. Increasingly, researchers are employing biomarkers—specific proteins in blood or cerebrospinal fluid (CSF) or imaging of brain structure and function—to identify cellular changes and measure risk for Alzheimer’s, even in symptom-free people.

Progress in Diagnosing, Assessing, and Monitoring Alzheimer’s Disease

Research now is focused on how imaging and fluid biomarkers might accurately predict who is at risk for Alzheimer’s. We are also ascertaining if such biomarkers can be a true measure of the effectiveness of therapies during the earliest stages of the disease. As we intensify research into preclinical markers and measures of disease progression and therapeutic effectiveness, we must also continue to refine neuropsychological and clinical measures in people at later disease stages to develop effective interventions.

Recent studies, upon which new funding would build, examine the following areas:

**Brain region where Alzheimer’s strikes first**

To learn more about where Alzheimer’s-related changes may first strike in the brain, a research team analyzed data from 62 participants (average age, mid- to late-70s) in the National Institute on Aging (NIA)-supported Alzheimer’s Disease Neuroimaging Initiative (Mattsson et al., 2014). The data included imaging that assessed changes in brain volume and CSF measures of amyloid levels. The tests were conducted annually for up to 4 years. At the start of the study, 15 of the volunteers had Alzheimer’s, and the rest were cognitively healthy.

Two-thirds of individuals in the cognitively healthy group showed abnormal CSF amyloid levels at the start of the study or developed them during subsequent years. They also showed progressive shrinkage in the frontoparietal cortex (an area that extends from behind the forehead to the top and upper sides of the brain). In contrast, people with clinical Alzheimer’s disease showed shrinkage in both the frontoparietal cortex and the temporal cortex (which lies roughly at the level of the ears).
This study suggests that neurons in the frontoparietal cortex may be the first to die during Alzheimer’s disease, a finding consistent with evidence that the region is the first to accumulate beta-amyloid. However, because the participants with frontoparietal degeneration remained cognitively healthy as long as their temporal cortex did not shrink, the onset of Alzheimer’s symptoms may be more closely tied to declines in that brain region.

Closer monitoring and more complete understanding of changes in certain brain regions and their link to Alzheimer’s symptoms via imaging may assist in diagnosing the disease as early as possible and tracking the effectiveness of interventions. Increasing FY 2017 funding would advance ongoing efforts to incorporate imaging and fluid biomarkers in all phases of clinical trials, where doing so would advance our understanding of this complex disease.

**Alzheimer’s Disease Progression**

*This diagram illustrates how Alzheimer’s disease-related changes may occur in the brain long before symptoms of cognitive decline first appear in people with mild cognitive impairment (MCI). The curves represent the sequence in which specific markers may play a role as people progress from normal cognition to MCI and, finally, to dementia. This model suggests that in typical late-onset Alzheimer’s disease, tau changes may begin before amyloid changes, but that amyloid changes occur faster and are usually the first ones detectable. It also suggests that amyloid accumulation drives progression of tau and other downstream events in the disorder (Jack et al., 2013).*
Blood biomarkers may predict future dementia risk
A panel of 10 blood lipids might be used to predict future cognitive impairment in asymptomatic older adults, according to researchers who observed 525 otherwise healthy participants, age 70 and older, for 5 years (Mapstone et al., 2014). Forty-six of the participants met the clinical criteria for mild cognitive impairment or Alzheimer’s disease at the start of the study, and 28 others (called “converters”) developed clinical symptoms over the course of the study.

The researchers analyzed blood samples donated by the volunteers. Among the thousands of metabolites (products of cellular metabolism) the researchers measured, they identified 10 lipids that distinguished the converters from those who remained cognitively healthy. To validate the finding, they studied another 40 participants and confirmed that the 10-lipid panel predicted with 90 percent accuracy who among the cognitively healthy group would later develop mild cognitive impairment or Alzheimer’s disease.

If the results of this study are confirmed in larger and more ethnically diverse groups of subjects, blood lipid tests could offer an easy and inexpensive way to predict risk for Alzheimer’s disease. Additional funding in FY 2017 would build on these blood biomarker insights, helping to identify the best candidates to incorporate in clinical trials to assess responses to the intervention.

Immediate recall is first memory function to decline
Understanding the trajectories of loss of different cognitive skills is important for evaluating the early indicators of disease, monitoring disease progression at the individual level, and validating proposed disease progression models. Recently, a team led by researchers at the National Institute on Aging confirmed that different memory skills decline at different rates in people with Alzheimer’s disease.

The investigators gave tests of different memory functions to 895 Baltimore Longitudinal Study of Aging volunteers (Bilgel et al., 2014). The participants, who had a mean age of 70 at the start of the study, were tested an average of five times during clinic visits spaced about 2 years apart.

Immediate recall (the ability to remember events that occurred in the past few minutes) was the first memory function to show signs of deterioration. Delayed recall (the ability to remember more distant events) declined at a later stage of the disease, but at a more rapid rate than immediate recall. This finding suggests that tests of immediate recall may be more useful for detecting Alzheimer’s during early stages of the disease, while tests of delayed recall may be better suited to tracking it at later stages.

These findings will inform the FY 2017 research goal of developing cognitive tests that detect the earliest stages of Alzheimer’s disease.

Screening tool may predict dementia risk
Screening for cognitive impairment is now mandated as part of the Medicare annual wellness visit, but there are no guidelines currently available for how to do these
screenings. Scientists developed and validated a brief Dementia Screening Indicator using data from four large, ongoing cohort studies: the Cardiovascular Health Study, the Framingham Heart Study, the Health and Retirement Study, and the Sacramento Area Latino Study (Barnes et al., 2014).

The Dementia Screening Indicator assigns points to seven factors—educational attainment, stroke, diabetes, difficulty managing money or medications, low body mass index, and depression—to calculate a person’s risk of dementia. The researchers used it to accurately predict who among the volunteers, age 65 to 75, in the four studies was at risk of developing dementia. This simple tool may help physicians and health care workers needing to screen patients for cognitive impairment and clinical trial participation, a priority of the FY 2017 research agenda.

**Abnormal tau and risk for Alzheimer’s-related psychosis**

Psychosis, or having hallucinations or delusions, occurs in 40 percent to 60 percent of people with Alzheimer’s disease and is associated with a more rapid descent into dementia. Researchers studied post mortem brain samples from 45 donors with Alzheimer’s disease and found that a diagnosis of psychosis in people with Alzheimer’s was associated with higher levels of abnormal (hyperphosphorylated) tau in the prefrontal cortex. This area of the brain is implicated in learning, memory, and behavior regulation (Murray et al., 2014).

Improved methods for imaging abnormal deposits of tau in the brains of people with Alzheimer’s disease may help identify those at greater risk for developing psychosis and, subsequently, a more rapid progression to Alzheimer’s dementia. In FY 2017, additional funding will advance the critically important development of tau imaging and fluid biomarkers.

**Promising Research Opportunities**

Research on Alzheimer’s disease diagnosis, assessment, and monitoring will continue to be central to NIH’s research portfolio, with its direct and immediate focus on patients. To help chart that discovery, we are guided by the research milestones developed following the Alzheimer’s Disease Research Summits in 2012 and 2015 and additional input. Please see the list of milestones to which additional funding in FY 2017 would apply. Also see the full list of milestones aimed at prevention and treatment by 2025.

**The way forward in biomarker research**

Advances in imaging and fluid biomarkers over the past decade have led to remarkable results. Researchers can now “see” Alzheimer’s-related pathology and structural and functional changes in the living brain, track disease onset and progression, and use these approaches for testing the effectiveness of promising drugs. Additional funding in FY 2017 is vital to build on these successes and seize research opportunities. Boosting funds would concentrate studies in this area by:

- Developing and validating a full range of translatable biomarkers for use in preclinical and clinical drug development
• Advancing the use of novel positron emission tomography ligands, as well as CSF and blood biomarkers, to identify and access Alzheimer’s pathologies, including tau, inflammation, and synaptic dysfunction

• Developing minimally invasive biomarkers (for example, EEG, blood) for detection and monitoring of Alzheimer’s-related pathology in the brain

• Developing and refining sensitive clinical and neuropsychological assessment measures to detect and track early-stage disease

**Improving care with disease-monitoring technologies**

Additional funding in FY 2017 would advance the use of new technologies that monitor the well-being of people with Alzheimer’s living at home. Advances in this field would not only improve the quality of life for patients and their loved ones, but reduce the higher costs of care provided by nursing facilities and hospitals. These funds would be directed at:

• Research programs developing innovative disease-monitoring technologies, such as wearable monitors and sensors used at home, that evaluate physical and cognitive function and quality of care

• Incorporating these technologies into existing longitudinal studies and clinical trials to capture relevant data
CATEGORY C. TRANSLATIONAL RESEARCH AND CLINICAL INTERVENTIONS

This category aims to capture projects focused on the identification and development of therapies (small molecules, natural products, and biologics) for Alzheimer’s disease from early therapeutic discovery through late-stage preclinical development and all stages of clinical testing. Also included are projects focused on repurposing pharmacological agents already in use for other conditions as well as nonpharmacological interventions.

Topics under this category include drug discovery (small molecules and biologics); preclinical drug development (small molecules and biologics); preclinical proof of concept for nonpharmacological interventions; clinical trial design; early-stage clinical drug testing (Phase I and Phase II clinical trials); late-stage clinical drug testing (Phase III clinical trials); and nonpharmacological interventions and clinical trial development for the neuropsychiatric symptoms of Alzheimer’s disease.

Translational Research

The National Institutes of Health (NIH) funds a broad array of translational research, in which scientists from multiple disciplines take basic science discoveries and then develop and use them to test medicines or other interventions. The projects in this category focus on the identification and development of therapies (small molecules, natural products, and biologics) for all stages of Alzheimer’s disease and from early therapeutic discovery through late-stage preclinical development and testing in clinical trials. We also support studies that test pharmacological agents already in use for other conditions as well as nonpharmacological interventions.

Currently, drugs approved by the U.S. Food and Drug Administration to treat Alzheimer’s symptoms include cholinesterase inhibitors and memantine, which support neurotransmitters important to memory function. These drugs provide symptomatic relief and may slow symptoms of cognitive decline in some people for a limited time. However, they neither halt nor reverse disease progression because they do not target the underlying molecular pathways and brain circuits involved in the development and progression of Alzheimer’s.

The process of discovering and developing drugs for neurodegenerative disorders like Alzheimer’s is extremely expensive and time-consuming. It takes 10 to 15 years from the discovery of a new therapeutic target until a new drug reaches the market, with an average cost of about $1.8 billion (Paul et al., 2010). In recent years, NIH, the U.S. Food and Drug Administration (which regulates drug approval), and the wider research community have worked collaboratively to overcome the many challenges of translational research.

From targets to trials

Alzheimer’s and related dementias are complex disorders with multiple disease pathways that influence disease onset and progression. These disease pathways likely vary from person to person. Accordingly, researchers are investigating an array of interventions that target many potential pathways, including the toxic accumulation...
of amyloid and tau proteins, inflammation and other cellular processes gone awry, environmental factors, and genetic factors. The ultimate goal is to develop multiple therapies to treat or prevent Alzheimer’s, similar to the treatment options developed for other complex diseases, such as cardiovascular disease and cancer.

