

# STOPPING ALZHEIMER'S DISEASE AND RELATED DEMENTIAS: *Advancing Our Nation's Research Agenda*

NIH BYPASS BUDGET PROPOSAL  
FOR FISCAL YEAR 2018



National Institutes of Health

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## INVESTING IN RESEARCH, INVESTING IN HOPE

July 25, 2016

On behalf of the National Institutes of Health (NIH), I am pleased to present our Fiscal Year (FY) 2018 Professional Judgment Budget for Alzheimer's disease and related dementias. This plan, commonly referred to as a Bypass Budget, outlines the optimal approach NIH would take to meet the research goals of the National Plan to Address Alzheimer's Disease. The additional support and initiatives discussed here would allow us to accelerate the real scientific progress we are making against these devastating disorders.

Through this budget proposal for FY 2018, NIH hopes to achieve several vital goals. First, we intend to build on the momentum achieved through recent expanded investment in research and sustain the unprecedented excitement of discovery that many in the field are feeling today. We expect to continue to inspire the sharpest and most creative scientific minds to develop new paradigms in prevention and treatment.

Most crucially, though, we present this document both as a roadmap for moving forward and as an expression of hope grounded in biomedical research. It is our firm belief—even in the face of the monumental challenge that is Alzheimer's—that if we expand and build upon our current base of scientific knowledge, we can identify and implement the strategies for combating the disease that are so urgently needed.

I am impressed by recent scientific discoveries in the field. We have identified additional genes that may place individuals at greater risk of—or, in some cases, protect them from—developing dementia. We have begun to develop new methods to screen hundreds of thousands of molecules for their treatment potential—rapidly, efficiently, and accurately. We have created networks, Centers, and consortia to make it easier for scientists to work together to solve the most complex and intractable puzzles related to Alzheimer's disease and related dementias. And we have established a broad new initiative to help us understand the genesis and development of Alzheimer's in people with Down syndrome, a uniquely vulnerable group.

We have accomplished much—but much remains to be done.

That's where this document enters the picture. Prepared at the request of the U.S. Congress, this comprehensive research agenda includes a set of specific, targeted milestones, as well as the resources that will enable us to reach those milestones toward a cure. Informed by a series of workshops involving a wide range of stakeholders from the public and private sectors, we estimate that an additional investment of \$414 million in FY 2018 above NIH's base appropriation for Alzheimer's and related dementias will help us to meet our goals. This Bypass Budget will be updated annually through FY 2025.

Eliminating the threat of these diseases is an enormous undertaking—one that requires courage, creativity, and commitment. At NIH, we will continue to do everything we can to bring those resources to bear in the fight against Alzheimer’s on behalf of patients, families, and caregivers everywhere.

A handwritten signature in black ink, appearing to read "Francis S. Collins". The signature is fluid and cursive, with a long horizontal stroke at the end.

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

## INTRODUCTION

[Alzheimer's disease and related dementias](#) are progressive and, currently, irreversible brain disorders that slowly destroy memory, thinking skills, and the ability to live independently. While a handful of drugs currently help—with some symptoms, for some people, for a limited time—no interventions have yet been demonstrated to delay the onset or slow the progression of these complex and devastating disorders.

Currently, as many as 5.2 million Americans age 65 and older are estimated to be living with Alzheimer's, the most common form of dementia, with significant numbers developing the disease earlier than age 65. Many thousands more are diagnosed with Alzheimer's disease-related dementias (ADRD), such as vascular dementia, Lewy body dementia, or frontotemporal degeneration. Age is the greatest risk factor for dementia, so these numbers are expected to grow in our aging Nation. Despite this dire situation, there is reason to hope for a future where the golden years of family, friends, and neighbors are no longer compromised or cut short by dementia.

The [National Institutes of Health](#) (NIH), which leads the Nation's biomedical research on Alzheimer's and related dementias, has embarked on an ambitious research agenda that explores these complex disorders on several scientific fronts. NIH-supported scientists are devoting their careers to better understand, diagnose, prevent, and treat Alzheimer's and related dementias.

Over the past several years, NIH has received unprecedented support in this critical endeavor from our national leadership, the American people, and the wider research community. This report outlines the NIH research agenda aimed at ending the devastation wrought by dementia and outlines the proposed funding needed to achieve that goal.

### **A National Imperative**

Fighting Alzheimer's disease and related dementias is a priority at NIH and other Federal agencies, across the Nation, and throughout much of the world. In the United States, attention to Alzheimer's disease took on heightened interest with passage of the [National Alzheimer's Project Act](#) (NAPA). Signed into law by President Obama in January 2011, the Act calls for an aggressive and coordinated national plan to accelerate research on Alzheimer's disease and related dementias, and to provide better clinical care and services for people living with dementia and their families.

Efforts under the National Plan are guided by an Advisory Council on Alzheimer's Research, Care, and Services, consisting of some of the Nation's foremost experts, which is convened by the Secretary of U.S. Department of Health and Human Services. With the Advisory Council's

guidance and public input, the first [National Plan to Address Alzheimer's Disease](#) was created in 2012. Its primary research goal is to prevent and effectively treat Alzheimer's disease and related dementias by 2025.

Updated annually, the research component of the National Plan is a collaborative, evolving framework. It outlines the basic, translational, and clinical research needed to understand and conquer Alzheimer's disease and related dementias. In support of the research goals of the National Plan, NIH embarked on an ambitious strategic planning process (described on page 6 in *Inclusive Approach to Shaping the Research Agenda*) that engaged key stakeholders and resulted in the development of implementation milestones and success criteria. A [Web-based tool](#) provides information on activities and programs directed at achieving the above milestones.

As the world's leading funder of dementia research, NIH plays a vital leadership role in a research effort that involves multiple stakeholders, including government, academia, industry, and advocacy groups. The increased funding enables not only greater investment in innovative investigator-initiated studies, but also allows NIH to foster new partnerships and initiatives, some of which focus on overcoming traditional barriers to the development of effective treatment and prevention strategies for Alzheimer's disease and related dementias.

The scientific agenda outlined here details an aggressive and coordinated approach toward the research goals outlined under the National Plan. This would not be possible without the support of the American public, especially their generous participation in clinical studies and trials.

### **Expanding Research Resources**

The passage of NAPA focused our national determination to end the personal and societal burden of Alzheimer's disease and related dementias by setting concrete goals and objectives. This resolve has been buoyed over the past few years by important boosts in funding:

- NIH redirected funds from other programs by \$50 million in fiscal year (FY) 2012 and \$40 million in FY 2013 to support promising research into Alzheimer's and related dementias.
- The [National Institute on Aging](#) (NIA), which leads Alzheimer's disease research at NIH, received additional Federal funding—approximately \$100 million in FY 2014 and \$25 million in FY 2015—primarily directed toward Alzheimer's research.
- Overall, NIH spending on Alzheimer's disease research increased just over 30 percent from FY 2011 to FY 2015.



The biggest boost in funding came in FY 2016, following congressional passage of the Consolidated Appropriations Act of 2016 (P.L. 114-113), which directed an unprecedented additional \$350 million toward Alzheimer's and related dementias research. This infusion of resources enabled the launch and expansion of research programs and invigorated investigator-initiated research as well as research conducted by dedicated NIH staff scientists.

**The boost in funding enables innovative new initiatives such as:**

- The [Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease Consortium](#), which supports more than a dozen research teams working collaboratively toward shared goals: to dissect the complex molecular mechanisms by which vascular risk factors influence Alzheimer's and to identify new targets for treatment and prevention.
- An initiative aimed at supporting [new translational centers](#) that will develop next-generation animal models of Alzheimer's disease and enable their rapid dissemination to qualified researchers for preclinical therapy development. The initiative will also implement guidelines for rigorous study design and transparent reporting of findings from preclinical testing of candidate therapeutics.
- The [Alzheimer's Biomarkers Consortium in Down Syndrome](#), a pioneering program designed to develop standardized biomarker measures that signal the onset and progression of Alzheimer's-like dementia in adults with Down syndrome.
- Intensified support for the discovery and development of novel therapeutics for Alzheimer's disease against a wide range of therapeutic targets.
- Clinical trials of therapies in people at the highest risk of dementia, to include the testing of promising therapies in cognitively normal people who carry two copies of a known Alzheimer's risk gene.
- Development of novel disease-monitoring and care-support interventions, such as new in-home technologies, to support dementia caregivers.

### **Budgeting to Fight the Threat of Dementia**

In summer 2015, NIH prepared its first-ever professional judgment budget as required by congressional legislation. That budget estimate outlined the *additional* funding needed during FY 2017 to help reach the ultimate research goal of the National Plan—to effectively treat and prevent Alzheimer's and related dementias by 2025.

NIH will submit this report to the President annually through FY 2025, for review and transmittal to Congress. Only two other areas of biomedical research—cancer and HIV/AIDS—have been the subject of such special NIH 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 annual opportunity to develop a budget for expanding research on Alzheimer's and related dementias—based on a carefully considered roadmap that moves us toward ending the tremendous physical, emotional, and financial devastation wrought by these fatal disorders.

This year, the professional judgment budget estimate outlines the additional funding required in FY 2018 to enhance investigator-initiated research grants and initiatives beyond NIH's current base budget to meet one of the greatest challenges of our time—the development of effective treatments for and prevention of Alzheimer's and related dementias by 2025. Toward this end, NIH has estimated that \$414 million in additional FY 2018 funds will be needed to accelerate this research, with an intense focus on better understanding the basic biology underlying dementia, translating findings into effective therapies, supporting clinical trials testing promising treatments, and improving the diagnosis, care, and support of those living with dementia.

### ***Why Alzheimer's, why now?***

Our Nation faces many healthcare demands. Why is it imperative to expand funding directed at Alzheimer's and related dementias? Recent findings shed light on the looming health crisis presented by these complex disorders, as well as the current financial toll they place on our citizens and Nation:

- **Dementia Poses a Growing Threat**

In the United States alone, as many as 5.2 million people age 65 and older are living with Alzheimer's disease, and thousands more have related dementias. These numbers are expected to rise with an aging population. Several recent studies, however, have shown that dementia rates may be declining in particular populations. For example, one analysis showed a progressive, decades-long decline in dementia incidence (newly reported cases) among older people in Framingham, MA, and examined factors that may influence this trend ([Satizabel, et al. 2016](#)).

By following thousands of older volunteers participating in the NIH-funded [Framingham Heart Study](#), researchers identified a steady decline in new cases of Alzheimer's and related dementias during several decades. Higher education levels, along with treatment of vascular disease, may have helped delay the onset of dementia. These findings may lead to strategies that delay or even prevent dementia in all populations.



Despite promising trends in specific populations, results of a recent meta-analysis indicated that 35.6 million people lived with dementia worldwide in 2010, with numbers expected to nearly double almost every 20 years—to 65.7 million people in 2030 and 115.4 million in 2050. Unless we identify ways to prevent or effectively treat Alzheimer’s and related dementias, the number of affected adults across the globe will rise exponentially as the population ages.