The NIH-hosted Alzheimer’s Disease Research Summits held in 2012 and 2015 underscored the importance of this approach and outlined other new directions in translational research. Experts at these meetings called for a transformation in the way we think about drug development for Alzheimer’s disease. The new approach is to look beyond the traditional paradigm of identifying a single drug target to investigating networks of targets and multiple drug-target interactions.

Accordingly, ongoing research funded by NIH and plans for future projects with additional funds reflect these new goals and objectives:

• The Accelerating Medicines Partnership-Alzheimer’s Disease’s Target Discovery and Preclinical Validation Project aims to shorten the time between the discovery of potential drug targets and the development of new drugs for Alzheimer’s disease treatment and prevention by integrating the analyses of large-scale molecular data from human brain samples with network modeling. This innovative approach not only identifies the novel pathways and genes involved in this complex disease, but shows how they interact with one another in networks. It also identifies targets for drug development and validation.

• The Accelerating Medicines Partnership investigators are applying cutting-edge systems and innovative approaches to study multidimensional human “omic” data (genomic, epigenomic, proteomic) from more than 2,000 human brains at all stages of the disease with clinical and pathological data. The goal is to discover novel therapeutic targets for Alzheimer’s disease, gain an understanding of genetic impact, assess the protein and metabolic networks within which these novel targets operate and interact with each other, and evaluate their sensitivity to therapeutic compounds tested in multiple model organisms.

• Researchers are partnering with the NIH-funded Alzheimer’s Disease Neuroimaging Initiative to use metabolomics—the study of unique chemical fingerprints in specific cell processes—that chart the trajectory of biochemical changes during Alzheimer’s progression. By correlating biochemical changes in the blood to brain pathology and cognitive changes, they hope to develop blood biomarkers that are less expensive and easier to use than brain imaging or cerebrospinal fluid biomarkers.

• Researchers are using “deep learning” algorithms, a sophisticated computer modeling tool that can learn to recognize patterns to rapidly scan and analyze massive data sets (genes, proteins, and molecular pathways) in thousands of volunteers. This tool for identifying promising drug targets has the potential to slice many years off drug development.
Clinical trials

- Neuropsychiatric symptoms in Alzheimer’s patients, such as agitation and apathy, add to caregivers’ burden and contribute to treatment costs. Researchers are developing a computer model to identify the brain circuits involved in these symptoms that may one day lead to effective therapies.

- NIH-funded researchers are developing diagnostic biomarkers of risk that can be used in routine medical practice. Two new approaches include imaging the retina of the eye to detect amyloid deposits and a simple scratch-and-sniff olfactory test that may predict progression to Alzheimer’s disease.

- The long history of failed drug trials targeting beta-amyloid may be due to testing the drugs in participants whose disease was too far advanced for the drugs to show significant effects. Researchers are now testing anti-amyloid drugs in symptom-free volunteers who have undergone brain scans that show a buildup of amyloid to track both brain changes and cognitive function over time.

- Among known players in the Alzheimer’s disease process, tau is an increasingly attractive drug target. Recent studies have shown that the buildup of tau proteins correlates with the loss of synapses and cognitive decline. Additionally, newly developed brain imaging agents enable researchers to “see” tau in the living brain and assess the effectiveness of drugs targeting the protein.

- It is possible that previous drug trials failed because the medication doses were too low or too high. Dosage and patient selection for future clinical trials can be better informed through the use of quantitative systems pharmacology. This growing field combines experimental and data-driven approaches to devise the treatment plan for the individual volunteer.

Progress in Translational Research

Additional funding in FY 2017 would build upon recent progress in drug discovery and development, in which a number of studies indicate how new approaches may modify underlying mechanisms of disease. Pursuit of innovative research will lead more quickly to design of new therapies and their testing.

Recent studies have shown:

Cancer drug offers hope for Alzheimer’s

NIH’s National Center for Advancing Translational Sciences (NCATS) is supporting the testing of an experimental drug, originally developed to fight cancer, that may prove effective against Alzheimer’s disease. The drug, saracatinib, proved safe in human trials but was shelved by the biopharmaceutical company AstraZeneca when it proved unsuccessful at targeting a family of enzymes (called src kinases) involved in the spread of cancer.

In 2012, researchers discovered that a related kinase called Fyn may play a key role in Alzheimer’s disease. They found that misfolded beta-amyloid protein—a hallmark
of Alzheimer’s—interacts with another protein to activate Fyn excessively and spur the loss of synapses (Um et al., 2012).

The scientists wanted to test whether a precisely targeted compound, such as saracatinib, could block Fyn. They reached out to NCATS’s Discovering New Therapeutic Uses for Existing Molecules program, a pioneering partnership between NIH and industry in which pharmaceutical companies offer compounds that have failed to the scientific community to repurpose for the development of new therapies.

AstraZeneca provided saracatinib at no cost. The researchers gave the compound to mice with Alzheimer’s-like symptoms for 4 weeks and found they could turn off Fyn, get brain synapses firing again, and reverse memory loss (Kaufman et al., 2015). Because saracatinib had already passed human safety tests, the researchers are now conducting a Phase II clinical trial to test its effectiveness in about 150 people with mild Alzheimer’s disease.

The promise of using existing drugs to treat Alzheimer’s is a focus of the FY 2017 research agenda. One goal is to initiate at least three Phase III trials with repurposed drugs or combinations of drugs.

**New compounds stabilize neurons**

Neurons are supported internally by networks of microtubules, microscopic rods of protein that help maintain a neuron’s complex structure and shuttle nutrients around inside it. The protein tau normally stabilizes microtubules, but the abnormal forms of tau that accumulate in Alzheimer’s cause microtubules to fall apart.

Drugs that stabilize microtubules have shown therapeutic benefit in Alzheimer’s model mice. However, when given orally, they became inactive and/or had the potentially lethal side effect of blocking the P-glycoprotein transporter, a protein that helps clear drugs and toxins from the body.

Researchers recently identified two new classes of compounds that substantially enhanced the stability of brain microtubules in normal mice within 4 to 6 days (Lou et al., 2014). These two new classes of microtubule-stabilizing agents can be taken orally, cross into the brain, and do not block the P-glycoprotein transporter. These results offer insights on the development and testing of compounds that may prevent damage to neurons, consistent with our FY 2017 goal of initiating drug trials against known therapeutic targets.

**Drug seems to suppress brain inflammation**

In Alzheimer’s disease, the brain shows signs of chronic inflammation, a tissue response to toxic proteins or cellular injury. The inflammatory response is mounted by glial cells (the support cells of the brain) through the release of proteins called cytokines. In the short term, inflammation promotes tissue repair. But if the inflammatory response persists for months or years, as it does in Alzheimer’s and other neurodegenerative diseases, it can ultimately contribute to neuronal damage.

Researchers recently developed a drug called MW181 to try to control destructive inflammation in neurons. It targets the enzyme p38 MAPK, which helps trigger the
production of pro-inflammatory and potentially damaging cytokines by glia and other cell types (Bachstetter et al., 2014).

The researchers showed that the drug delivered orally in mice inhibited the targeted enzyme. They then administered the drug to mice shortly before injecting them with a bacterial membrane molecule that provokes a strong brain inflammatory response. The drug significantly suppressed the production of several pro-inflammatory cytokines in the brain. These results, while preliminary, offer promise for taking the compound into an early-stage human trial. Such trials are a goal of the FY 2017 translational research agenda.

**Protein may help neurons repair damaged DNA**

In people with Alzheimer’s, the ability to repair damaged neurons is severely impaired. Scientists in the National Institute on Aging (NIA) Intramural Research Program, Baltimore, studied whether and how brain-derived neurotrophic factor (BDNF), a protein that protects neurons, could affect the ability of brain cells to repair DNA damaged by oxidative stress (Yang et al., 2014).

Previous animal studies have shown that exercise can increase the low levels of BDNF found in Alzheimer’s mouse models. The NIA team found that mice exercising on running wheels increased BDNF by activating the CREB protein, which then stimulated the production of APE1, an enzyme that helps repair DNA.

These findings provide a possible explanation for the protective effect of exercise on cognition that has been observed in some studies and offer further rationale for ongoing and new studies of exercise to prevent cognitive decline. This is an important goal identified in the FY 2017 research agenda. In addition, these findings suggest that exercise may enhance the ability of neurons to repair oxidative damage to DNA and that APE1 may be a promising new therapeutic target.

**NIH Clinical Trials**

NIH supports and conducts clinical trials on Alzheimer’s disease, mild cognitive impairment (MCI), and age-related cognitive decline. Mostly sponsored by NIA, these trials take different and varied approaches. Some trials focus on Alzheimer’s treatments that may preserve cognitive function for as long as possible, while others look at how to alleviate behavioral or psychiatric problems. Other trials involve efforts to slow disease progression, such as delaying the progression of MCI to Alzheimer’s dementia, a type of research known as secondary prevention. Still others focus on primary prevention, or helping cognitively healthy people reduce their risk of developing Alzheimer’s disease.

**Testing interventions in clinical trials**

NIA, which oversees NIH’s Alzheimer’s research efforts, funds and conducts clinical trials for Alzheimer’s and age-related cognitive decline. NIA currently supports 38 active clinical trials in this area, including pilot and large-scale trials of a wide range of interventions to prevent, slow, or treat Alzheimer’s disease and/or MCI (see Table 1 and Table 2). Areas of investigation include the connection between Alzheimer’s and certain diseases, such as diabetes and cardiovascular disorders,
and whether treatments for these conditions may affect the development or course of Alzheimer’s. Lifestyle factors that may influence disease onset and progress, such as exercise and stress, are also being examined.