- **Dementia Care Costs Top Other Diseases**

Alzheimer’s disease has a major impact on the U.S. economy. NIH-supported economists have calculated that caring for people with Alzheimer’s disease in 2010 cost the U.S. healthcare 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 at \$109 billion in 2010. To place that figure in context, that same year, direct healthcare costs for heart disease and cancer were estimated at \$102 billion and \$77 billion, respectively.

In 2015, [NIH-supported research](#) expanded our knowledge of the tremendous financial toll of late-stage dementia ([Kelley et al., 2015](#)). In the last 5 years of life, total healthcare spending for people with dementia was more than a quarter-million dollars per person, about 57 percent greater than costs associated with death from other diseases, including cancer and heart disease. Such insights are critically important as we examine how best to support an aging Nation.

### ***Inclusive approach to shaping the research agenda***

Increasing FY 2018 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. The dynamic research agenda detailed in this report was developed by NIH scientific leaders to target specific research goals and was enriched by input from stakeholders from the wider Alzheimer’s and related dementias community.

### **NIH maps out the way forward**

The [National Institute on Aging](#) (NIA), which oversees NIH research on Alzheimer’s, led the development of [implementation research milestones](#) in collaboration with the [National Institute of Neurological Disorders and Stroke](#) (NINDS) and other NIH Institutes and Centers. This strategic framework, which integrated research on Alzheimer’s disease and related dementias, served as the basis for this bypass budget.

Many other NIH Institutes and Centers also helped refine the milestones by providing feedback and identifying scientific gaps and opportunities to consider. These included: 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](#).

### **Thought leaders lend voices to goal-setting**

The research framework outlined in the [implementation research milestones](#) was a result of extensive input from a variety of sources and perspectives outside of NIH. Central to this process was a series of research summits organized by NIH that brought together leading experts and innovators from academia, industry, and advocacy groups.

Planning under NAPA began in 2012 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.

In early 2015, the [Alzheimer's Disease Research Summit 2015: Path to Treatment and Prevention](#) brought together hundreds of experts and innovators working on Alzheimer's and other chronic diseases to update and enhance our research agenda. Among a number of topics, they examined critical knowledge gaps and the kinds of new resources, infrastructure, and partnerships 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 and were the basis for the implementation milestones detailed in this FY 2018 budget proposal.

Most recently, in March 2016, NIH hosted the [Alzheimer's Disease-Related Dementias 2016 Summit](#) to update the recommendations on national research priorities for frontotemporal degeneration, Lewy body dementia, multiple etiology dementia, vascular contributions to dementia, and health disparities in dementia that came out of the earlier [2013 ADRD Summit](#).

The meeting drew hundreds of experts across diverse fields of dementia research as well as advocates, patients, and caregivers. Their goal: to update recommendations based on a review of scientific progress, to prioritize the important scientific questions that must be answered to advance our understanding of these complex disorders, and to identify how Federal and non-Governmental organizations can most effectively collaborate to address these research priorities. Final recommendations from this meeting will be presented later in 2016.

### ***How NIH prioritizes its research investment***

NIH funds and conducts a diverse and productive research program:

- basic biology of Alzheimer’s disease and related dementias
- factors that influence disease development and progression
- genetic and environmental risk and protective factors
- diagnosis, possible treatment, and prevention strategies
- care of people living with Alzheimer’s and related dementias 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 and related dementias? How can they be diagnosed early and accurately? How might they 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. The majority of these research projects will proceed to completion over a number of years.

### ***Working together for a future free of dementia***

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, there is a palpable sense of hope that we are heading in the right direction, thanks to the renewed commitment from the American public, the dedication of study volunteers and their families, and the relentless work of researchers and clinicians. NIH-supported researchers—and the Alzheimer’s and related dementias community at large—are heartened by the unprecedented infusion of public funding for FY 2016. NIH and its partners in this endeavor will not rest until there are effective treatments and cures for Alzheimer’s and related dementias.

### ***How to navigate the bypass budget***

This bypass budget proposal outlines the additional FY 2018 funding needed to advance NIH-supported research on Alzheimer’s and related dementias aimed at the key research goal of the

National Plan: to treat and prevent these disorders by 2025. The development process for the FY 2018 bypass budget estimates involved consideration of several financial and programmatic factors, including but not limited to:

- The estimates to speed discovery in Alzheimer’s disease and related dementias research provided in the first [bypass budget proposal for FY 2017](#)
- The complete list of updated Alzheimer’s [implementation research milestones](#) for calendar years 2016 through 2025, which are the products of summits held in 2012 and 2015. Also see [draft recommendations](#) on related dementias, to be finalized later in 2016.
- A subset of [Alzheimer’s and related dementias research milestones](#) that could be started or accelerated in FY 2018, upon which the current bypass budget estimates were based
- The ability to accelerate some planned FY 2017 activities into FY 2016 as a result of the substantially increased appropriations for FY 2016
- The evolution of opportunities and needs in basic and clinical research since the FY 2017 bypass budget was released
- The research applications submitted thus far to the 10 ongoing NIA Funding Opportunity Announcements in Alzheimer’s Disease released in fall 2015, as well as NINDS initiatives in Alzheimer’s disease-related dementias

The bypass budget is organized into research areas defined in the [Common Alzheimer’s Disease Research Ontology](#) (CADRO) and used to classify current investment in Alzheimer’s and related dementias research, made publicly available through the [International Alzheimer’s Disease Research Portfolio](#). Read more about these tools under Research Resources.

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.

Beyond the bypass budget estimates, the narrative in this document covers specific areas of research that describe key areas of study, important recent progress—including specific research highlights for calendar years 2015 and early 2016—and how NIH intends to build on this progress under the FY 2018 professional judgment budget.

### ***Improved reporting of NIH-funded dementia research***

The funding needs estimated in the bypass budget are in addition to NIH’s baseline spending on Alzheimer’s disease and related dementias. In February 2016, [NIH reported spending](#) on “Alzheimer’s Disease, Including Alzheimer’s Disease-Related Dementias (AD/ADRD)” for the first time, applying this new spending category to FY 2015 NIH-supported research. This is helpful

not only as a baseline for this and future bypass budgets, but also in enabling NIH to more accurately track relevant spending if additional funds are received.

As an example, the difference between the FY 2015 actual NIH spending for AD/ADRD (\$631 million) and the FY 2016 estimate for AD/ADRD (\$991 million) is \$360 million—reflecting the increased appropriations received for this area of research in FY 2016. Increases from the FY 2015 actuals to the FY 2016 estimates in the categories of “Alzheimer’s Disease” and “Alzheimer’s Disease-Related Dementias (ADRD)” contribute to the \$360 million increase. (Note, however, that the FY 2016 funding numbers will not be finalized until after the end of the current fiscal year, Sept. 30.)

While this new AD/ADRD number will be used extensively in planning and implementation of funds for these research areas, Alzheimer’s-specific funding levels, as well as funding for the related dementias (“Lewy Body Dementia,” “Frontotemporal Dementia,” and “Vascular Cognitive Impairment/Dementia,” as well as the overarching category of “Alzheimer’s Disease-Related Dementias”) will continue to be reported as well.

## FISCAL YEAR 2018 PROFESSIONAL JUDGMENT BUDGET: ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

### Baseline Estimate, Fiscal Year 2017

(dollars in thousands)

Alzheimer's Disease, Including Alzheimer's Disease-Related Dementias  
(AD/ADRD)\*

**\$991,000\*\***

### Professional Judgment Budget FY 2018 Additional Resources

(increase above FY 2017 baseline)

(dollars in thousands)

Area of Research	Amount
Molecular Pathogenesis and Physiology of Alzheimer's Disease	\$83,000
Diagnosis, Assessment, and Disease Monitoring	\$58,100
Translational Research and Clinical Interventions	\$118,600
Epidemiology	\$33,325
Care and Caregiver Support	\$28,000
Research Resources	\$49,950
Alzheimer's Disease-Related Dementias	\$40,200
Staff Needs, Support, and Misc.	\$3,250
<b>Total Additional Resources Needed</b>	<b>\$414,425</b>
<b>TOTAL RESOURCES NEEDED (estimate, in thousands)</b>	<b>\$1,405,425</b>

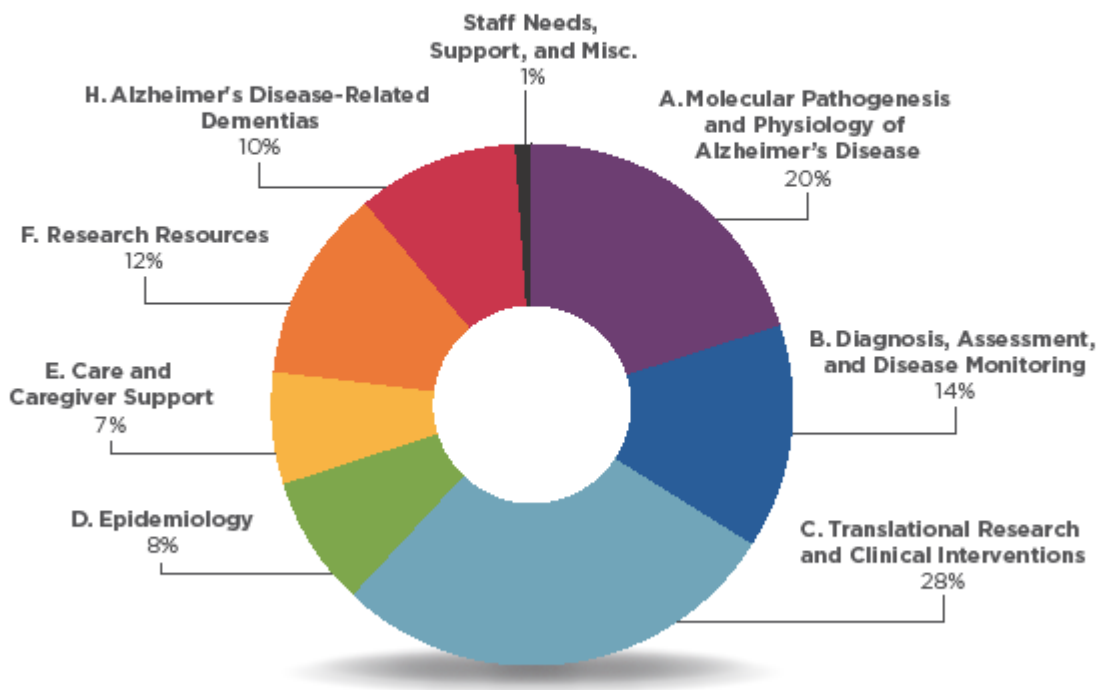
\*New category established pursuant to Section 230, Division G of the Consolidated and Further Continuing Appropriations Act of 2015 as related to reporting of NIH initiatives supporting the National Alzheimer's Project Act (NAPA), <https://aspe.hhs.gov/national-alzheimers-project-act>. The new Alzheimer's Disease-Related Dementias (ADRD) category reflects the sum of the three existing categories: Frontotemporal Dementia, Lewy Body Dementia, and Vascular Cognitive Impairment/Dementia, where duplicates are removed. The new category Alzheimer's Disease, Including Alzheimer's Disease-Related Dementias reflects the sum of two existing categories: Alzheimer's Disease and Alzheimer's Disease-Related Dementias, where duplicates are removed.

\*\*Estimate from the FY 2017 President's Budget



## Distribution of Budget Funding Across Research Areas, FY 2018

TOTAL: \$414,425,000



## 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.*

The National Institutes of Health (NIH) supports a robust and innovative research program investigating the complex cellular, molecular, and genetic brain changes that may play a role in Alzheimer's disease and related dementias.

Researchers are especially keen to learn more about the influences of beta-amyloid and tau proteins in dementia onset and progression. Achieving a deeper understanding of the molecular and cellular mechanisms involved in the abnormal buildup of these hallmarks of the disease—and how they may interact with each other—is believed to be one route to the development of promising therapies.

Equally intense investigations are underway across a range of brain functions and factors—including immune response, inflammation, cell death, and synaptic, vascular, and metabolic function. Scientists from diverse disciplines are working together to discover the basic mechanisms involved, as well as the disease pathways and complex networks that underlie dementia.

Thanks to advances in technology and dynamic collaborative efforts, studies supported and conducted by NIH are identifying the genetic factors that may contribute to overall risk for—or protection against—developing Alzheimer's and related dementias. Research into how genes influence specific disease pathways involved in disease progression may result in targets for effective interventions.

### Genetics

Three genetic mutations—presenilin 1, presenilin 2, and amyloid precursor protein—are known to cause the rare early-onset form of the disease. Evidence is mounting for a number of gene variants that contribute to risk for late-onset Alzheimer's.

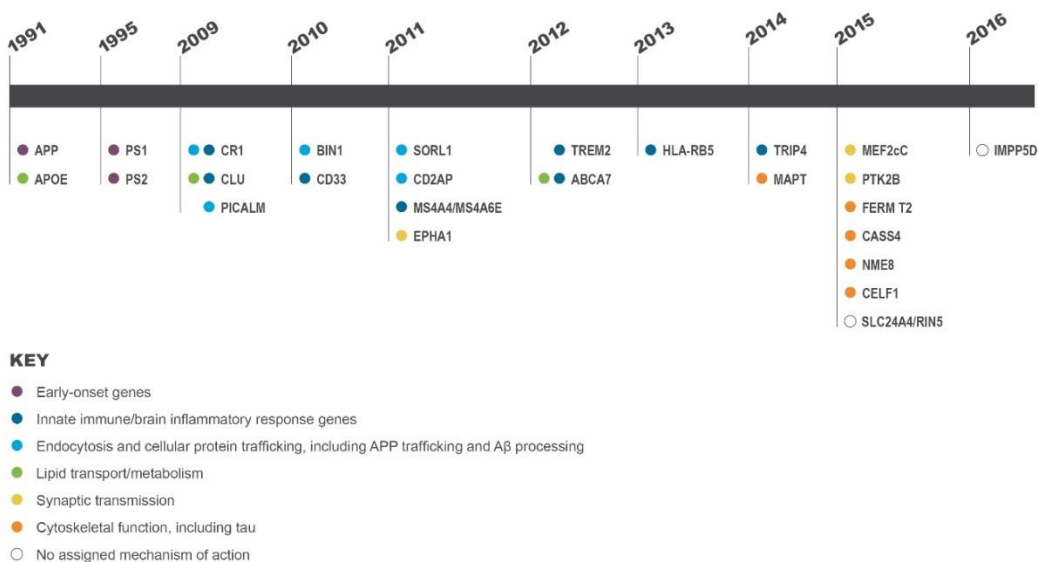
Apolipoprotein E (APOE)  $\epsilon$ 4, one form of the APOE gene, was the only known genetic risk factor for late-onset Alzheimer's until 2009. Since then, rapidly changing technologies in genetics have resulted in a growing list of others. These newly discovered genetic risk factors have

strengthened evidence about the involvement in Alzheimer's disease in certain biological pathways, including amyloid metabolism, immune responses, and cellular function. Genes may also interact with environmental and lifestyle factors to contribute to the risk of developing late-onset Alzheimer's.

## Genetic Regions of Interest in Alzheimer's Disease

By year of discovery

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



NIH supports teams of scientists working on genome-wide association studies (GWAS), an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. Once new genetic associations are identified, researchers can use the information to develop better strategies to detect, treat, and prevent the disease. Their ability to scan thousands of DNA samples from volunteers both with and without the disease has revolutionized the detection of the elusive gene variants involved in Alzheimer's.

We can now analyze, for example, how genome sequences may contribute to increased risk for or protection against the disease. Genome sequencing is figuring out the order of DNA nucleotides, or bases—the As, Cs, Gs, and Ts—that make up an organism's DNA. The ultimate goal is to find new pathways for treatments and prevention. Recently, the NIH [Alzheimer's Disease Sequencing Project](#) (ADSP) determined the order of all 3 billion letters in the individual genomes of 580 participants.

- In 2015, ADSP investigators began to identify variations in the genomes of families in which three or more members are affected by Alzheimer's. The specific regions are now being closely examined to determine which genes are involved. The ADSP also generated whole exome sequencing data (focused on the proteins influencing the disorder) from an additional 11,000 volunteers—6,000 with Alzheimer's—compared with 5,000 participants free of the disorder.
- ADSP also initiated the Discovery Extension Phase of the study with whole genome sequencing on more than 430 family members. The goal is to identify rare gene variants and explore differences in data from different racial and ethnic groups.
- Two NIH-funded entities are collaborating on managing and making available to the genetics research community the massive amounts of ADSP data: the [Genetics of Alzheimer's Disease Data Storage Site](#) (NIAGADS) and the [Database for Genotypes and Phenotypes](#).
- In 2015, NIAGADS released genotypic data generated on more than 11,500 people and responded to data requests from 30 labs at 26 institutions to facilitate the sharing of sequencing data with the genetics community. NIAGADS has established several data and information technology resources for the research community at large and provides a Web interface that integrates Alzheimer's genetic findings with other genetic data for rapid analysis of sequence data.

### **Progress in Understanding Alzheimer's Genetics**

Recent discoveries have not only identified additional genes involved in Alzheimer's, but have helped scientists figure out what they may do. Discovering the mechanisms involved in Alzheimer's onset and progression, as well as disease-related brain changes, directs researchers to pathways that might be targeted by drug or nondrug interventions to help stop disease or protect against it.

Recent examples illustrate how such discoveries are moving this area of research forward:

#### ***Hunting for rare Alzheimer's risk genes***

To date, GWAS have uncovered 20 genes associated with risk of late-onset Alzheimer's disease, the most common form of the disease. It is estimated that these genes together account for about 30 percent of inherited risk for this common form of Alzheimer's. Scientists are trying to understand what accounts for the other 70 percent of genetic risk. To help identify these unknown mutations, research teams are now focusing GWAS on ethnic groups and large families with unusually high rates of Alzheimer's.

- One team studied DNA samples from 282 Caribbean Hispanic families with five or more members with late-onset Alzheimer's ([Barral et al., 2015](#)). They discovered 13 genetic

loci (small regions of DNA) associated with the disease, most significantly at a locus on chromosome 11, near the *MS4AE* gene. This gene activates a cell membrane protein thought to be involved in activating immune cells.

- Researchers conducted a GWAS of DNA donated by 41 non-Hispanic white families with four or more members affected by late-onset Alzheimer's and identified 15 loci associated with increased disease risk ([Kunkle et al., 2016](#)). Three of these loci had never been associated with the disease before. The statistically strongest association was at a locus on chromosome 14 that contains three genes: *C14orf177*, *BCL11B*, and *Mir\_320*. *C14orf177* has been previously linked with increased risk of amyotrophic lateral sclerosis and heart disease. Both *BCL11B* and *Mir\_320* are involved in regulating the health and survival of neurons.
- Another team looked for recessive mutations associated with late-onset Alzheimer's ([Ghani et al., 2015](#)). A recessive mutation is one that causes disease only if a person inherits two copies of the change in DNA sequence. Studying genomic data donated by 1,917 African Americans diagnosed with Alzheimer's and 3,858 free of the disorder, they found a region on chromosome 3, containing 43 different genes, that was associated with increased risk of Alzheimer's disease. They also found greater rates of Alzheimer's among participants with long stretches of the DNA sequence inherited from two parents that were identical on both strands.

By identifying small regions of the genome that may harbor rare mutations contributing to the risk of late-onset Alzheimer's disease, studies like these are paving the way for future efforts to pin down potential disease mutations in those regions.

### ***PICALM risk gene and amyloid clearance***

Geneticists believe that PICALM, a known Alzheimer's genetic risk factor, affects the levels of beta-amyloid deposits in the brain. The accumulation of this protein over time forms the basis for the hallmark plaques of Alzheimer's in the brain. NIH-funded research now suggests that PICALM plays a role in clearing amyloid from the brain ([Zhao et al., 2015](#)).

In donated human brains with Alzheimer's, they found lower-than-normal levels of PICALM proteins in cells that line brain blood vessels. In Alzheimer's mouse models with one copy of the gene, amyloid plaque levels were four times greater than in similar mice with two copies of PICALM. The PICALM-deficient Alzheimer's disease model mice also performed significantly worse on tests of nest-building, burrowing, and learning to recognize new objects.

Further observations in tissue culture suggested that PICALM helps endothelial cells, which form the lining of blood vessels, by capturing beta-amyloid from the fluid around neurons and transporting it across blood vessel walls for release into the bloodstream. This study has

improved our understanding of how the brain clears excess beta-amyloid and suggests that increasing PICALM protein levels could be of therapeutic benefit.

### ***Targeting a pathway involved in amyloid production***

Scientists have identified a cellular pathway that might be harnessed to reduce beta-amyloid production ([Ceglia et al., 2015](#)). When amyloid precursor protein is broken down to form beta-amyloid, other proteins are released, including amyloid precursor protein's intracellular domain (AICD). The AICD protein can turn the activity of specific genes on or off. In mice and cell cultures, it had been shown to inhibit other proteins in a pathway that can lead to increased beta-amyloid production.

The investigators wondered whether the normally protective function of AICD may be altered or overwhelmed in Alzheimer's disease. They showed that genetically manipulating this pathway in Alzheimer's disease model mice could dramatically lower beta-amyloid levels and restore memory performance. These findings suggest AICD might be targeted therapeutically to reduce beta-amyloid.

## **Dementia-Related Brain Changes**

### ***Blocking astrocyte immune responses to amyloid***

Astrocytes, named for their star-like shapes, are brain cells that promote inflammation to ward off toxic proteins or agents. Normally, this response would help the brain, but not if astrocytes become chronically activated and do more harm than good, as many scientists believe is the case in Alzheimer's.

An NIH-funded study identified how an astrocyte-generated molecule, complement protein C3, may provoke the damaging inflammatory responses found in Alzheimer's disease ([Lian et al., 2015](#)). When mouse neurons in tissue culture were exposed for 2 weeks to astrocytes producing high levels of C3 or to purified C3, the brain cells began losing their dendritic spines and branches. Mice genetically engineered to express high C3 levels also lost dendritic spines and scored lower on learning and memory tests. The scientists were able to restore memory and learning in the mice with a drug that blocks one of the receptors for C3. This study heightens interest in developing such receptor blockers to treat Alzheimer's disease.