The primary prevention trials listed in Table 1 include an NIA-funded add-on to a large NIH trial that addresses other primary outcomes. The Systolic Blood Pressure Intervention Trial (SPRINT), run by NIH’s National Heart, Lung, and Blood Institute, is evaluating the health effects of lowering systolic blood pressure from 140 mm Hg to 120 mm Hg. The SPRINT-MIND add-on study, supported by NIA and NIH’s National Institute of Neurological Disorders and Stroke, is assessing the effect of lowering systolic blood pressure on cognitive decline and the development of MCI and Alzheimer’s disease. The study will also use brain imaging to measure treatment effects on brain structure, including white matter lesions typical of vascular disease.
### Table 1: Ongoing Alzheimer’s Disease Presymptomatic/Primary Prevention Trials Funded by NIA

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/Institution</th>
<th>Anticipated Completion</th>
</tr>
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<tbody>
<tr>
<td><strong>Immunotherapy/Anti-Amyloid</strong></td>
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<tr>
<td><strong>API ADAD</strong> (Alzheimer’s Prevention Initiative Autosomal Dominant Alzheimer’s Disease Trial)</td>
<td>Eric Reiman, Banner Alzheimer’s Institute</td>
<td>2018</td>
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<tr>
<td><strong>API APOE4</strong> (Alzheimer’s Prevention Initiative Apolipoprotein E4 Trial)</td>
<td>Eric Reiman, Banner Alzheimer’s Institute</td>
<td>2019</td>
</tr>
<tr>
<td><strong>DIAN-TU</strong> (Dominantly Inherited Alzheimer Network Trial)</td>
<td>Randall Bateman, Washington University</td>
<td>2019</td>
</tr>
<tr>
<td><strong>A4 Trial</strong> (Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease)</td>
<td>Reisa Sperling, Harvard Medical School</td>
<td>2019</td>
</tr>
<tr>
<td><strong>Active Immunotherapy for Cognitive Decline in Adults with Down Syndrome</strong></td>
<td>Michael Rafii, University of California, San Diego</td>
<td>2020</td>
</tr>
<tr>
<td><strong>Dominantly Inherited Alzheimer Network Trials Unit—Adaptive Prevention Trial</strong></td>
<td>Randall Bateman, Washington University</td>
<td>2020</td>
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<tr>
<td><strong>Hormones</strong></td>
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<tr>
<td><strong>Estrogen Receptor-beta PhytoSERMs for Management of Menopause and Age-Associated Memory Decline</strong></td>
<td>Lon Schneider, University of Southern California</td>
<td>2020</td>
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<tr>
<td><strong>Cardiovascular</strong></td>
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<tr>
<td><strong>Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for Alzheimer’s Disease</strong></td>
<td>Cynthia Carlsson, University of Wisconsin, Madison</td>
<td>2015</td>
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<tr>
<td><strong>SPRINT-MIND</strong> (Systolic Blood Pressure Intervention Trial-MIND)</td>
<td>David Reboussin, Wake Forest University</td>
<td>2017</td>
</tr>
<tr>
<td><strong>ASPREE</strong> (Aspirin in Reducing Events in the Elderly)</td>
<td>Richard Grimm, Berman Center for Outcomes &amp; Clinical Research; John McNeil, Monash University</td>
<td>2017</td>
</tr>
</tbody>
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(continued)

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1. **Trial supported through Alzheimer’s Disease Cooperative Study (ADCS).**
2. **NIA funded add-on trials: SPRINT-MIND (add-on to National Heart, Lung, and Blood Institute’s and National Institute of Diabetes and Digestive and Kidney Diseases’ SPRINT trial; co-funded with the National Institute of Neurological Disorders and Stroke).**
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/ Institution</th>
<th>Anticipated Completion</th>
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<tbody>
<tr>
<td><strong>Nonpharmacological—Exercise</strong></td>
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<tr>
<td><strong>LIFE</strong> (Lifestyle Interventions and Independence for Elders)</td>
<td>Marco Pahor, University of Florida</td>
<td>2015</td>
</tr>
<tr>
<td><strong>Effect of Physical Activity on Cognition Relative to APOE Genotype</strong></td>
<td>Jennifer Etnier, University of North Carolina at Greensboro</td>
<td>2018</td>
</tr>
<tr>
<td><strong>Effect of Aerobic Exercise on Alzheimer’s Pathophysiology in Preclinical Alzheimer’s Disease</strong></td>
<td>Jeffrey Burns, University of Kansas</td>
<td>2019</td>
</tr>
<tr>
<td><strong>Nonpharmacological—Cognitive Training</strong></td>
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<tr>
<td><strong>Plasticity-based Adaptive Cognitive Remediation for Alzheimer’s Disease</strong></td>
<td>Hyun Lee, Brain Plasticity, Inc.</td>
<td>2020</td>
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<tr>
<td><strong>Other Interventions</strong></td>
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<tr>
<td><strong>Citalopram Decreases CSF Aβ: A Randomized Dose Finding Trial</strong></td>
<td>Yvette Sheline, Washington University</td>
<td>2018</td>
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</tbody>
</table>

*Note:* For information on new and currently recruiting trials, visit [www.nia.nih.gov/alzheimers/clinical-trials](http://www.nia.nih.gov/alzheimers/clinical-trials) or [ClinicalTrials.gov](https://clinicaltrials.gov).
## Table 2.
Ongoing Alzheimer's Disease/MCI Clinical Trials Funded by NIA

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/Institution</th>
<th>Anticipated Completion</th>
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<tbody>
<tr>
<td><strong>Nutritional</strong></td>
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<tr>
<td>Lipoic Acid and Omega-3 Fatty Acids in Alzheimer's Disease</td>
<td>Lynne Shinto, Oregon Health &amp; Science University</td>
<td>2015</td>
</tr>
<tr>
<td>Benfotiamine in Alzheimer's Disease: A Pilot Study</td>
<td>Gary Gibson, Burke Medical Research Institute</td>
<td>2020</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilot Trial of Carvedilol in Alzheimer's Disease</td>
<td>Giulio Maria Pasinetti, Mt. Sinai School of Medicine, and Paul Rosenberg, Johns Hopkins University</td>
<td>2015</td>
</tr>
<tr>
<td>Hypertension, Angiotensin Receptor Blockers, and Cognition Effects and Mechanisms</td>
<td>Ihab Hajjar, University of Southern California</td>
<td>2018</td>
</tr>
<tr>
<td>Modulation of microRNA Pathways by Gemfibrozil in Predementia Alzheimer's Disease</td>
<td>Gregory Jicha, University of Kentucky</td>
<td>2019</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopregnanolone Regenerative Therapeutic for MCI/Alzheimer's Disease</td>
<td>Roberta Diaz Brinton, University of Southern California</td>
<td>2019</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic Effect of Intrasal Insulin on Cognition, Function, and Alzheimer's Disease Biomarkers</td>
<td>Suzanne Craft, University of Washington</td>
<td>2018</td>
</tr>
<tr>
<td><strong>Nonpharmacological—Exercise</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI: Cerebrovascular Dysfunction and Exercise Training</td>
<td>Rong Zhang and Hanzhang Lu, University of Texas Southwestern Medical Center</td>
<td>2015</td>
</tr>
<tr>
<td>Aerobic Exercise in Alzheimer's Disease</td>
<td>Fang Yu, University of Minnesota</td>
<td>2019</td>
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</tbody>
</table>

[^1]: Trial supported through Alzheimer's Disease Cooperative Study (ADCS).

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<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/ Institution</th>
<th>Anticipated Completion</th>
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</thead>
<tbody>
<tr>
<td>Genes, Exercise, Neurocognitive and Neurodegeneration: Community-Based Approach</td>
<td>Thomas Obisesan, Howard University</td>
<td>2020</td>
</tr>
<tr>
<td><strong>Nonpharmacological—Combination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Benefits of Interactive Mental and Physical Exercise for MCI</td>
<td>Cay Anderson-Hanley, Union College</td>
<td>2019</td>
</tr>
<tr>
<td>Cognitive and Aerobic Resilience for the Brain</td>
<td>Frederick Unverzagt, Indiana University</td>
<td>2020</td>
</tr>
<tr>
<td><strong>Nonpharmacological—Home Based Interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADMIT (Alzheimer’s Disease Multiple Intervention Trial)</td>
<td>Chris Callahan, Indiana University</td>
<td>2016</td>
</tr>
<tr>
<td>Preventing Cognitive Decline in African Americans with MCI</td>
<td>Barry Rovner, Thomas Jefferson University</td>
<td>2016</td>
</tr>
<tr>
<td>MIND: Care Coordination for Community-Living Persons With Dementia</td>
<td>Quincy Samus, Johns Hopkins University</td>
<td>2020</td>
</tr>
<tr>
<td><strong>Nonpharmacological—Cognitive Training</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Training and Practice Effects in MCI</td>
<td>Kevin Duff, University of Utah</td>
<td>2020</td>
</tr>
<tr>
<td>Processing Speed Training to Preserve Driving and Functional Competencies in MCI</td>
<td>Virginia Bradley, University of Alabama at Birmingham</td>
<td>2020</td>
</tr>
<tr>
<td><strong>Nonpharmacological—Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic Effects of Cataract Removal in Alzheimer’s Disease</td>
<td>Grover Gilmore, Case Western Reserve University</td>
<td>2015</td>
</tr>
<tr>
<td>Pilot Combination Treatment Trial of MCI with Depression</td>
<td>Davangere Devanand, New York State Psychiatric Institute/Columbia University</td>
<td>2015</td>
</tr>
<tr>
<td>Mild Cognitive Impairment and Obstructive Sleep Apnea</td>
<td>Kathy Richards, George Mason University</td>
<td>2016</td>
</tr>
<tr>
<td>Deep Brain Stimulation for Alzheimer’s Disease</td>
<td>Constantine Lyketsos, Johns Hopkins University</td>
<td>2018</td>
</tr>
</tbody>
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### Table 2. continued

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/Institution</th>
<th>Anticipated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other Interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAV-NGF Gene Delivery in Alzheimer’s Disease</td>
<td>Paul Aisen, University of California, San Diego</td>
<td>2015</td>
</tr>
<tr>
<td>Clinical Intervention of T3D-959 as a Potential Disease Remedial Therapeutic for the Treatment of Alzheimer’s Disease</td>
<td>John Didsbury, T3D Therapeutics</td>
<td>2018</td>
</tr>
<tr>
<td>Olfactory Deficits and Donepezil Treatment in Cognitively Impaired Elderly</td>
<td>Davangere Devanand, Columbia University</td>
<td>2019</td>
</tr>
<tr>
<td>Immune System Stimulation with Sargramostim in Subjects with MCI Due to Alzheimer’s Disease</td>
<td>Ted Ashburn, Sanofi Aventis U.S., Inc.</td>
<td>2019</td>
</tr>
</tbody>
</table>

**Note:** For information on new and currently recruiting trials, visit [www.nia.nih.gov/alzheimers/clinical-trials](http://www.nia.nih.gov/alzheimers/clinical-trials) or ClinicalTrials.gov.
In addition, NIA supports clinical trials focused on understanding and treating age-related cognitive decline and its relationship to Alzheimer’s disease and related dementias (see Table 3.) These trials are testing many possible interventions that may help preserve or improve cognition in older people, including dietary supplements and vitamins, hormones, exercise, cognitive training, and drugs.

### Table 3.
**Ongoing Age-Related Cognitive Decline Clinical Trials Funded by NIA**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/ Institution</th>
<th>Anticipated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Training</strong></td>
<td></td>
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<tr>
<td>ALERT (Neuroplasticity Based Training for Age-Related Cognitive Decline)</td>
<td>Thomas Van Vleet, Posit Science Corp.</td>
<td>2016</td>
</tr>
<tr>
<td>Cognitive Training Effects in Adults Using Brain-Plasticity-Based Computer Games</td>
<td>Kristi Multhaup, Davidson College, and Mark Faust, University of North Carolina, Charlotte</td>
<td>2016</td>
</tr>
<tr>
<td>Examining the Mechanisms of Immersive Computerized Training Interventions for Old</td>
<td>Jason Allaire, North Carolina State University</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Omega-3 Fatty Acids and Antioxidants</strong></td>
<td></td>
<td></td>
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<tr>
<td>VITAL-Cog (A Large Randomized Trial of Vitamin D, Omega-3 Fatty Acids, and Cognitive Decline)</td>
<td>Jae Kang, Brigham and Women’s Hospital</td>
<td>2016</td>
</tr>
<tr>
<td>Omega-3 PUFAs for the Vascular Component of Age-Related Cognitive Decline</td>
<td>Lynne Shinto, Oregon Health &amp; Science University</td>
<td>2017</td>
</tr>
<tr>
<td><strong>Active Engagement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acting Out: Influence of an Acting Intervention on Cognition and Brain Function</td>
<td>Arthur Kramer, University of Illinois, Urbana-Champaign</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td></td>
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<tr>
<td>Estrogen Effects on Cholinergic Function in Older Women</td>
<td>Paul Newhouse, Vanderbilt University</td>
<td>2015</td>
</tr>
<tr>
<td>Testosterone Trial in Older Men</td>
<td>Peter Snyder, University of Pennsylvania</td>
<td>2016</td>
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</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/Institution</th>
<th>Anticipated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
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<tr>
<td>Cognitive Benefits of Aerobic Exercise Across the Age Span</td>
<td>Yaakov Stern and Richard Sloan, Columbia University</td>
<td>2015</td>
</tr>
<tr>
<td>Aerobic Exercise, Neurotrophins, and fMRI of Hippocampal Function and Structure</td>
<td>Karin Schon, Boston University</td>
<td>2016</td>
</tr>
<tr>
<td>Cognitive/Brain Effects of Adding Weight Loss to Exercise in Obese Older Adults</td>
<td>Christina Hugenschmidt, Wake Forest University</td>
<td>2018</td>
</tr>
<tr>
<td>Enhancing Function in Later Life: Exercise and Functional Network Connectivity</td>
<td>Angela Bryan, University of Colorado at Boulder</td>
<td>2019</td>
</tr>
<tr>
<td><strong>Exercise and Cognitive Training</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Control and Physical Exercise</td>
<td>Yaakov Stern, Columbia University</td>
<td>2016</td>
</tr>
<tr>
<td>FAST (Fit &amp; Active Seniors Trial)</td>
<td>Arthur Kramer, University of Illinois, Urbana-Champaign</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Exercise and Stress Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remediating Age-Related Cognitive Decline: Mindfulness-Based Stress Reduction and Exercise</td>
<td>Eric Lenze, Washington University</td>
<td>2019</td>
</tr>
</tbody>
</table>

*Note:* For information on new and currently recruiting trials, visit [www.nia.nih.gov/alzheimers/clinical-trials](http://www.nia.nih.gov/alzheimers/clinical-trials) or [ClinicalTrials.gov](https://clinicaltrials.gov).
NIA-supported clinical trials investigating drugs and protocols to prevent and treat delirium in older people are listed in Table 4. Normally a transitory state of confusion, delirium may occur following surgery, as a result of trauma, or after a serious illness. In older people, delirium sometimes has a long-lasting, negative impact on cognition.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/Institution</th>
<th>Anticipated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology of Postoperative Delirium in Older Patients</td>
<td>Jacqueline Leung, University of California, San Francisco</td>
<td>2015</td>
</tr>
<tr>
<td>Perioperative Cognitive Function—Dexmedetomidine and Cognitive Reserve</td>
<td>Jeffrey Silverstein, Mt. Sinai School of Medicine</td>
<td>2015</td>
</tr>
<tr>
<td>Placebo Controlled Trial of L-Tryptophan in Post-Operative Delirium</td>
<td>Thomas Robinson, University of Colorado, Denver</td>
<td>2015</td>
</tr>
<tr>
<td>Pharmacological Management of Delirium</td>
<td>Malaz Boustani, Indiana University School of Medicine</td>
<td>2016</td>
</tr>
<tr>
<td>STRIDE (Postoperative Delirium in Elderly Surgical Patients)</td>
<td>Frederick Sieber, Johns Hopkins University</td>
<td>2016</td>
</tr>
<tr>
<td>Effects of Light vs. Deep Anesthesia on Postoperative Cognitive Outcomes</td>
<td>Jacqueline Leung, University of California, San Francisco</td>
<td>2017</td>
</tr>
<tr>
<td>MIND-USA (Modifying the Impact of ICU-Associated Neurological Dysfunction-USA Study)</td>
<td>E. Wesley Ely, Vanderbilt University Medical Center</td>
<td>2017</td>
</tr>
<tr>
<td>ENGAGES (Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes)</td>
<td>Michael Avidan, Washington University</td>
<td>2019</td>
</tr>
</tbody>
</table>

Note: For information on new and currently recruiting trials, visit [www.nia.nih.gov/alzheimers/clinical-trials](http://www.nia.nih.gov/alzheimers/clinical-trials) or [ClinicalTrials.gov](https://clinicaltrials.gov).
NIA-funded trials listed in Table 5 focus on psychiatric conditions and symptoms—agitation, apathy, and depression—commonly associated with MCI and Alzheimer’s disease. Researchers are investigating ways to alleviate these distressing symptoms, which strongly impact both patients’ and caregivers’ quality of life.

Table 5.
Ongoing Alzheimer’s Disease/MCI Neuropsychiatric Symptom Clinical Trials Funded by NIA

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/Institution</th>
<th>Anticipated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIADS-3: An RCT of Venlafaxine for Depression in Alzheimer’s Disease</td>
<td>Paul Rosenberg, Johns Hopkins University</td>
<td>2016</td>
</tr>
<tr>
<td>ADMET 2 (Apathy in Alzheimer’s Disease Methylphenidate Trial 2)</td>
<td>Jacobo Mintzer, Medical University of South Carolina</td>
<td>2020</td>
</tr>
<tr>
<td>Treatment of Psychosis and Agitation in Alzheimer’s Disease</td>
<td>Davangere Devanand, Columbia University</td>
<td>2020</td>
</tr>
<tr>
<td>Nonpharmacological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reducing Agitation in Dementia Patients at Home: Customized Activity Trial</td>
<td>Laura Gitlin, Johns Hopkins University</td>
<td>2018</td>
</tr>
<tr>
<td>Function and Behavior-Focused Care for Nursing Home Residents with Dementia</td>
<td>Elizabeth Galik, University of Maryland</td>
<td>2019</td>
</tr>
</tbody>
</table>

Note: For information on new and currently recruiting trials, visit [www.nia.nih.gov/alzheimers/clinical-trials](http://www.nia.nih.gov/alzheimers/clinical-trials) or [ClinicalTrials.gov](https://clinicaltrials.gov).
**Recruitment and empowering citizens**

Increasingly, NIH promotes patient engagement in every step of the research process. Including the patient perspective in trial design not only builds trust, it enables investigators to design studies that measure outcomes that are important to patients and caregivers. This engagement also improves researcher interaction with and access to people who may volunteer to participate in a clinical study.

More than 70,000 volunteers with Alzheimer’s, mild cognitive impairment, or normal cognition are needed for ongoing clinical trials and studies. Researchers will need to screen at least half a million potential volunteers to reach this goal.*

NIH promotes clinical trial participation through the Alzheimer’s Disease Education and Referral (ADEAR) Center. This center is the primary Federal resource for information about Alzheimer’s disease, research, and caregiving.

The ADEAR Center provides information and referrals to ongoing studies via a toll-free number (1-800-438-4380) and at adear@nia.nih.gov. Learn more about participating in clinical trials at [www.nia.nih.gov/alzheimers/volunteer](http://www.nia.nih.gov/alzheimers/volunteer).

*Calculated based on data from ClinicalTrials.gov on open trials in the United States for the condition Alzheimer’s disease or mild cognitive impairment. National Institutes of Health [Internet]. Bethesda (MD): NIH.

**Prevention trials launch new era in Alzheimer’s research**

Alzheimer’s-related brain changes take place years, even decades, before symptoms appear, and scientists have long sought to test therapies early in the disease process. With recent advances in imaging and biomarkers that enable researchers to detect the earliest signs of Alzheimer’s-related brain changes, interventions are beginning to be tested in at-risk but symptom-free volunteers and in those in the early stages of the disease.

These prevention trials, described below, are testing promising drugs that target amyloid proteins that form plaques in the brain, a key feature of Alzheimer’s disease. Although previous trials of anti-amyloid agents failed in people with mild to moderate late-onset Alzheimer’s, these groundbreaking prevention trials will help determine if the interventions are effective if begun earlier in the disease process.

The [Dominantly Inherited Alzheimer Network-Trial Unit](http://www.nia.nih.gov/diagnoses-alzheimers) is testing two anti-amyloid drugs in volunteers who carry a gene for a rare form of early-onset Alzheimer’s disease. The trial is recruiting 160 volunteers with no or mild symptoms at several U.S. and international sites. The trial will test two anti-amyloid drugs, gantenerumab and solanezumab, provided by Eli Lilly and Company and Hoffmann-La Roche, aimed at delaying or preventing Alzheimer’s. The agent that performs best with regard to...
safety, tolerability, and biomarker efficacy will advance to a Phase III trial. Recruiting is underway.

The Alzheimer’s Prevention Initiative (API) is an international collaborative formed by the Banner Alzheimer’s Institute, Phoenix, to evaluate promising prevention therapies in cognitively normal people who, based on their age and genetic background, are at the highest imminent risk of developing Alzheimer’s disease symptoms. These trials include:

- **API Autosomal Dominant Alzheimer’s Disease Trial.** This trial is evaluating an anti-amyloid treatment in approximately 300 adult members of a Colombian clan with a family history of rare, early-onset Alzheimer’s. The study is using brain scans, fluid biomarkers, and cognitive testing to track amyloid levels, changes in brain structure and function, and cognitive performance in participants taking the drug crenezumab. The trial is co-funded by the Banner Alzheimer’s Foundation and Genentech, a biotechnology company that is providing the test drug.

- **API APOE4 Trial.** This trial will test two anti-amyloid therapies, an active immunotherapy and a BACE (beta-secretase1) inhibitor, that may prevent or delay the development of Alzheimer’s symptoms in people at high risk for the disease because of their age and genetic status. The 1,300 cognitively normal volunteers will be age 60-75 and carry two copies of the APOE ε4 gene, the best known risk factor for late-onset disease. Pending regulatory approval, the 5-year study will begin in late 2015/early 2016 at sites in North America and Europe. The trial is co-funded by the Banner Alzheimer’s Foundation and Novartis, a pharmaceutical company that is providing the test drugs.

**NIH supports research network and groundbreaking trials**

NIH is a primary funder of the Alzheimer’s Disease Cooperative Study (ADCS), the Nation’s premier clinical-trials study network focused on innovative Alzheimer’s treatments. ADCS has enabled researchers to take intriguing findings from basic and clinical studies and test them in clinical trials.

Made up of more than 70 research sites in the United States and Canada, ADCS investigates both the cognitive and behavioral symptoms of Alzheimer’s disease, including therapies that might not otherwise be developed by industry. ADCS investigators also have developed novel clinical-trial designs and tools.