### ***Tau antibody blocks neurodegeneration after brain injury***

Traumatic brain injury (TBI) may result in tau tangles in the brain, a hallmark of Alzheimer's and other dementias. But just how tau damages the brain after TBI has been unclear. NIH-funded research showed that severe TBI caused phosphorylated tau (P-tau) to change shape from its normal form to a toxic type named *cis* P-tau ([Kondo et al., 2015](#)). Imaging revealed *cis* P-tau in people with a history of sports- or military-related TBI, compared to those with healthy brain tissue.



In mouse models of TBI, the scientists found upsurges in brain *cis* P-tau levels that lasted for months and damaged axons, the branch-like structures in brain cells that carry electrical charges necessary for communication. The scientists then treated mice with an antibody targeting *cis* P-tau for 2 weeks after TBI and found that it blocked the toxic tau from damaging neurons and behaviors. The findings suggest that therapies targeting *cis* P-tau in human brains may help prevent the progression of brain cell deterioration after TBI and in people with Alzheimer's and related dementias.

### ***Leakiness in the aging blood-brain barrier***

The integrity of the blood-brain barrier (BBB) is critical to brain health. In a new study, researchers have shown that the BBB, which helps prevent toxic substances in the bloodstream from entering the brain, becomes leaky with age ([Montagne et al., 2015](#)). The researchers developed a new, high-resolution magnetic resonance imaging method that measures how fast a dye injected into the bloodstream enters the brain. They conducted scans of 24 cognitively normal volunteers, age 23 to 91 years, and of 21 volunteers with mild cognitive impairment (MCI), age 55 to 91 years. They found that the BBB became more permeable as people aged and was leakier in older people with MCI than in older people with normal cognition.

The age-related breakdown of the BBB started in the hippocampus, a brain region involved in learning and memory, while the BBB in other brain regions remained intact. Analysis of the volunteers' cerebrospinal fluid showed that BBB breakdown correlated with damage to pericytes, cells that help seal the walls of brain blood vessels. These findings suggest that BBB breakdown contributes to age-related cognitive decline, and that therapeutics might be aimed at helping to maintain pericyte health and BBB integrity.

### ***Brain pathology in the oldest-old***

The brains of people who live to 90 and older—the oldest-old—often have a mix of pathologies associated with dementia. NIH-funded researchers are learning more about how Alzheimer's disease-related brain changes and other pathologies, such as infarcts, Lewy bodies, hippocampal sclerosis, and white matter disease, may influence the cognitive health of this special group.

A post mortem study of these oldest-old individuals suggests that Alzheimer's disease is not an inevitable consequence of old age ([Neltner et al., 2016](#)). Scientists analyzed the donated brains of 77 people who lived to age 98 to 107 years, as well as cognitive testing data, to look for signs of neurodegenerative diseases.

Most of the brains showed at least one kind of pathology, but 66 percent showed two or more pathologies, most commonly Alzheimer's disease and arteriosclerosis (thickening and

narrowing of blood vessels). About a quarter of the brains showed signs of Lewy bodies and degeneration of the hippocampus, but no signs of frontotemporal dementia.

Notably, 20 percent of the brains were free of pathological hallmarks of Alzheimer's disease (amyloid plaques and tau tangles). Indeed, no single kind of pathology was universally found in the brains of these very long-lived people, suggesting that brain aging is not necessarily accompanied by the emergence of Alzheimer's disease or related dementias.

For the first time, researchers examined the relationship between the number of pathologies found at autopsy and the severity of dementia in the oldest-old ([Kawas et al., 2015](#)). The 183 volunteers received physical and cognitive testing every 6 months. When they died at an average age of 97, about 54 percent were diagnosed with dementia. The donated brains were examined for eight different Alzheimer's-related pathologies. The results showed that the more pathologies present in the brain, the more severe the dementia, and that Alzheimer's pathology alone was less damaging to cognition than mixed pathologies. This suggests the importance of developing therapies directed at multiple targets.

### ***Identifying ways to keep neurons healthy***

In animal models of Alzheimer's and in human disease, brain cells may not produce enough energy to remain fully functional. Scientists using a new mouse model discovered that an enzyme, SIRT3, may protect brain cells against stresses believed to contribute to energy loss ([Cheng et al., 2016](#)). They also found that physical exercise increases the expression of SIRT3—found in mitochondria, the cell's powerhouse—which helped to protect the brain against degeneration in the mice. The findings suggest that bolstering mitochondrial function and stress resistance by increasing SIRT3 levels may offer a promising therapeutic target for protecting against age-related cognitive decline and brain diseases such as Alzheimer's.

### ***Alzheimer's and Down syndrome***

Many people with Down syndrome have Alzheimer's-related brain changes in their 30s that can lead to dementia in their 50s and 60s. Little is known about how the disease progresses in this vulnerable group. However, a recent study identified an Alzheimer's-related immune response that may be unique to people with Down syndrome ([Wilcock et al., 2015](#)).

Macrophages are immune cells that clear away cellular debris to reduce brain inflammation and promote repair. The scientists examined brain tissues at autopsy donated by young, middle-aged, and older people with Down syndrome and volunteers without the condition; each group included people diagnosed with Alzheimer's. Each group consisted of 6 to 29 volunteers.

By staining the tissue with antibodies that recognize markers specific to each of the four macrophage types, scientists discovered that only one form—the M2b macrophage—predominated in the brains of people with Down syndrome and Alzheimer's disease. This form

was almost never seen in the brains of participants with Alzheimer's but not Down syndrome. These findings suggest that Alzheimer's disease in people with Down syndrome involves unique inflammatory processes and may require different therapeutic approaches than sporadic Alzheimer's disease.

### **Promising Research Opportunities**

Our understanding of Alzheimer's disease at the biological level is mounting rapidly, spurred by the creative thinking and new technologies that allow scientists to explore uncharted territory at the genetic, molecular, and cellular levels. Such research was not possible just a few years ago. As translational and clinical studies build on what we have learned, it is critical to 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.

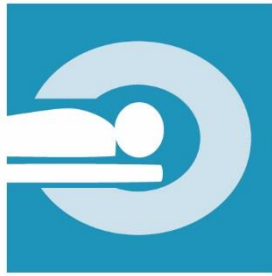
Please see the [list of milestones](#) to which additional funding in FY 2018 would apply. Also see the [full list of milestones](#) aimed at Alzheimer's disease research by 2025.

### ***Moving ahead in basic research***

Additional funding in FY 2018 would build on rapidly expanding research opportunities 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, the microbiome (the combined genetic material of all microorganisms, such as various bacteria, that reside in the skin, gut, and other parts of the human body), 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 biomarkers; multimodal biomarkers; novel biomarkers; and novel methodologies and techniques.*

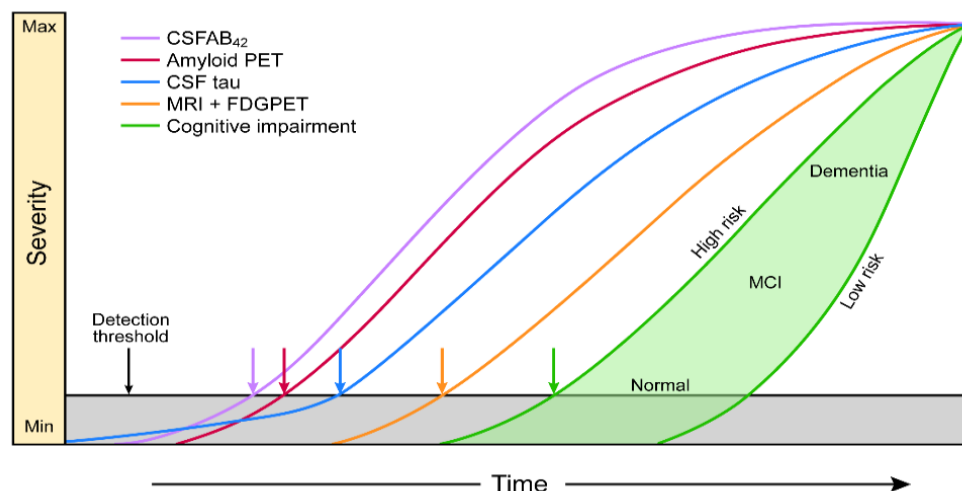
In the last decade, scientists have greatly advanced the ability to detect the brain changes that can occur years, even decades, before the first symptoms of Alzheimer’s and related dementias appear. Some studies focus on changes in personality and mental functioning, measured through memory and recall tests, while others focus on the relationship between early damage to brain tissue and outward clinical signs detected via brain imaging, such as computed tomography, magnetic resonance imaging (MRI), or positron emission tomography (PET).

Another promising area of diagnostic research is the analysis of biomarkers—biological signs of disease found in brain images, cerebrospinal fluid (CSF), and blood—to detect early changes in the brains of people with mild cognitive impairment (MCI) and in cognitively normal people who may be at greater risk for Alzheimer’s disease. NIH researchers have been in the forefront of identifying biomarkers that can monitor disease onset and progression.

### **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 NIH intensifies research into preclinical markers and measures of disease progression and therapeutic effectiveness, it must also continue to refine neuropsychological and clinical measures in people at later disease stages to develop effective interventions.

## 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](#)).*

Recent studies, upon which 2018 funding would build, examined the following areas:

### ***Neurogranin: a new biomarker of synaptic decline***

Scientists have been searching for a biomarker in CSF that identifies synaptic degeneration, an Alzheimer's-related brain change. They may have identified such a marker in neurogranin, a protein found in dendritic spines ([Kester et al., 2015](#)). Researchers measured neurogranin levels in CSF samples of 163 volunteers with Alzheimer's disease, MCI, or normal cognition (average age, 64 to 68 years). The volunteers each provided two CSF samples about 2 years apart and were followed clinically for 4 years.

The investigators found neurogranin levels at the start of the study were higher in people with Alzheimer's disease than in those free of the disease, and that higher levels predicted who among the MCI group would progress to Alzheimer's disease. However, over the 4 years of the study, only the cognitively normal participants showed increases in the protein. This pattern supports the idea that synaptic degeneration occurs primarily in the earliest stages of Alzheimer's and then plateaus. These findings may one day result in a clinical test for early-stage diagnosis of Alzheimer's disease and related dementias.

### ***Identifying Alzheimer's biomarker patterns in the middle-aged***

In the first major longitudinal study of its kind, scientists detected biomarkers predictive of Alzheimer's disease in the CSF of cognitively healthy people as young as age 45 ([Sutphen et al., 2015](#)). Researchers sampled CSF and clinically assessed 169 symptom-free volunteers age 45 and older every 3 years over an average of 6 years. They measured:

- Known Alzheimer's-related proteins in the CSF (beta-amyloid 40, beta-amyloid 42, total tau, and phosphorylated tau)
- Two recently identified potential Alzheimer's disease biomarkers: visinin-like protein 1 (VILIP-1, a neuronal death marker) and chitinase-3-like protein 1 (YKL-40, an inflammation marker)
- Amyloid levels by imaging the brains of 74 volunteers

Researchers found abnormal CSF beta-amyloid 42 levels in some people by early middle age (45-54 years); this group went on to develop brain amyloid deposits by mid-middle age (55-64 years). Markers for neuronal injury (total tau, P-tau, and VILIP-1) increased dramatically in some volunteers in their mid-50s, while the YKL-40 inflammation marker rose steadily over the years among all participants. These patterns of biomarker changes were more pronounced in APOE  $\epsilon$ 4 carriers, who are at greater genetic risk of developing Alzheimer's disease.

These results suggest that CSF biomarker changes will be useful for identifying symptom-free people who might benefit most from participating in Alzheimer's disease trials seeking early interventions.

### ***CSF biomarkers reveal influence of cognitive reserve***

Cognitive reserve refers to the brain's ability to function normally despite having Alzheimer's-related brain changes, such as abnormal levels of amyloid and tau proteins. A new study suggests that cognitive reserve not only protects cognitive function after amyloid has begun to accumulate, but may also stave off Alzheimer's disease pathology in the first place ([Almeida et al., 2015](#)).

Scientists collected CSF samples from 211 cognitively normal and 57 cognitively impaired volunteers to test levels of tau pathology. The participants were enrolled in the NIH-supported Wisconsin Registry for Alzheimer's Prevention and the Wisconsin Alzheimer's Disease Research Center. As expected, older participants (average age, 80) had higher levels of Alzheimer's-related tau than younger volunteers (average age, 50). Notably, people with fewer than 16 years of education showed bigger age-related increases in tau levels than did their peers with more years of education.



How early-life education builds late-life cognitive reserve is still a matter of active research. One idea is that cognitive stimulation increases the number of synapses in the brain. Education also correlates with other lifestyle factors that influence brain health, such as socioeconomic status, physical activity, and better overall health. Whatever the mechanism, this study adds to growing evidence that positive lifestyle factors such as cognitive stimulation may delay the onset of Alzheimer's disease.

### ***New tracer images tau in the living brain***

Abnormal levels of the tau protein in the brain are one hallmark of Alzheimer's disease. Brain imaging to detect tau levels holds promise for distinguishing Alzheimer's from other forms of dementia and the testing of drugs that target tau. Scientists have discovered a new chemical compound, T807, that may detect tau in the living brain ([Johnson et al., 2016](#)).

The investigators first injected 75 symptom-free, MCI, and mild Alzheimer's volunteers with T807, then scanned their brains using PET. T807 showed up significantly higher in certain brain regions in the MCI and Alzheimer's volunteers compared with those with normal cognition. More significantly, the more T807 showed up in the scans, the greater the level of cognitive impairment. This correlation to cognitive decline was even stronger than that found by imaging levels of a compound that binds to beta-amyloid. These findings suggest that T807 PET is a promising biomarker for detecting and monitoring the emergence of brain pathology and clinical symptoms in Alzheimer's disease.

### ***Identifying Alzheimer's disease with Lewy bodies***

Lewy bodies, abnormal deposits of the protein alpha-synuclein found inside brain cells, are a hallmark of Parkinson's disease and Lewy body dementia. The brains of people with Alzheimer's disease are often found at death to contain Lewy bodies, resulting in a post mortem diagnosis of "Alzheimer's disease with Lewy bodies." Because certain medications used to treat Alzheimer's may worsen the symptoms of Alzheimer's disease with Lewy bodies, scientists are searching for ways to distinguish between the two disorders in living patients.

To identify clinical symptoms unique to each disease, researchers studied clinical data and brain tissue from 531 deceased people diagnosed with Alzheimer's disease pathology ([Chung et al., 2015](#)). They found that 40 percent of the group had Alzheimer's disease with Lewy bodies; significantly, they developed symptoms earlier, died younger, and had worse motor performance and more behavioral problems (including more severe delusions, hallucinations, abnormal motor behaviors, and sleep problems) than those without Lewy bodies. Participants with Alzheimer's disease with Lewy bodies were also more likely to be male and to carry at least one copy of the APOE ε4 allele.

These findings may help clinicians to more easily identify, predict the course of disease, and tailor treatments for patients with Alzheimer's disease with Lewy bodies.

### **Detecting and Tracking Early Cognitive Decline**

Researchers have now defined a preclinical phase of Alzheimer's disease, in which brain degeneration has begun but affected people do not show problems on standard clinical cognitive tests. Because treatment would ideally begin at the earliest possible stages of disease, researchers need more sensitive tests to detect and track these stages. In 2015, several studies advanced the field:

#### ***Easy-to-use models predict risk for early cognitive decline***

Finding brief, inexpensive, and noninvasive ways to predict risk for progressing from healthy cognition to MCI would identify high-risk individuals, providing a window of opportunity for joining early-intervention clinical trials. Using clinical data from the National Institutes of Health (NIH)-supported Mayo Clinic Study of Aging, the researchers developed scoring models for predicting MCI risk scores using easily obtained variables ([Pankratz et al., 2015](#)).

The study involved 1,449 participants, age 70 to 89, who were cognitively normal in 2004; 28 percent developed MCI during the median 5-year follow-up period. The researchers developed a scoring system based on demographic and clinical variables, including sex-specific factors, that could predict risk for MCI. The factors they scored included education, self-reported memory concerns, diabetes, alcohol problems, stroke, and atrial fibrillation. Sex-specific predictors included smoking, high blood fat levels, hypertension for women, and obesity and single marital status for men.

The researchers found that several markers were linked to higher risk for decline, such as self-reported memory complaints, diabetes, and slow gait. These scoring models offer a brief, inexpensive, and noninvasive method for primary care physicians to evaluate risk in patients or to screen for participation in research studies.

#### ***Developing simple but sensitive measures of cognitive function***

The Cognitive Function Instrument (CFI), developed over the last decade by the Alzheimer's Disease Cooperative Study, is designed to test a person's ability to function in everyday life. The test can be given by mail, over the phone, or online and asks 14 questions of both the study participant and a partner. The questions ask about problems with everyday function (such as misplacing things, forgetting appointments or names, and difficulties managing money or driving) and also about self-perceived decline.

Researchers road-tested the CFI in a group of 468 older individuals (average age, 79) who scored as cognitively healthy on three other tests at the start of the study ([Amariglio et al.,](#)

[2015](#)). For the next 4 years, participants completed the CFI annually and were tested in the clinic the month after they took the CFI. Both participant and partner CFI scores correlated well with cognitive function as measured in the clinic, and the combined scores correlated even better. The CFI could provide a simple, sensitive outcome measure for use in preventive drug trials for Alzheimer's disease.

### ***Sense of smell and early-stage dementia***

Problems with the sense of smell, or olfaction, are a known early warning sign of Alzheimer's disease and may be a more accurate predictor of future cognitive decline than memory or language problems.

- Researchers followed 1,037 volunteers (average age, 80) who had either normal cognition or MCI at the start of the study ([Devanand et al., 2015](#)). The participants were members of the NIH-funded Washington Heights-Inwood Community Aging Project. At baseline and every 2 years, the researchers gave the volunteers a "scratch and sniff" odor discrimination test, along with a verbal memory test and other cognitive tests. The University of Pennsylvania Smell Identification Test, or UPSIT, proved superior to the memory test in predicting both cognitive decline and transition to Alzheimer's disease during the 4 years. It was also the only test that predicted cognitive decline in volunteers who were cognitively normal at baseline.
- The UPSIT could be an inexpensive tool for selecting patients and monitoring cognitive performance in clinical trials ([Pelton et al., 2016](#)). In a 12-week clinical trial of the cholinesterase inhibitor donepezil, 11 Alzheimer's disease volunteers who had lower UPSIT scores at the start of the trial were more likely to respond to the drug with improved memory performance than those who had higher UPSIT scores at baseline.
- Scientists looked at the relationship between olfactory function and the APOE ε4 allele ([Oleson & Murphy, 2015](#)). Alzheimer's disease patients with two copies of the ε4 allele have a faster rate of cognitive decline than those with only one or no copies. In this study of older adults diagnosed with probable Alzheimer's disease, those with two copies of ε4 also showed worse deficits than the other two groups in an odor identification test and in their ability to recall odors smelled in the past. In contrast, the three groups showed no differences in performance on a word retrieval test.

### **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. Additional funding would support milestones aimed at developing biomarkers that can detect and track Alzheimer's-related changes and the effectiveness of promising treatments. In addition, funding would support research into innovative technologies that capture research-relevant data on

dementia patients and caregivers in the comfort of their own homes. Please see the [list of milestones](#) to which additional funding in FY 2018 would apply. Also see the [full list of milestones](#) aimed at Alzheimer's disease research by 2025. 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 PET ligands, as well as CSF and blood biomarkers, to identify and assess Alzheimer's pathologies, including tau, inflammation, and synaptic dysfunction
- Developing minimally invasive biomarkers (for example, EEG, blood) to detect and monitor Alzheimer's-related pathology in the brain
- Developing and refining sensitive clinical and neuropsychological assessment measures to detect and track early-stage disease

## 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. NIH also supports studies that test pharmacological agents already in use for other conditions as well as nondrug interventions.

Currently, drugs approved by the U.S. Food and Drug Administration (FDA) to treat Alzheimer's symptoms include cholinesterase inhibitors and memantine, which support neurotransmitters important to memory function. These drugs 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 believed to be 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. One study estimated that 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 FDA (which regulates drug approval), and the wider research community have worked

collaboratively to overcome the many challenges of translational research to help speed drug discovery and the testing of possible therapies.

### ***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, the immune system, and environmental 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.

NIH-hosted Alzheimer's Disease Research Summits in 2012 and 2015 underscored the importance of this multi-target approach and outlined other new directions in translational research. Experts at these meetings also offered new ways to think about drug development for Alzheimer's disease, to look beyond the traditional approach of identifying a single drug target to investigating networks of targets and multiple drug-target interactions.

Ongoing research funded by NIH and plans for future projects with additional funds incorporate such state-of-the-art thinking:

The [Accelerating Medicines Partnership-Alzheimer's Disease](#) 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 novel pathways and genes involved in this complex disease, but shows how they interact with one another in networks. The goal is to identify targets for drug development and validation.

The project will apply cutting-edge systems and innovative approaches to study large sets of human biological data—"omic" data, as in genomic, epigenomic, and proteomic—from more than 2,000 human brains at all stages of the disease. The study also incorporates enriched clinical and pathological data. The goal is to discover novel therapeutic targets for Alzheimer's disease, gain an understanding of genetic impact, assess protein and metabolic networks within which these novel targets operate and interact, 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, scientists hope to develop blood biomarkers, from easily obtained blood samples, that are less expensive and easier to use than brain imaging or cerebrospinal fluid biomarkers. A new phase of the initiative is scheduled to launch in mid-2016.

To map these complex brain networks, 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. Deep learning enables a computer system to teach itself from lots of data rather than simply following preset rules. This tool for identifying promising drug targets has the potential to slice many years off drug development.

### **Progress in Translational Research**

Additional funding in FY 2018 would build on recent progress in drug discovery and development. A number of studies indicate how new approaches may modify underlying mechanisms of disease. Recent studies in animal models are promising:

#### ***Test drug blocks harmful cellular stress response***

Enzymes that stress cells are of special interest in dementia research, due in part to their known involvement in the loss of healthy synapses. NIH-funded researchers working with mouse models of Alzheimer’s disease found that a drug that inhibits cellular responses to stress showed therapeutic promise ([Roy et al., 2015](#)).