The current round of ADCS studies focuses on a variety of promising areas:

- **Study of Nasal Insulin in the Fight Against Forgetfulness (SNIFF).** This Phase II/III, double-blind, placebo-controlled study is evaluating growing evidence that insulin carries out multiple functions in the brain, and that poor regulation of glucose may contribute to the development of Alzheimer’s disease. Interestingly, insulin administered through the nasal cavity is transported within a few minutes into the brain but does not affect blood sugar or blood insulin levels.
The SNIFF trial is evaluating whether a type of insulin, when administered as a nasal spray, improves memory in adults with mild memory impairment or Alzheimer’s disease. Participants will use a nasal spray device with either insulin or a placebo for 12 months, followed by 6 months in which all will receive insulin. Recruitment of 250 volunteers diagnosed with amnestic MCI or early Alzheimer’s at about 30 research clinics nationwide is ongoing.

- **A4 Trial** *(Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease)*: A4 is testing an amyloid-clearing drug in 1,000 symptom-free older volunteers who have abnormal levels of amyloid detected by positron emission tomography (PET) brain scans. Researchers want to see if decreasing amyloid burden during the symptom-free stage of Alzheimer’s will reduce damage to the brain and delay cognitive decline. Clinically normal volunteers age 65 and older will be screened with PET imaging. Those with amyloid loads that place them at risk will be treated for 3 years with solanezumab or a placebo. Eli Lilly and Company is providing the drug and co-funds the trial. Recruitment is underway.

- **CSF Pharmacodynamic Trial**: When testing potential new drug therapies, specifically those targeting key Alzheimer’s disease pathways, scientists use cerebrospinal fluid (CSF) and blood plasma biomarkers to see if the compound crossed the blood-brain barrier and engaged the relevant target. To increase the efficacy and speed of drug development, ADCS is working to develop advanced methods that sample CSF and plasma levels over time. These methods will enable researchers to track levels of several Alzheimer’s-related proteins to better understand how a drug influences Alzheimer’s disease and to help guide decisions about whether a drug warrants further clinical testing.

- **EXERT (Exercise MCI Trial)**: It is well established that exercise can help maintain physical function and reduce the risk of a number of age-related medical conditions, including cardiovascular disease and diabetes. Although exercise has been shown to improve cognition in animal models and short-term human studies, it has not been shown in major clinical trials to improve cognition or alter the hallmarks of Alzheimer’s disease in the brain. This randomized, controlled trial will test whether supervised aerobic exercise can influence cognitive decline, slow brain atrophy, or delay Alzheimer’s in older adults with MCI. Sedentary older adults with MCI will participate in a year-long program at local YMCAs in which one group will do high-intensity aerobic exercise and the other will do stretching. Cognitive testing, CSF biomarkers, and magnetic resonance imaging results will provide critical data on the effects of aerobic exercise on cognition and Alzheimer’s-related pathology.
• **Prazosin for Treating Agitation Trial.** Disruptive agitation is often a chronic problem in people with Alzheimer’s. It can dramatically increase caregiver burden and patient distress, often leading to long-term care outside the home. Drugs currently used to treat agitation are not very effective and may even cause additional harm in older people, such as increased risk of stroke or excessive sedation. Research has shown that prazosin, a generic drug used to treat high blood pressure, may be effective in treating behavioral problems by reducing excess adrenalin effects in the brain. Planning for the trial is underway.

### Progress in Clinical Trials

As the clinical trials noted above are nearing completion or getting underway, recent findings, while not affecting the course of Alzheimer’s disease, have shown some promise in symptom management. Positive outcomes have been reported in drugs that might help manage behaviors and aid cognitive training:

**Ritalin improves attention and apathy in people with dementia**

Attention problems and apathy, both common in people with Alzheimer’s disease, may involve shared brain pathways. Methylphenidate (also known as Ritalin®) has been shown to reduce apathy in Alzheimer’s patients, and it may improve attention as well. In one recent study, investigators tested methylphenidate in 60 patients with mild to moderate Alzheimer’s disease and significant apathy (Lanctôt et al., 2014). In the randomized trial, participants were given either methylphenidate (10 mg twice daily) or placebo for 6 weeks, with clinical tests of attention and apathy administered at the start of the study and then every 2 weeks.

Over the course of the study, the people taking methylphenidate showed significantly greater improvement on tests of attention than the placebo group. Apathy was also reduced in about one-third of those on the drug therapy, but this reduction did not correlate with improvements in attention.

The results of this Phase II trial suggest that methylphenidate improves attention deficits and may help improve apathy in people with Alzheimer’s disease. The promise of repurposed drugs will be explored under the FY 2017 research agenda.

**Treating agitation**

People with Alzheimer’s disease are frequently agitated, which can lead to disruptive behavior and aggressiveness. Such behaviors are commonly cited by family members as a primary reason for moving Alzheimer’s patients to nursing homes.

A team of researchers evaluated the efficacy of citalopram, a type of antidepressant called a selective serotonin reuptake inhibitor (SSRI), for treating agitation in people with Alzheimer’s disease (Porsteinsson et al., 2014).

In 186 volunteers with moderate to severe agitation, half were given citalopram (up to 30 mg daily for 9 weeks), and the other half, a placebo. All received a nondrug intervention consisting of educational materials and counseling sessions for themselves and their caregiver.
After 9 weeks, citalopram significantly reduced agitation. Forty percent of the patients receiving citalopram showed marked or moderate improvement, compared with 26 percent receiving a placebo. Importantly, caregivers of patients on the drug reported significantly less stress than caregivers of those in the placebo group. Citalopram treatment did have some adverse effects, however, as some patients taking the drug developed an abnormal heart rhythm and performed slightly worse on cognitive tests.

This study shows the potential utility of citalopram in treating agitation in Alzheimer’s patients. Additional funding to support the FY 2017 research agenda will expand such promising investigations into repurposed drugs.

**Cognitive training in older people has positive results**

There is considerable interest in cognitive training for maintaining brain function and staving off impairment. Findings from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, funded by NIA and the National Institute of Nursing Research at NIH, showed 10 years ago that particular types of cognitive training in older people could improve or maintain function in laboratory tests. Scientists wanted to see if the training benefits would last over time, so they tested some of the original ACTIVE participants 10 years later. A recent report from that follow-up study showed that benefits accrued from the training were evident even a decade later (Rebok et al., 2014).

The original 2,832 volunteers in the ACTIVE study—healthy, community-dwelling adults who averaged age 74 at the beginning of the study—were divided into a control group and three training groups, which measured effects on memory, reasoning, and speed of processing. The training groups participated in ten 60- to 70-minute sessions over 5 to 6 weeks, with some participants randomly selected for later booster sessions. The study measured effects for each specific cognitive ability trained immediately following the sessions and at intervals for up to 10 years after the training.

At the end of 10 years, all groups showed declines from their baseline test performance in memory, reasoning, and speed of processing. However, the participants who had training in reasoning and speed of processing a decade earlier experienced less decline than those in the memory and control groups. There was no difference in memory performance between the memory group and the control group, however.

Studies to advance such promising nonpharmacological approaches aimed at delaying or preventing Alzheimer’s disease are one area of focus for the FY 2017 research agenda.

**Promising Research Opportunities**

The recommendations and subsequent research milestones resulting from the Alzheimer’s Disease Research Summits held in 2012 and 2015 provide a broad framework targeting the key research goal of the National Plan to Address Alzheimer’s—finding effective interventions by 2025. Please see the list of milestones.
to which additional funding in FY 2017 would apply. Also see the full list of milestones aimed at prevention and treatment by 2025.

**Stepping up translational research and testing of interventions**

FY 2017 funding of the specific goals outlined below would speed NIH discoveries made in the lab into clinical trials and, ultimately, result in effective treatments so desperately needed to delay, prevent, or treat Alzheimer’s disease. Preclinical studies and clinical trials are among the most expensive of our investments in Alzheimer’s disease research, with trials often involving hundreds or thousands of individuals over many years.

Critically needed additional investments in FY 2017 would be used for:

- Sophisticated systems biology/pharmacology programs building models of disease that pursue brain networks as drug targets
- Public-private partnerships that work noncompetitively to validate targets developed through the Accelerating Medicine Partnership-Alzheimer’s Disease initiative
- Phase I, II, and III clinical trials investigating both existing and new targets, to include some using innovative trial designs
- Clinical trials for nonpharmacological interventions aimed at preventing Alzheimer’s disease
- Programs to support drug repurposing and combination therapies
- Drug discovery efforts to develop novel therapeutic agents against novel targets
- Programs that improve clinical studies and trials recruitment, such as community partnerships, to make participation easier by “bringing the trial” to a volunteer’s home and using electronic consent forms
CATEGORY D. EPIDEMIOLOGY

This category includes all types of epidemiological studies (cross-sectional, prospective, and longitudinal) that examine how genetic, lifestyle, and environmental factors influence the incidence, prevalence, and clinical course of Alzheimer’s disease.

Topics under this category include genetic/epigenetic risk; cardiovascular and metabolic factors; nutrition and other environmental factors; and multimodal risk factors due to race, ethnicity, gender, and age.

Here are some sobering facts:

- While estimates vary, studies to date find that as many as 5.1 million Americans age 65 and older have Alzheimer’s disease.
- The greatest risk factor for Alzheimer’s is age. The number of people with the disease doubles for every 5-year interval beyond age 65.
- The Bureau of the Census estimates that the number of people age 65 and older in the United States will almost double to 72.1 million by 2030.
- Further, the number of Americans over age 85—those at highest risk—is expected to increase from 5.5 million in 2010 to 8.7 million in 2030.

The implication is clear: Unless we find effective interventions to prevent or treat Alzheimer’s disease, the number of affected Americans will soar in the coming decades.

Preparing for the human, financial, and societal challenges of Alzheimer’s disease and related dementias requires an understanding of the disease not just at the level of molecules and cells, but at the level of communities and populations. The National Institutes of Health (NIH) supports a broad range of population studies to address these and related questions.

Studies to date have told us a great deal about who may be at risk for Alzheimer’s, factors that influence the disease, and societal impacts, but it is critical to refine and update this knowledge. Additional funding in FY 2017 would expand our understanding of this complex and devastating disease and further the 2025 goal of identifying effective interventions by addressing:

- Who develops Alzheimer’s disease, and who seems to be protected?
- What other conditions are associated with development of the disease?
- What are the financial, economic, social, and policy costs of the disease?

The NIH-led Precision Medicine Initiative, which plans to launch a national cohort study of a million or more Americans to propel the understanding of diseases such as Alzheimer’s and related dementias, will take population studies to the next level. The Precision Medicine Initiative’s ultimate goal is to develop therapies that take into account the variability in genes, environment, and lifestyle of each patient.
Progress in Identifying Risk and Protective Factors

Advancing age and genetics are known risk factors for Alzheimer’s disease, but it is becoming evident that a highly complex mix of genetic, environmental, and lifestyle factors may also influence the disease’s onset and progression. Scientists are trying to not only identify risk factors, but tease out how these factors interact with one another, in the search for effective interventions. Recent studies have suggested directions to pursue:

**Is reduced brain blood flow a risk factor?**

Having a maternal history of Alzheimer’s disease may put one at greater risk for developing Alzheimer’s-associated reduced blood flow in the brain by midlife. Scientists studied cerebral blood flow using a technique called arterial spin labeling magnetic resonance imaging in middle-aged and older volunteers. The study involved 252 cognitively normal people with an average age of 59 and 75 volunteers with an average age of 75. People in the older group were either cognitively normal, had mild cognitive impairment (MCI) or had Alzheimer’s disease (Okonkwo et al., 2014).