The drug, MW150, was designed to inhibit the enzyme p38 $\alpha$  MAP. This enzyme, found in both neurons and glia cells (which surround and support brain cells), is induced by cellular stress and rises to abnormally high levels in the early stages of human Alzheimer’s disease. It plays a role in a number of cellular processes that contribute to neurodegeneration, including brain inflammation and loss of synaptic plasticity.

In this study, mice were given oral doses of MW150 at an age when memory deficits could develop. In an early-onset Alzheimer’s mouse model, daily treatment with MW150 for 2 months starting at 8 weeks of age prevented memory declines. In models of the more common late-onset Alzheimer’s, just 2 weeks of drug treatment at 11 weeks of age reversed memory declines. Results so far show promise, but more research is needed to move the drug into human testing.

#### ***Curcumin-derived drug influences age-related brain changes***

The small-molecule drug J147 is derived from curcumin (the main ingredient in the spice turmeric), which is believed to have a variety of anti-aging properties. In previous studies, the drug was shown to reverse cognitive impairment in mouse models of Alzheimer’s disease. In a



new study focused on the molecular contributions of aging to Alzheimer's, researchers examined the effects of the drug in a mouse model that ages unusually rapidly and develops cognitive impairment, including some symptoms of Alzheimer's disease ([Currais et al., 2015](#)).

The researchers monitored a broad spectrum of age- and Alzheimer's disease-related changes in cognition, gene and protein expression, and cellular metabolism in the mice. They fed the mice a J147-supplemented diet starting at 3 months of age. At 10 months, the supplement-fed mice showed significantly fewer cognitive deficits, as well as improvements in multiple markers associated with human aging and Alzheimer's disease, including inflammation, impaired synaptic function, vascular and glial dysfunction, and metabolic aging. These results suggest that drugs targeting age-related brain changes might be pursued for their possible effects in staving off Alzheimer's disease.

### ***New class of drugs inhibit toxic amyloid***

Researchers have identified a new class of drugs that may reduce beta-amyloid accumulation without producing toxic side effects. The enzyme gamma-secretase is responsible for cleaving amyloid precursor protein to produce a toxic form of amyloid called beta-amyloid 42. Inhibiting gamma-secretase would therefore seem a logical approach to reducing levels of beta-amyloid 42. However, gamma-secretase performs a variety of necessary biological functions, and drugs that inhibit it can cause unwanted side effects.

Researchers have developed a new class of drugs, called soluble gamma-secretase modulators (SGSMs), which block gamma-secretase's ability to cleave amyloid precursor protein but otherwise do not interfere with the enzyme's other biological functions. A new study, in human brain cells grown in tissue culture, tested how three different SGSMs influenced the cells ([D'Avanzo et al., 2015](#)).

One week of treatment with any of the SGSMs reduced beta-amyloid 42 levels in the cultures by 80 percent, and the SGSMs (unlike a traditional gamma-secretase inhibitor) allowed the neurons to develop normally in the cultures. In addition, the study suggests that this neural culture system could be used in the future to screen similar drugs for their potential therapeutic efficacy and side effects.

### ***Testing safety of brain hormone destined for clinical trials***

Allopregnanolone is a brain hormone that stimulates the production of new neurons in a process known as neurogenesis. Past animal studies have shown that the hormone can restore learning and memory while also reducing beta-amyloid and brain inflammation. A new animal study found that a single intravenous dose of the hormone caused no adverse side effects yet significantly increased neurogenesis in aged mice and in an Alzheimer's disease mouse model.

This investigation paved the way for the use of this hormone in an [NIH-funded clinical trial \(Irwin et al., 2015\)](#).

### ***Cancer drug offers hope for Alzheimer's***

NIH's National Center for Advancing Translational Sciences (NCATS) supports the testing of an experimental cancer drug 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' [Discovering New Therapeutic Uses for Existing Molecules](#) program, a pioneering partnership between NIH and industry in which pharmaceutical companies offer the scientific community compounds that have been unsuccessful in initial testing for one condition but may be developed for another use.

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 2018 research agenda. One goal is to initiate at least three Phase III trials with promising repurposed drugs or combinations of drugs.

### **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 the National Institute on Aging (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 currently funds and conducts 38 clinical trials for Alzheimer's and age-related cognitive decline. These include 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). They involve new or repurposed drugs, lifestyle interventions like exercise or diet, and behavioral approaches like cognitive training.

One area of investigation involves 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. The primary prevention trials listed in Table 1 include an NIA-funded add-on to a large NIH trial that addressed 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**

<b>Trial Name</b>	<b>Principal Investigator/ Institution</b>	<b>Anticipated Completion</b>
<b>Immunotherapy/Anti-Amyloid</b>		
<a href="#"><u>API ADAD</u></a> (Alzheimer’s Prevention Initiative Autosomal Dominant Alzheimer’s Disease Trial)	Eric Reiman, Banner Alzheimer’s Institute	2018
<a href="#"><u>API APOE4</u></a> (Alzheimer’s Prevention Initiative Apolipoprotein E4 Trial)	Eric Reiman, Banner Alzheimer’s Institute	2019
<a href="#"><u>DIAN-TU</u></a> (Dominantly Inherited Alzheimer Network Trial)	Randall Bateman, Washington University	2019
<a href="#"><u>A4 Trial</u></a> (Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease)	Reisa Sperling, Harvard Medical School	2019
<a href="#"><u>Active Immunotherapy for Cognitive Decline in Adults with Down Syndrome</u></a>	Michael Rafii, University of California, San Diego	2020
<a href="#"><u>Dominantly Inherited Alzheimer Network Trials Unit—Adaptive Prevention Trial</u></a>	Randall Bateman, Washington University	2020
<b>Cardiovascular</b>		
<a href="#"><u>SPRINT-MIND</u></a> (Systolic Blood Pressure Intervention Trial-MIND) <sup>1</sup>	David Reboussin, Wake Forest University	2016
<a href="#"><u>ASPREE</u></a> (Aspirin in Reducing Events in the Elderly)	Richard Grimm, Berman Center for Outcomes & Clinical Research; John McNeil, Monash University	2017
<b>Nonpharmacological—Exercise</b>		
<a href="#"><u>Effect of Physical Activity on Cognition Relative to APOE Genotype</u></a>	Jennifer Ethier, University of North Carolina at Greensboro	2018
<a href="#"><u>Effect of Aerobic Exercise on Alzheimer’s Pathophysiology in Preclinical Alzheimer’s Disease</u></a>	Jeffrey Burns, University of Kansas	2019
<a href="#"><u>EXERT</u></a> (Exercise MCI Trial) <sup>2</sup>	Laura Baker, Wake Forest University; Carl Cotman, University of California, Irvine	2022

<b>Trial Name</b>	<b>Principal Investigator/ Institution</b>	<b>Anticipated Completion</b>
<b>Nonpharmacological—Cognitive Training</b>		
<a href="#">Plasticity-based Adaptive Cognitive Remediation for Alzheimer's Disease</a>	Hyun Lee, Brain Plasticity, Inc.	2020
<b>Nonpharmacological—Dietary</b>		
<a href="#">MIND Diet Intervention to Prevent Alzheimer's Disease</a>	Martha Clare Morris, Rush University	2022
<b>Other Interventions</b>		
<a href="#">Citalopram Decreases CSF A<math>\beta</math>: A Randomized Dose Finding Trial</a>	Yvette Sheline, Washington University	2018

<sup>1</sup> Add-on to National, Heart, Lung, and Blood Institute's and National Institute of Diabetes and Digestive and Kidney Diseases' SPRINT trial; co-funded by NIA and National Institute of Neurological Disorders and Stroke.

<sup>2</sup> Trial supported through Alzheimer's Disease Cooperative Study (ADCS).

**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](http://ClinicalTrials.gov).

**Table 2. Ongoing Alzheimer's Disease/MCI Clinical Trials Funded by NIA**

<b>Trial Name</b>	<b>Principal Investigator/ Institution</b>	<b>Anticipated Completion</b>
<b>Nutritional</b>		
<a href="#"><u>Benfotiamine in Alzheimer's Disease: A Pilot Study</u></a>	Gary Gibson, Burke Medical Research Institute	2020
<b>Cardiovascular</b>		
<a href="#"><u>Hypertension, Angiotensin Receptor Blockers, and Cognition Effects and Mechanisms</u></a>	Ihab Hajjar, University of Southern California	2018
<a href="#"><u>Modulation of microRNA Pathways by Gemfibrozil in Predementia Alzheimer's Disease</u></a>	Gregory Jicha, University of Kentucky	2019
<b>Hormones</b>		
<a href="#"><u>Allopregnanolone Regenerative Therapeutic for MCI/Alzheimer's Disease</u></a>	Roberta Diaz Brinton, University of Southern California	2019
<b>Pharmaceutical Repurposing</b>		
<a href="#"><u>Clinical Intervention of T3D-959 as a Potential Disease Remedial Therapeutic for the Treatment of Alzheimer's Disease</u></a>	John Didsbury, T3D Therapeutics; Suzanne de la Monte, Rhode Island Hospital	2018
<a href="#"><u>Immune System Stimulation with Sargramostim in Subjects with Mild Cognitive Impairment due to Alzheimer's Disease</u></a>	Owen Hagino, Sanofi-Aventis US, Inc.	2019
<a href="#"><u>Phase II/III Trial for Slowing Progression in Mild Cognitive Impairment</u></a>	Michela Gallagher and Marilyn Albert, Johns Hopkins University	2021
<a href="#"><u>Long-Term Nicotine Treatment of Mild Cognitive Impairment</u></a>	Paul Newhouse, Vanderbilt University; Paul Aisen, University of Southern California	2021
<b>Metabolic</b>		
<a href="#"><u>Therapeutic Effect of Intranasal Insulin on Cognition, Function, and Alzheimer's Disease Biomarkers</u></a>	Suzanne Craft, Wake Forest University	2018
<b>Nonpharmacological—Exercise</b>		
<a href="#"><u>Aerobic Exercise in Alzheimer's Disease</u></a>	Fang Yu, University of Minnesota	2019

<b>Trial Name</b>	<b>Principal Investigator/ Institution</b>	<b>Anticipated Completion</b>
<a href="#">Genes, Exercise, Neurocognitive and Neurodegeneration: Community-Based Approach</a>	Thomas Obisesan, Howard University	2020
<a href="#">Effects of Physical Activity on Brain Function and Network Connectivity in MCI</a>	Judy Pa, University of California, San Francisco	2021
<b>Nonpharmacological—Combination</b>		
<a href="#">Cognitive Benefits of Interactive Mental and Physical Exercise for MCI</a>	Cay Anderson-Hanley, Union College	2019
<a href="#">Cognitive and Aerobic Resilience for the Brain</a>	Frederick Unverzagt, Indiana University	2020
<b>Nonpharmacological—Home Based Interventions</b>		
<a href="#">ADMIT</a> (Alzheimer's Disease Multiple Intervention Trial)	Chris Callahan, Indiana University	2016
<a href="#">Preventing Cognitive Decline in African Americans with MCI</a>	Barry Rovner, Thomas Jefferson University	2016
<a href="#">MIND: Care Coordination for Community-Living Persons with Dementia</a>	Quincy Samus, Johns Hopkins University	2020
<b>Nonpharmacological—Cognitive Training</b>		
<a href="#">Cognitive Training and Practice Effects in MCI</a>	Kevin Duff, University of Utah	2020
<a href="#">Processing Speed Training to Preserve Driving and Functional Competencies in MCI</a>	Virginia Bradley, University of Alabama at Birmingham	2020
<b>Nonpharmacological—Other</b>		
<a href="#">Mild Cognitive Impairment and Obstructive Sleep Apnea</a>	Kathy Richards, George Mason University	2016
<a href="#">Deep Brain Stimulation for Alzheimer's Disease</a>	Constantine Lyketsos, Johns Hopkins University	2018
CSF Pharmacodynamic Trial <sup>1</sup>	Martin Farlow, Indiana University	2022
<b>Other Interventions</b>		
<a href="#">Olfactory Deficits and Donepezil Treatment in Cognitively Impaired Elderly</a>	Davangere Devanand, Columbia University	2019



<b>Trial Name</b>	<b>Principal Investigator/ Institution</b>	<b>Anticipated Completion</b>
<a href="#"><u>Phase I Clinical Studies with Gamma-Secretase Modulator NGP 555 to Establish Safety, Pharmacokinetics, and Biomarker Efficacy</u></a>	Maria Kounnas and William Comer, Neurogenetics, Inc.	2018

<sup>1</sup> Trial supported through Alzheimer's Disease Cooperative Study (ADCS).