The researchers found that the older participants with MCI or Alzheimer’s disease showed reduced blood flow to the frontoparietal cortex and hippocampus. Reductions in blood flow to these brain regions were also seen in the middle-aged volunteers with normal cognition but who had a maternal history of Alzheimer’s disease. This finding suggests reduced cerebral blood flow in midlife might be a marker for Alzheimer’s risk. Additional funding in FY 2017 would further research into who might be at higher risk for Alzheimer’s due to cardiovascular or other health issues.

**Brain amyloid, sleep-disordered breathing, and mild cognitive impairment**

Sleep disturbances, including sleep apnea and other abnormal breathing patterns, are common in people with MCI and Alzheimer’s disease. Researchers studied the possible link between sleep disturbances and levels of brain beta-amyloid in eight cognitively normal volunteers (average age, 69) and five with MCI (average age, 75) (Spira et al., 2014).

For two consecutive nights, the participants’ sleep and breathing patterns were followed by tests that monitor body functions such as eye movements, muscle activity, and heart rhythm during sleep. Their blood oxygen levels and brain beta-amyloid burden were measured as well.

Among participants with MCI, greater severity of sleep disturbance and lower blood oxygen levels were strongly associated with higher levels of brain beta-amyloid deposition. This association was not seen in volunteers with normal cognition. These results suggest that in people with MCI, abnormal breathing during sleep may contribute to beta-amyloid deposition and possibly speed progression to Alzheimer’s disease. In addition, most of the MCI participants in this study were found to have moderate to severe disordered breathing during sleep that had not been previously diagnosed, compared with only one of the eight participants with normal cognition. Increased clinical screening for sleep-disordered breathing could aid the identification of people at risk for developing Alzheimer’s disease.
Expanded research in FY 2017 would enable investigation into the impact of disrupted sleep on brain aging and risk for Alzheimer’s and related dementias—knowledge that may lead to effective interventions by 2025.

**BDNF proteins may protect against dementia**

Brain-derived neurotrophic factor (BDNF) is a protein found in the blood and brain that promotes the survival of neurons and long-term memory in animal models. New research suggests that BDNF also may help maintain cognitive health in some older people (Weinstein et al., 2014).

Researchers measured BDNF levels in serum samples from 2,131 volunteers from the NIH-supported Framingham Heart Study (whose average age at the start of this particular study was 72) and then tracked their cognitive function over 10 years. During the follow-up period, 140 of the participants developed dementia, including 117 with Alzheimer’s disease.

Participants with higher serum BDNF levels at the start of the study were significantly less likely to develop dementia than those with lower BDNF levels. The reduction in dementia risk was 50 percent for those with the highest serum BDNF levels compared to those with the lowest. Of note, the association between higher BDNF and lower dementia risk was seen only in women, people older than 80, and people with college degrees.

This research suggests that further study should explore treatment with BDNF in preventing dementia, especially in women and in older and more highly educated people. Because BDNF levels can be increased by physical activity and reduced caloric intake, the findings also suggest that exercise and a healthy diet may help reduce dementia risk—but more research is needed.

**Diabetes may speed age-related cognitive decline**

Diabetes is an established risk factor for Alzheimer’s disease. A research team has now found that diabetes may also increase one’s risk of age-related cognitive decline (Rawlings et al., 2014). The team followed 13,351 black and white volunteers, age 48 to 67 years, participating in the NIH-supported Atherosclerosis Risk in Communities (ARIC) Study. Participants received cognitive tests at the start and twice more during the 20-year study that began in 1985.

After two decades, the researchers found, cognitive decline was 19 percent more severe in participants who had diabetes at the start of the study than in those who were diabetes-free. Of the cognitive abilities tested, processing speed and executive function were the most strongly affected; a smaller impact was seen on verbal memory.

The participants’ blood sugar levels, which are elevated in prediabetes and diabetes, were also measured at the start of the study. People with levels indicative of prediabetes at the start of the study showed greater cognitive decline than those with normal levels, as did people whose diabetes was poorly controlled or of longer duration. The association between diabetes and cognitive decline was similar for black people and white people.
This study suggests that having diabetes or prediabetes in middle age significantly increases one’s risk of cognitive decline in later years. As diabetes and prediabetes are usually treatable, screening for these conditions and managing diabetes may influence cognitive decline. Clinical trials have not yet demonstrated specifically that diabetes management will reduce the risk of cognitive decline or Alzheimer’s. As studies pursue this question, there are many reasons for individuals to manage diabetes and prediabetes.

Population studies supported by additional NIH funding in FY 2017 would support investigations into metabolic disorders and Alzheimer’s risk.

**Examining Health Disparities**

NIH funds research that evaluates whether certain racial, ethnic, and socioeconomic groups may be at greater risk than others for cognitive decline and dementia. Understanding these differences is critical to developing appropriate risk assessments and diagnostic tools and providing the most effective interventions to prevent and treat Alzheimer’s disease for everyone.

**Earlier age of dementia onset in Hispanics**

Past studies suggest that U.S. Hispanics have a younger age of dementia onset than white non-Hispanics. However, most of those studies were performed on the East Coast. Since backgrounds and family origins of Hispanics differ in various regions of the United States, investigators set out to determine if the same pattern was true for Hispanics living on the West Coast (Fitten et al., 2014).

In a study of 110 Hispanic and 180 white non-Hispanic adults age 50 and older with either Alzheimer’s disease or vascular dementia at the time of their entry into the study, researchers found that on average, Hispanics were 4 years younger than white non-Hispanics at the time of diagnosis of both forms of dementia. This age difference was not explained by the apolipoprotein ε4 genotype, gender, years of education, or history of vascular disease or diabetes.

This study suggests that the age of dementia onset tends to be younger for Hispanics living on both coasts of the United States compared with non-Hispanic peers. More research is needed to identify and better understand the factors that may contribute to this disparity.

The FY 2017 research agenda, if funded, would accelerate the identification of genetic variants and other risk and protective factors for dementia in diverse populations.

**Education and literacy contribute to disparities in late-life cognition**

A number of studies have found that cognitively normal, older black adults have lower performance on cognitive tests compared with white peers, even given equal years and levels of education. Research suggests that more subtle factors related to education and literacy contribute to the racial disparity in late-life cognitive performance (Sisco et al., 2015).

The researchers studied data from 1,679 non-Hispanic, community-dwelling adults age 65 to 102 (71 percent black, 29 percent white, and 70 percent women).
participating in the Washington Heights-Inwood Columbia Aging Project in New York City. They assessed the participants’ early-life educational quality (based on a variety of measures, such as school location and teacher-student ratios) and current literacy (based on scores on reading and writing tasks) and scored their performance on a battery of cognitive tests.

As has been found previously, the black volunteers scored lower on the cognitive tests than whites of the same age. Accounting for early educational quality and current literacy substantially reduced but did not eliminate the racial disparity in test performance, with literacy generally having a stronger effect than educational quality. More research is needed to fully understand these disparities.

The FY 2017 agenda sets a goal of increasing African-American participation in Alzheimer’s research, in part by building strong partnerships in diverse communities.

**Promising Research Opportunities**

Population studies offer insights into the “who, what, and why” of Alzheimer’s disease: Who is at risk or protected from developing the disorder? What genetic, lifestyle, and environmental factors are involved? Why do certain populations experience higher rates of dementia and cognitive decline compared with other groups?

NIH investment into population studies is guided by the research milestones developed following the Alzheimer’s Disease Research Summits held in 2012 and 2015, with additional input. Please see the full list of milestones aimed at prevention and treatment by 2025. Also see the list of milestones to which additional funding in FY 2017 would apply.

In FY 2017, efforts in this category will focus on support of the following efforts:

- Investigating the impact of environmental exposures on Alzheimer’s pathogenesis and/or response to treatment
- Increasing under-represented populations involved in studies to help identify the diverse genetic variants and other risk and protective factors involved in Alzheimer’s
- In existing longitudinal cohorts, adding molecular phenotyping studies (genomic, epigenomic, proteomic) and incorporating the collection of nontraditional data using wearable sensors and mobile health technology
CATEGORY E. CARE AND CAREGIVER SUPPORT

The research in this category includes projects aimed at improving the quality of care and quality of life for Alzheimer’s disease patients in a variety of settings (for example, in the home, nursing home facilities, hospice programs) and across diverse populations. This category also includes research focused on alleviating the physical and emotional burden associated with caregiving as well as projects assessing the socioeconomic burden of Alzheimer’s disease.

Topics under this category include care interventions and quality of life, technology-assisted care, caregiver support, cultural values and beliefs, and the economic burden of Alzheimer’s disease.

Caring for a loved one with Alzheimer’s can be rewarding. But the financial, emotional, and physical demands—which can last for years—can also be overwhelming. Providing at-home care can be especially stressful and can lead to depression and anxiety for caregivers, particularly older people facing their own health and aging issues. National Institutes of Health (NIH)-funded research is deepening our understanding of the mental, physical, and financial consequences of caring for people with Alzheimer’s.

Progress in Research on Caregiving, Quality of Life

Recent findings focused on improving the lives of caregivers and people with dementia include the following studies:

*Overmedication during the advanced stages of dementia*

Family members of people with dementia may question the need for some drugs prescribed in the later stages of the disease. Most people with advanced dementia living in nursing homes receive an average of five to 15 medications daily, some of which may be of questionable benefit in providing comfort or improving their condition. To better understand this issue, researchers reviewed lists of medications prescribed during 3 months in 2009 for 5,406 patients with advanced dementia (Tija et al., 2014).

They found that more than 50 percent of the patients had received at least one medication of questionable benefit for people with advanced dementia; however, the drugs did not ease symptoms or provide comfort. Cholinesterase inhibitors and memantine, two types of drugs prescribed for symptom management in Alzheimer’s, and lipid-lowering agents were among the most commonly prescribed.

Because of drug side effects and the difficulty many dementia patients have swallowing pills, overmedication can have negative impacts. In addition, costs for medications of questionable benefit accounted for more than one-third of patients’ total expenditures for medications.

These findings call attention to a need for increased vigilance of medications administered to people in the advanced stages of dementia. Additional FY 2017 funding will further our understanding of such caregiving issues.
Relief for caregiver depression may be a telephone call away

Caregivers of people with dementia are at increased risk for their own mental and physical health problems. But they seldom seek help, due in part to demands on their time and financial and practical constraints. Researchers studied the possible value of a low-cost, phone-based intervention for caregivers (Tremont et al., 2015). They recruited 250 caregivers of people with dementia who were experiencing psychological distress related to caregiving demands and then randomly assigned them to intervention or control groups.

The intervention group received 16 phone calls over 6 months that provided dementia education; emotional support; advice on potentially helpful resources; encouragement to attend to the caregiver’s own physical, emotional, and social needs; and specific strategies to cope with ongoing problems. The control group received calls in which they were offered an opportunity to talk about their problems.