**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](http://ClinicalTrials.gov).

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

<b>Trial Name</b>	<b>Principal Investigator/ Institution</b>	<b>Anticipated Completion</b>
<b>Cognitive Training</b>		
<a href="#"><u>ALERT</u></a> (Attention Training for Learning Enhancement and Resilience Trial)	Thomas Van Vleet, Posit Science Corp.	2016
<a href="#"><u>Cognitive Training Effects in Adults Using Brain-Plasticity-Based Computer Games</u></a>	Kristi Multhaup, Davidson College; Mark Faust, University of North Carolina, Charlotte	2016
<a href="#"><u>Examining the Mechanisms of Immersive Computerized Training Interventions for Old</u></a>	Jason Allaire, North Carolina State University	2016
<a href="#"><u>Working Memory Training in Older Adults</u></a>	Susanne Jaeggi, University of California, Irvine	2020
<a href="#"><u>CREM</u></a> (Cognitive Remediation to Improve Mobility in Sedentary Seniors)	Joe Verghese, Albert Einstein College of Medicine	2020
<b>Cognitive Training and Stress Reduction</b>		
<a href="#"><u>Enhancing Cognitive Control in Older Adults with Complementary Interventions</u></a>	Adam H. Gazzaley, University of California, San Francisco	2020
<b>Omega-3 Fatty Acids and Antioxidants</b>		
<a href="#"><u>VITAL-Cog</u></a> (A Large Randomized Trial of Vitamin D, Omega-3 Fatty Acids, and Cognitive Decline)	Jae Kang, Brigham and Women's Hospital	2016
<a href="#"><u>Omega-3 PUFA for the Vascular Component of Age-Related Cognitive Decline</u></a>	Lynne Shinto, Oregon Health & Science University	2017
<b>Active Engagement</b>		
<a href="#"><u>Acting Out: Influence of an Acting Intervention on Cognition and Brain Function</u></a>	Arthur Kramer, University of Illinois, Urbana-Champaign	2016
<b>Hormones</b>		
<a href="#"><u>Testosterone Trial in Older Men</u></a>	Peter Snyder, University of Pennsylvania	2016

<b>Trial Name</b>	<b>Principal Investigator/ Institution</b>	<b>Anticipated Completion</b>
<b>Exercise</b>		
<a href="#"><u>Cognitive Benefits of Aerobic Exercise Across the Age Span</u></a>	Yaakov Stern and Richard Sloan, Columbia University	2017
<a href="#"><u>Aerobic Exercise, Neurotrophins, and fMRI of Hippocampal Function and Structure</u></a>	Karin Schon, Boston University	2016
<a href="#"><u>Cognitive/Brain Effects of Adding Weight Loss to Exercise in Obese Older Adults</u></a>	Christina Hugenschmidt, Wake Forest University	2018
<a href="#"><u>Enhancing Function in Later Life: Exercise and Functional Network Connectivity</u></a>	Angela Bryan, University of Colorado at Boulder	2019
<a href="#"><u>Bridging Acute and Long-Term Exercise Effects on Brain Function in Older Adults</u></a>	Michelle Webb Voss, University of Iowa	2017
<b>Exercise and Cognitive Training</b>		
<a href="#"><u>FAST</u></a> (Fit & Active Seniors Trial)	Arthur Kramer, University of Illinois, Urbana-Champaign	2016
<b>Exercise and Stress Reduction</b>		
<a href="#"><u>Remediating Age-Related Cognitive Decline: Mindfulness-Based Stress Reduction and Exercise</u></a>	Eric Lenze, Washington University	2019

**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](http://ClinicalTrials.gov).

**Table 4. Ongoing Delirium Prevention and Treatment Clinical Trials Funded by NIA**

<b>Trial Name</b>	<b>Principal Investigator/ Institution</b>	<b>Anticipated Completion</b>
<a href="#"><u>Pharmacological Management of Delirium</u></a>	Malaz Boustani, Indiana University School of Medicine	2016
<a href="#"><u>STRIDE</u></a> (Postoperative Delirium in Elderly Surgical Patients)	Frederick Sieber, Johns Hopkins University	2016
<a href="#"><u>Effects of Light vs. Deep Anesthesia on Postoperative Cognitive Outcomes</u></a>	Jacqueline Leung, University of California, San Francisco	2017
<a href="#"><u>MIND-USA</u></a> (Modifying the Impact of ICU-Associated Neurological Dysfunction-USA Study)	E. Wesley Ely, Vanderbilt University Medical Center	2017
<a href="#"><u>ENGAGES</u></a> (Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes)	Michael Avidan, Washington University	2019

**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](http://ClinicalTrials.gov).

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

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

**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](http://ClinicalTrials.gov).

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 Alzheimer’s 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](mailto: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](http://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.*

### ***Promise of intervening earlier in disease progress***

Scientists have long wanted to test therapies for Alzheimer's and related dementias early in the disease process, when they might have the most effect. Over the past few years, thanks to advances in imaging and biomarkers, interventions are being tested in at-risk but symptom-free volunteers and in people in the early stages of the disease.

NIH-supported prevention trials, described below, are testing promising drugs that target amyloid proteins that form plaques in the brain, a hallmark 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 may prove the value of early-stage interventions.

The [Dominantly Inherited Alzheimer Network–Trial Unit \(DIAN-TU\)](#) is testing two anti-amyloid drugs in 210 volunteers who carry a gene for a rare form of early-onset Alzheimer's disease. The trial at U.S. and international sites 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.

The [Alzheimer's Prevention Initiative](#) 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:

- **Autosomal Dominant Alzheimer's Disease Trial (ADAD).** 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. ADAD is co-funded by NIH, the Banner Alzheimer's Foundation, and Genentech, a biotechnology company that is providing the test drug.
- **Generation Study.** This 5-year trial is testing 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 to 75 and carry two copies of the APOE ε4 gene, the best known risk factor for late-onset disease. Recruitment at sites in North America and Europe will begin in late 2016. The trial is co-funded by NIH, the Banner Alzheimer's Foundation, and Novartis, a pharmaceutical company that is providing the test drugs.

**Study of Nasal Insulin in the Fight Against Forgetfulness (SNIFF)**. This Phase II/III, double-blind, placebo-controlled study is evaluating whether insulin carries out multiple functions in the brain, and if 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 will test if a type of insulin, when administered as a nasal spray, improves memory and daily function in adults with mild cognitive 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 amnesic (memory-related) MCI or early Alzheimer's at about 20 research clinics nationwide is ongoing.

**Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4)**. This groundbreaking trial is evaluating an amyloid-clearing drug in 1,000 symptom-free older volunteers who have abnormal levels of amyloid detected by positron emission tomography brain scans. Researchers will test whether decreasing amyloid burden during the symptom-free stage of Alzheimer's will reduce damage to the brain and delay cognitive decline. 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 with NIH. Recruitment is underway more than 60 sites nationwide.

**Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diet Intervention to Prevent Alzheimer Disease**. A Phase III randomized controlled trial, MIND is testing the cognitive effects of a 3-year intervention of a hybrid of the Mediterranean and DASH diets. A Mediterranean diet includes vegetables, legumes, fruits, cereals, fish, and monounsaturated fats; mild to moderate alcohol use; and low intake of saturated fats, dairy products, meat, and poultry. The DASH diet aims to lower blood pressure by eating foods that contain less salt and sodium, added sugars, and fats. The trial will measure how the hybrid diet influences cognitive decline among 600 participants, age 65 and older, who are overweight and whose poor diets may place them at risk for developing dementia.

#### ***NIH supports research network and groundbreaking trials***

NIH is the primary funder of the [Alzheimer's Disease Cooperative Study](#) (ADCS), a clinical-trials study infrastructure focused on innovative Alzheimer's treatments.

ADCS has provided a framework for the investigation of both the cognitive and behavioral symptoms of Alzheimer's disease, including therapies that might not otherwise be pursued by the pharmaceutical industry. ADCS investigators also have developed novel clinical-trial designs and tools.



The current round of ADCS studies supported all or in part by the NIA including the following trials:

- **Discover Trial.** When testing potential new drug therapies, specifically those targeting key Alzheimer's disease pathways, scientists now often use cerebrospinal fluid (CSF) and plasma biomarkers to see if the compound crosses the blood-brain barrier and engages 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 multiple Alzheimer's-related proteins to better understand how a drug influences Alzheimer's disease, which will help guide decisions about whether a drug warrants further clinical testing. This trial will get underway in mid-2016.
- **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 studies of animal models and in short-term human trials, it has not been shown in major clinical trials to improve cognition or alter the hallmarks of Alzheimer's disease in the brain. EXERT will test whether a prescribed and supervised aerobic exercise regimen can influence cognitive decline, slow brain atrophy, or delay Alzheimer's in older adults with MCI. Sedentary older adults with MCI will participate in an 18-month 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 MRI results will provide critical data on the effects of aerobic exercise on cognition and Alzheimer's-related pathology. Recruitment is underway.
- **Prazosin for Treating Agitation Trial.** Disruptive agitation is often a chronic problem in people with Alzheimer's. It can dramatically increase patient distress and caregiver burden, 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. Recruitment may be underway by late 2016.
- **3 Star Trial.** ADCS will collaborate with AC Immune, a biotechnology company, to test the safety and tolerability of an immunotherapy vaccine that targets Alzheimer's disease-like characteristics in adults with Down syndrome. The first clinical trial of its type, the study will primarily test the safety of AC Immune's ACI-24 vaccine and secondarily whether the vaccine influences cognitive function and Alzheimer's biomarkers in 24 adult volunteers with Down syndrome. Recruitment is underway.