Compared with the control group, the intervention group showed significant improvements in symptoms of depression and their response to the problem behaviors exhibited by their loved one. This improvement was equal to that previously reported for caregivers receiving face-to-face interventions. This study points the way to lower-cost and more readily accessible interventions for caregivers of people with dementia in the community, a goal of the 2017 research agenda.

Promising Research Opportunities

To build on these insights, NIH is investing in research milestones developed following the Alzheimer’s Disease Research Summits held in 2012 and 2015, along with additional input. Please see the full list of milestones aimed at prevention and treatment by 2025. Also see the list of milestones to which additional funding in FY 2017 would apply.

In FY 2017, additional research funding on caregiving issues would enable NIH to:

- Develop and validate assessments to determine the impact of caregiving on psychological, financial, and physical health in observational, interventional, and longitudinal population-based studies
- Develop a project to inform the design of cost-effective, community-based caregiving interventions that enable people with Alzheimer’s to remain in their homes
- Develop effective intervention programs to support caregiver well-being at different stages of the care continuum
- Establish a data infrastructure for the study of dementia caregiving
CATEGORY F. RESEARCH RESOURCES

This category includes a variety of resources used to conduct, translate, and disseminate high-quality Alzheimer’s disease research. These resources include research centers, related infrastructure, data and tissue repositories, and projects focused on generating disease models. Training and career development programs are also included in this category.

Topics under this category include Alzheimer’s Disease Centers, program projects, repositories and bioinformatics tools and resources, other infrastructure, and disease models.

The National Institutes of Health (NIH) maintains a research infrastructure that supports and enhances scientific discovery and translation of discoveries into Alzheimer’s disease prevention and treatment. The coordinating mechanisms and key initiatives of the National Institute on Aging (NIA) are central to this effort. Specifically, important advances are being made by supporting high-quality research, from which data can be pooled and shared widely and efficiently through a well-established Alzheimer’s disease research infrastructure.

Alzheimer’s Disease Centers (ADCs). NIH-supported research centers form the backbone of the national Alzheimer’s disease research effort. These multidisciplinary centers, located at 29 institutions nationwide, promote research, training and education, and technology transfer. The basic and clinical research conducted at the ADCs support virtually every goal outlined in the National Plan to Address Alzheimer’s Disease. The Centers serve as sites for a number of major studies, such as national clinical trials and imaging and biomarker research. Working with research volunteers, the Centers are expanding our understanding of Alzheimer’s disease and related dementias.

Alzheimer’s Disease Translational Research Program: Drug Discovery, Preclinical Drug Development, and Clinical Trials. This program supports all steps of drug discovery through clinical development. The goal is to seed preclinical drug discovery and development projects from academia and small biotechnology companies and, in doing so, to increase the number of investigational new drug candidates that can be tested in humans.

This strategic investment has led to the relatively rapid creation of a large, diverse portfolio of projects aimed at discovery and preclinical development of novel candidate therapeutics. To date, NIA has supported more than 60 early drug discovery projects and 18 preclinical drug development projects through this program. Fifteen of the 18 preclinical drug development projects are for compounds against non-amyloid therapeutic targets, such as tau, ApoE4, pathogenic signaling cascades, and neurotransmitter receptors. Four candidate compounds projects have advanced to the clinical development stage.

Thanks in part to additional funding for Alzheimer’s disease over the past few years, NIH has initiated a network of Translational Centers for Predictive Drug Development that will unite the experts and technology necessary to integrate data analysis,
mathematical modeling, and empirical testing in the preclinical development of drug treatments for Alzheimer's disease. The first of these Centers will open in 2017.

**Alzheimer's Disease Cooperative Study (ADCS).** NIA launched ADCS in 1991 to develop and test new interventions and treatments for Alzheimer's disease that might not otherwise be developed by industry. This large clinical trials consortium comprises more than 70 sites throughout the United States and Canada that focus on interventions to benefit Alzheimer's patients across the disease spectrum. This work includes testing agents that lack patent protection, agents that may be useful for Alzheimer's but are under patent protection and marketed for other indications, and novel compounds developed by individuals, academic institutions, and small biotech companies. ADCS also develops new evaluation instruments for clinical trials and innovative approaches to clinical trial design.

**National Alzheimer's Coordinating Center (NACC).** NACC pools and shares data on participants in ADC studies. The data is made available to Alzheimer's researchers worldwide. Today, NACC stores detailed longitudinal data from 26,500 participants and 2,100 brain autopsies. NACC data are helping to reveal different symptom patterns in subsets of people with Alzheimer's, patterns that would not have become apparent without analyzing a data set of this size.

**National Cell Repository for Alzheimer's Disease (NCRAD).** This NIH-funded repository provides resources that help researchers identify the genes that contribute to Alzheimer's and other types of dementia. NCRAD collects and maintains biological specimens and associated data on study volunteers from a variety of sources, primarily people enrolled at ADCs, as well as those in the Alzheimer's Disease Neuroimaging Initiative, the Alzheimer's Disease Genetics Consortium, and other studies. NCRAD also houses DNA samples and data from more than 900 families with multiple members affected by Alzheimer's. Since it was funded 22 years ago, more than 150,000 biological samples have been requested and sent to more than 120 investigators and research centers across the world.

**NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS).** NIAGADS is a Web-based warehouse for Alzheimer's disease genetics data. NIAGADS currently houses 22 data sets with nearly 44,000 subjects and more than 24 billion genotypes. Data from genome-wide association studies (GWAS) that are stored at NIAGADS are also made available through the NIH database of Genotype and Phenotype (dbGaP) at the National Library of Medicine's National Center for Biotechnology Information, which archives and distributes the results of large-scale GWAS analyses. Through dbGaP, data sets from multiple GWAS done on different platforms can be merged, and data from thousands of study participants can be analyzed together, increasing the probability of gene discovery.

**Alzheimer's Disease Education and Referral (ADEAR) Center.** The ADEAR Center compiles, archives, and disseminates information about Alzheimer's disease for people with Alzheimer's disease, their families, health professionals, and the public. All of its information and referrals about research and materials on causes, diagnosis, treatment, prevention, and caregiving are carefully researched, evidence-based, and reviewed for accuracy and integrity.
**Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative.** This NIH-led initiative is revolutionizing our understanding of the human brain. Its focus is accelerating work on technologies that give a dynamic picture of how individual cells and complex neural circuits interact in real time. The ultimate goal is to enhance understanding of the brain and improve prevention, diagnosis, and treatment of brain diseases such as Alzheimer’s.

**Promising Research Opportunities**

NIH is investing in research milestones developed and updated following the Alzheimer’s Disease Research Summits held in 2012 and 2015. Please see full list of milestones aimed at prevention and treatment by 2025. Also see the list of milestones to which additional funding in FY 2017 would apply.

In FY 2017, additional funding would accelerate NIH efforts to improve and standardize data collection and sharing among scientists and clinicians focused on developing effective treatments for Alzheimer’s disease and related dementias. Specific projects are listed below.

**Translational infrastructure and capabilities**

- Develop and standardize high-throughput methods for isolation and “omic” profiling of different types of brain cells for research
- Develop standardized protocols for generation of induced pluripotent stem cells for major brain cell types
- Create a network of translational centers that will apply the principles of quantitative and systems pharmacology to Alzheimer’s drug development
- Create training and career development programs to develop a translational and data science workforce

**Data sharing and reproducibility**

- Develop new policies and incentives to enable open, reproducible, and translatable research
- Devise new metrics for recruitment, career advancement, and publication attribution
- Annotate, curate, and make widely available the data sets from publicly funded Alzheimer’s clinical research studies

**Portfolio analysis tools and methods**

- Maintain and expand the NIH-supported International Alzheimer’s Disease Research Portfolio, a database and research ontology that enables funding agencies in the United States and abroad to compare, analyze, and strategically plan their Alzheimer’s research portfolios
CATEGOR Y G. CONS ORTI A AND PUBL IC-PRIV AT E PARTNERSHIPS

This category includes partnership enterprises created to enable major national and international efforts in basic, translational, and clinical Alzheimer’s research.

The National Institutes of Health (NIH) is helping the public and private sectors to leverage financial and human resources to move science forward. Alzheimer’s disease is no exception, and efforts in this area have been groundbreaking in their approach, bringing together government agencies, academic institutions, industry, and professional and advocacy organizations. These ongoing efforts include:

- NIH spearheads initiatives aimed at speeding discovery and overcoming obstacles in translational research. Working with biopharmaceutical companies and several nonprofit organizations, NIH established the Accelerating Medicines Partnership (AMP) to identify and validate the most promising biological targets for new diagnostics and drugs for Alzheimer’s disease and two other disease areas. Its ultimate goals are to foster drug development by increasing the number of new diagnostics and therapies and reducing the time and cost of developing and testing them. Importantly, the AMP data and analyses are being made publicly available to the broader biomedical community.

- In early 2015, the Accelerating Medicines Partnership-Alzheimer’s Disease (AMP-AD) initiative launched an Alzheimer’s Big Data portal—and delivered the first wave of data—for use by the wider research community. By enabling the sharing and analyses of large and complex biomedical data sets, the AMP-AD Knowledge Portal will speed the development of predictive models of Alzheimer’s disease and enable the selection of novel targets. These targets will drive changes in molecular networks that lead to the clinical signs and symptoms of the disease.

- The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a groundbreaking study that uses imaging techniques and biomarker measures in blood and cerebrospinal fluid to track changes in the living brains of older people who are cognitively normal, have mild cognitive impairment, or have mild Alzheimer’s disease. Researchers hope to identify who is at risk for Alzheimer’s, track progression of the disease, and devise tests to measure the effectiveness of potential interventions.

Expanded several times since its 2004 launch, ADNI continues to recruit volunteers at 55 sites in the United States and Canada. It is the largest public-private partnership to date in Alzheimer’s disease research. It receives generous support from private-sector companies and foundations through the Foundation for the National Institutes of Health.

To speed the pace of analysis and findings, ADNI investigators make their collected data widely available. Magnetic resonance imaging and positron emission tomography brain images as well as clinical, genetic, and fluid
biomarker data are available to qualified researchers worldwide through a Web-based database.

Findings from ADNI have generated excitement about using brain and fluid biomarkers to identify people at risk for developing Alzheimer’s or to characterize the progression of the disease. Its success has inspired similar efforts in Europe, Japan, and Australia.

- The NIH-led **Precision Medicine Initiative** (PMI) is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. Advances in technology—including large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data—make this effort possible. The Precision Medicine Initiative will launch a national cohort study of a million or more Americans to propel our understanding of many diseases, including Alzheimer’s.
CATEGORY H. ALZHEIMER’S DISEASE-RELATED DEMENTIAS (ADRD) RESEARCH

Topics under this category include frontotemporal degeneration, Lewy body dementia, vascular dementia, and mixed dementia.

Although Alzheimer’s disease is the most common cause of dementia in older adults, an estimated 20 percent to 40 percent of people with dementia have some other form, such as Lewy body, frontotemporal, or vascular dementia. Moreover, autopsy studies looking at the brains of people who had dementia indicate that a majority of those age 80 and older had “mixed dementia,” a combination of Alzheimer’s disease (amyloid and tau), cerebrovascular disease (such as stroke), and, in some instances, Lewy body pathology.

Clinically, it can be difficult sometimes to determine whether dementia symptoms are due to Alzheimer’s or another form of dementia, so researchers are developing tools that may aid in distinguishing among these diseases. At the molecular and cellular level, researchers are investigating the genetics and underlying disease processes shared by, or unique to, various dementias.

These efforts are informed by recommendations developed by panels of expert scientists as part of the National Institutes of Health (NIH)-hosted Alzheimer’s Disease-Related Dementias (ADRD): Research Challenges and Opportunities 2013 Summit. To further advance this research agenda, the National Institute of Neurological Disorders and Stroke, which leads NIH research on ADRD, is planning a follow-on meeting in March 2016. Gaining a better understanding of ADRD should help lead to prevention strategies and therapeutics for all forms of dementia.

Progress in Understanding ADRD

Scientists at and funded by NIH have made great progress in understanding the biology, genetics, prevalence, and other factors involved in ADRD. Translational research and clinical trials are also taking place.

Vascular cognitive impairment

Vascular dementia and vascular cognitive impairment are caused by injuries to the vessels supplying blood to the brain. These disorders can be caused by brain damage from multiple strokes or any injury to the small vessels carrying blood to the brain. Factors that increase the risk for stroke, including atrial fibrillation, hypertension, diabetes, and high cholesterol, also play a role in vascular dementia and vascular cognitive impairment.

Numerous studies during several decades have linked atherosclerosis, arteriosclerosis, microinfarcts, silent stroke, and diffuse white matter disease to an increased risk of dementia, including Alzheimer’s. Evidence also suggests that midlife hypertension and midlife obesity are risk factors. Researchers are making promising advances in understanding and targeting these factors to prevent or treat dementia.
Scientists have recently identified two measures of vascular dysfunction that may be useful biomarkers for the earliest stages of dementia. In one study, researchers showed that pulse pressure (the difference between systolic and diastolic blood pressure readings), which is due to increased stiffness of blood vessel walls, was correlated with an increase in phosphorylated tau in cerebrospinal fluid, a biomarker of the earliest, preclinical stages of Alzheimer’s (Nation et al., 2015).

Remarkably, this study suggested that increased pulse pressure is associated with neurodegenerative changes prior to the onset of dementia across a broad age range. If validated in future studies, pulse pressure may be used clinically as an inexpensive and easily obtainable biomarker of early neurodegenerative changes. Additional FY 2017 funding will enable similar efforts to develop noninvasive biomarkers for vascular dementia.

In another study, scientists used specialized magnetic resonance imaging technology to measure how easily a dye flowed out of blood vessels and into the brain (Montagne et al., 2015). They found that volunteers experiencing mild problems with thinking and memory had much “leakier” blood vessels in the hippocampus, a part of the brain important to learning and memory, than did those free of memory problems. They also found that hippocampal blood vessels were leakier than blood vessels in other areas of the brain in the cognitively impaired participants.

The finding suggests that imaging biomarkers that measure the leakiness of blood vessels may eventually be used to help identify people at risk for dementia, and that developing novel drugs to seal up leaky blood vessels may be a potential therapeutic strategy to delay or prevent Alzheimer’s and other forms of dementia.

Expanded research in FY 2017 would support the development of imaging and other biomarkers to assist in diagnosing dementia risk. Such tools would be useful in recruitment efforts for clinical trials that may lead to effective therapies for ADRDs by 2025.

**Frontotemporal degeneration (FTD)**

Frontotemporal degeneration (FTD) is the second leading cause of dementia in people under 60 years old. In people with FTD, areas of the brain that are important for decisionmaking, behavioral control, emotion, and language progressively degenerate. Many forms of FTD are familial, but heritability differs across the spectrum of the disease. Familial forms are most commonly caused by mutations in the tau gene (MAPT) and the granulin gene (GRN).

The genetic mutation C9ORF72 plays a role in both familial FTD and familial amyotrophic lateral sclerosis (ALS), a disease in which the nerve cells that control voluntary movement progressively degenerate. Recent research on this mutation told us more about the molecular mechanisms underlying FTD-ALS spectrum disorder and animal and cell models that can be used for understanding disease processes and developing therapies (Sareen et al., 2013).

Using human induced pluripotent stem cells (iPSCs) derived from people with C9ORF72 mutations, investigators have learned about changes in the shape of DNA
and other toxic changes. Researchers have also used human iPSCs to show that DNA-based therapies may reduce this damage.

Scientists have also created a mouse model of FTD by injecting mutant C9ORF72 DNA into the brains of newborn mice (Haeusler et al., 2014). As the mice aged, they developed behavioral and movement problems similar to the symptoms seen in people with these mutations. The mouse brains had key hallmarks of FTD and ALS, including aggregates of the protein TDP-43, a characteristic feature of both FTD and ALS. Researchers are currently using this model to further understand the relationship between mutated C9ORF72 and these toxic protein clusters. This model may be used to test potential new therapies.

In addition to studying how mutated C9ORF72 causes FTD, scientists are investigating the mechanisms by which mutations in other genes cause FTD or influence the onset and severity of the disease. They are also conducting studies to discover new genes that increase the risk of FTD. The goal is to identify potential molecular targets for developing new therapies (Chew et al., 2015). Scientists are also conducting natural history studies to better understand the course of the disease and identify biomarkers that may improve diagnosis, enhance tracking of disease progression, and facilitate therapy development.

Expanded funding in FY 2017 will support gene discovery studies for FTD and ALS that may lead to therapeutic targets.

Lewy body dementia (LBD)

People with Lewy body dementia (LBD) have problems with thinking, movement, behavior, and mood. The brains of people with this form of dementia, as well as those with Parkinson’s disease, contain Lewy bodies—clumps of abnormally folded alpha-synuclein protein. Indeed, the spread of Lewy bodies in the brain contributes to the cognitive problems that occur in the later stages of Parkinson's disease.

Although scientists do not fully understand how Lewy bodies form, recent animal studies indicate that this misfolded protein can be transmitted from cell to cell, spreading this pathology throughout the brain. When scientists injected alpha-synuclein fibrils (fine fibers of alpha-synuclein protein created in a test tube) into the brains of mice, they found that the fibrils caused native alpha-synuclein to misfold, aggregate, and form Lewy bodies (Luk et al., 2012). The pathology spread from cell to cell and from one brain region to the next, and the mice exhibited movement symptoms consistent with Lewy body disease.

In another study, researchers demonstrated that introduction of alpha-synuclein fibrils can lead to either alpha-synuclein pathology alone or alpha-synuclein and tau pathology together, depending on the initial structure of the fibrils (Guo et al., 2013). These results suggest that differences in the structure of misfolded alpha-synuclein may account for some of the pathological and clinical variability seen in people with Lewy body disease. Understanding how Lewy bodies form and spread throughout the brain, and why some people with Lewy bodies have movement problems while others develop both dementia and movement problems, are important steps toward developing treatments to stop or prevent LBD.
In addition to investigating the molecular mechanisms that lead to Lewy bodies, researchers have recently identified several genes that are associated with Lewy body pathology and are conducting studies to identify additional genes that place people at risk for developing LBD (Clark et al., 2015). They are also evaluating candidate biomarkers and using that information to create a tool for predicting significant cognitive decline in people with Lewy body disease, which could be used for identifying subjects for clinical trials of therapies to prevent dementia.

Expanded FY 2017 funding would support efforts to improve the research tools needed to gain a better understanding of the disease mechanisms involved in Lewy body dementia.

**Promising Research Opportunities**

The NIH research program will continue to expand our understanding of ADRD. To help chart that discovery, we are guided by the research milestones developed following the [Alzheimer’s Disease-Related Dementias (ADRD): Research Challenges and Opportunities 2013 Summit](#). To see the full list of milestones to reach the National Plan’s research goal of prevention or treatment by 2025, please go to [ADRD 2013 Conference and Recommendations](#). Also see the [list of milestones](#) to which additional funding in FY 2017 would apply.

In FY 2017, expanded funding would focus on:

- Achieving consensus on clinical diagnostic criteria and developing diagnostic tools to help primary care physicians and clinical researchers discern different types of dementia, including criteria and tools that can be used in ethnically and culturally diverse populations
- Discovering and validating neuroimaging and biochemical biomarkers that will enhance diagnostic accuracy and improve assessments of disease progression in people with ADRD, especially mixed Alzheimer’s/vascular dementia
- Determining the incidence and prevalence of ADRD through population-based studies that involve diverse populations and that utilize biomarkers
- Supplementing ongoing clinical trials and studies to maximize representation of diverse populations in dementia research, with a particular focus on clinical trials of vascular health interventions
- Developing and improving experimental models of dementia that can be used to advance our understanding of the disease processes in ADRD and to translate these discoveries into new therapies
- Identifying genetic variations that cause or contribute to FTD and studying the mechanisms by which they contribute to the disease process
## Fiscal Year 2017 Professional Judgment Budget: Alzheimer’s Disease and Related Dementias

### Baseline Estimates, Fiscal Year 2016
(dollars in thousands)

<table>
<thead>
<tr>
<th>Type of Dementia</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>$638,000</td>
</tr>
<tr>
<td>Vascular Cognitive Impairment/Dementia</td>
<td>$46,000</td>
</tr>
<tr>
<td>Frontotemporal Dementia</td>
<td>$38,000</td>
</tr>
<tr>
<td>Lewy Body Dementia</td>
<td>$15,000</td>
</tr>
</tbody>
</table>

**Note:** All four estimates above are from the FY 2016 President’s budget. None of these categories are mutually exclusive; thus they are not additive for the purposes of generating an overall funding baseline for Alzheimer’s disease plus Alzheimer’s disease-related dementias (ADRD). NIH does not currently report a total for Alzheimer’s disease plus ADRD funding but is in discussions regarding future reporting of this number.

### Fiscal Year 2017 Professional Judgment Additional Resources
(increase above baseline)
(dollars in thousands)

<table>
<thead>
<tr>
<th>Category</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category A. Molecular Pathogenesis and Physiology</td>
<td>$68,680</td>
</tr>
<tr>
<td>Category B. Diagnosis, Assessment, and Disease Monitoring</td>
<td>$36,500</td>
</tr>
<tr>
<td>Category C. Translational Research and Clinical Interventions</td>
<td>$92,800</td>
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<tr>
<td>Category D. Epidemiology</td>
<td>$45,100</td>
</tr>
<tr>
<td>Category E. Care and Caregiver Support</td>
<td>$9,800</td>
</tr>
<tr>
<td>Category F. Research Resources</td>
<td>$31,050</td>
</tr>
<tr>
<td>Category H. Alzheimer’s Disease-Related Dementias</td>
<td>$35,375</td>
</tr>
<tr>
<td>Staff Needs, Support, and Miscellaneous</td>
<td>$4,050</td>
</tr>
<tr>
<td><strong>TOTAL ADDITIONAL RESOURCES</strong></td>
<td><strong>$323,355</strong></td>
</tr>
</tbody>
</table>
REFERENCES