## Progress in Clinical Trials

As the clinical trials noted above move forward, recent findings, while not yet reporting any intervention that can affect the course of Alzheimer's disease, have shown some promise in improving the lives of people living with cognitive decline or at high risk of developing Alzheimer's. Positive outcomes have been reported in drug and nondrug intervention that may help better manage cognitive and behavioral symptoms:

### *Daily online conversation may improve cognitive function*

In a pilot clinical trial, researchers tested whether increasing social stimulation through a 6-week, online chat program could benefit cognitive function in older people ([Dodge et al., 2015a](#)). The trial randomly assigned 83 cognitively normal and MCI volunteers (average age, 80) into two groups. Trained interviewers chatted face-to-face via online video for a half-hour, 5 days a week, with the intervention group; the other participants received a weekly phone call to ask about their level of social activity the previous week.

The volunteers assigned to the online chat intervention showed cognitive improvement compared with those receiving the weekly phone call. The cognitively normal participants improved in tests of verbal fluency, the ability to quickly list words of a particular category, like "animals" or words starting with a specific letter. Those with MCI gained in a test of psychomotor speed, or the connection between cognition and physical motion. This small study suggests that online communications technologies could offer an inexpensive way to increase daily social contacts in older people and may help prevent cognitive decline.

### *Estrogen therapy and cognition*

Study findings regarding the usefulness of estrogen therapies for cognition have been difficult to assess. Previous research has shown an increased risk of dementia among women taking hormonal therapies after menopause. But the question has remained whether hormone replacement therapy might help prevent or delay dementia in younger, premenopausal women.

In one recent study of this "timing" issue, estrogen therapy was found to help prevent cognitive decline in some menopausal women ([Woolie et al., 2015](#)). Researchers studied 54 women (average age, 58) who were at heightened risk of developing Alzheimer's disease because they had one or more of the following risk factors: a first-degree relative with Alzheimer's disease, the APOE  $\epsilon 4$  risk gene, or a history of major depression. All had been on estrogen therapy for at least 1 year at the start of the trial. During the trial, 30 of the women continued on estrogen and 24 stopped treatment.

When tested 2 years later, the women who had stayed on estrogen treatment performed significantly better on tests of verbal memory and executive function, such as decision-making,

than those who had discontinued treatment. In addition, comparison of estrogen formulations showed that women on 17- $\beta$ -estradiol did better on verbal memory tests than those on conjugated equine estrogen, regardless of whether they stayed on the hormone when the trial started or stopped it. Estrogen therapy appears to protect cognition in women at heightened risk of Alzheimer's disease, at least when the therapy is initiated close to menopause onset.

### ***New in-home activity monitoring may speed clinical trials***

Because individual performance on cognitive tests typically varies from day to day and even over the course of a day, it is difficult to capture subtle cognitive and functional changes early in the disease process. As a result, researchers must test large numbers of volunteers to detect significant differences between those receiving treatment and volunteers in control groups.

One way around this problem is to make more frequent measurements in each participant over time. Toward that end, scientists developed a new approach to monitor continuous measurements of activity and health-related data ([Dodge et al., 2015b](#)). They used an unobtrusive, in-home sensor system to follow 119 volunteers (average age, 84) who were cognitively normal at the start of the 3-year study. Data on walking speed and personal computer use, two measures known to correlate well with cognitive function in older people, were analyzed and neuropsychological testing conducted once a year.

The researchers then used the data to calculate patient sample sizes that would be needed to detect clinical-trial treatment effects using in-home monitoring versus cognitive tests. They estimated that using annual cognitive tests, a total of 2,000 people would have to be followed for 4 years to detect a 30 percent change from a drug treatment. In contrast, only 262 participants would be needed using walking speed as the outcome measure, and only 26 people with computer use as the measure. These findings suggest that the use of continuous monitoring systems should be further studied to see how they might drastically reduce the cost and improve the efficiency of clinical trials in Alzheimer's disease.

### **Promising Research Opportunities**

Additional funding in FY 2018 would support speeding basic discoveries in biology and genetics into therapies to treat the underlying causes and symptoms of Alzheimer's and related dementias. A boost in funding would also make possible new preclinical studies and possibly expand on existing clinical trials for interventions to change the course of the disease or better manage symptoms. Treatment and prevention trials—sometimes involving hundreds or thousands of volunteers over many years and a deep investment by NIH and collaborating partners—are key to reaching the main goal of the [National Plan to Address Alzheimer's Disease](#)—to find effective treatments by 2025.

Please see the [list of milestones](#) to which additional funding in FY 2018 would apply. Also see the [full list of milestones](#) aimed at Alzheimer’s disease research by 2025. Critically needed additional investments in FY 2018 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, including 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.*

The current—and future—impact of Alzheimer's disease and related dementias cannot be overstated. Effective therapies are desperately needed for those living with the disease. If we do not find ways to prevent or delay the disorders, the number of affected Americans will soar in the coming decades.

- While estimates vary, studies find that as many as 5.2 million Americans age 65 and older may 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 U.S. Census Bureau estimates that the number of people age 65 and older in the United States will almost double, to 88 million, by 2050.
- Further, the number of Americans over age 85—those at highest risk—is expected to increase from 6.3 million in 2015 to 19 million in 2050.

The National Institutes of Health (NIH) supports a broad range of population and observational studies to address the personal and societal impact of dementia. Additional funding in FY 2018 would expand our understanding of:

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

To gain new insights into these critical areas of investigation, NIH is investing in new research tools and groundbreaking initiatives:

- The NIH-funded [Health and Retirement Study](#), a 20-year-old nationwide survey of the health, economic, and social status of older Americans, is adding a new data resource—the Harmonized Cognitive Assessment Protocol—to help advance population studies of cognitive impairment and dementia. Additional grants are funding harmonized assessments for nationally representative studies in England, Mexico, and India, as well

as a smaller-scale field study in rural South Africa. These investments will provide unprecedented scientific opportunities for the epidemiological study of Alzheimer's and related dementias beginning in 2018.

- The NIH-led [Precision Medicine Initiative](#) will begin recruitment of a national cohort study of a million or more Americans to propel better understanding of a variety of diseases, including Alzheimer's and related dementias. This initiative will take into account the variability in genes, environment, and lifestyle of each person to produce new knowledge, with the goal of developing more effective ways to prolong health and treat disease.

## **Progress in Identifying Risk and Protective Factors**

Advancing age, specific genes, and family history 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 its onset and progression. Scientists are trying not only to identify risk factors, but also tease out how these factors interact with one another in the search for effective interventions. Recent studies have suggested directions to pursue:

### ***Prevalence of amyloid pathology in the cognitively normal***

Scientists have long wondered about the presence of amyloid pathology commonly found in the brains of cognitively normal older people. The first definitive answer to this question has now emerged from one of the largest data analyses undertaken to date ([Jansen et al., 2015](#)). Scientists compiled data from 55 studies that had imaged brain amyloid plaque and/or beta-amyloid 42 levels in cerebrospinal fluid in 7,583 participants. The group consisted of 2,914 people with normal cognition, 697 with subjective cognitive impairment (SCI, when a person reports memory problems but performs normally on clinical tests), and 3,972 with mild cognitive impairment (MCI).

In people with normal cognition, the prevalence of amyloid pathology increased with age, from 10 percent in 50-year-olds to 44 percent in 90-year-olds. Similar numbers were seen for people with SCI. In people with MCI, the prevalence of amyloid pathology increased from 27 percent at age 50 to 71 percent at age 90, supporting the idea that MCI is an early stage of Alzheimer's disease in many cases. However, some MCI patients had no amyloid pathology. Participants with the APOE  $\epsilon$ 4 risk gene had two to three times the risk for developing Alzheimer's compared with noncarriers.

These findings suggest a 20- to 30-year interval between initial development of amyloid in the brain and the onset of dementia and may be used to improve the design of prevention studies made possible with additional funding.

### ***How midlife brain changes may influence Alzheimer's onset***

Brain changes beginning in middle age may set the stage for cognitive decline and the onset of amyloid pathology later in life ([Jack et al., 2015](#)). Researchers used brain imaging and cognitive testing to examine how age, sex, and having the APOE ε4 risk gene affect memory, brain structure, and levels of amyloid plaque in 1,209 cognitively normal volunteers, age 30 to 95.

While memory worsened for both sexes from age 30 through their 90s, men overall showed worse memory declines as well as greater shrinkage of the hippocampus, a brain region important for learning and memory. For both sexes, having the APOE ε4 genotype did not influence memory or hippocampal volume, but by age 70 those with the risk gene had a greater amyloid load.

Because memory performance and hippocampal shrinkage began in middle age before brain amyloid was detected, these results suggest that biological processes other than beta-amyloid accumulation may underlie cognitive decline starting in middle age.

### ***Weight at midlife may affect dementia risk***

Being obese or overweight in middle age has been linked to increased risk of dementia. NIH staff scientists discovered that being obese or overweight at midlife—as measured by body mass index (BMI) at age 50—may also predict earlier age of onset of Alzheimer's ([Chuang et al. 2016](#)).

The investigators found that in study participants who developed Alzheimer's, each unit increase in BMI at age 50 accelerated onset by nearly 7 months and that a higher midlife BMI was associated with greater levels of neurofibrillary tangles and amyloid in the brain, hallmarks of the disease. A healthy BMI at any age is important for good health. These findings suggest that maintaining a healthy BMI at midlife might be linked to delayed onset of Alzheimer's.

### ***Chronic depression a risk factor for Alzheimer's***

Symptoms of depression are common in older people with MCI and may put them at greater risk of progressing to Alzheimer's disease ([Sacuiu et al., 2016](#)). Researchers analyzed data from 94 older adults participating in the NIH co-funded [Alzheimer's Disease Neuroimaging Initiative](#). The volunteers were diagnosed with MCI at an average age of 76, followed by neuropsychiatric and cognitive tests and brain scans for 3 years.

Thirty-two of the participants had chronic depression with one or more depressive symptoms (as reported by a family member or other informant) at all follow-up visits. The other 62 volunteers were free of depressive symptoms throughout the study.

Of the 38 subjects who progressed to Alzheimer's disease during the follow-up period, those with chronic depression had a 60 percent shorter conversion time than those free of



depression. The entire group with chronic depression also showed faster shrinkage of certain brain regions. These findings associate chronic depression with brain structural changes that increase risk of progressing from MCI to Alzheimer's disease.

### ***Use of anticholinergic drugs linked to dementia risk***

Older adults who take anticholinergic drugs, which are commonly prescribed for a wide range of health conditions, may be at significantly higher risk of developing dementia—and the greater the use of the drugs, the higher the potential risk.

Anticholinergics are prescribed for overactive bladder, seasonal allergies, depression, and other health conditions. Some are available over the counter and are often used as sleep aids. These medications block a neurotransmitter, acetylcholine, in the brain and body and may cause side effects such as impaired cognition, especially in older people. This side effect was thought to be reversible once the person stopped taking the medication.

However, researchers have shown that these medications may have a lasting impact ([Gray et al., 2015](#)). By analyzing records and data for drugs prescribed over 10 years to 3,434 adults age 65 and older, they calculated cumulative exposure to drugs with strong anticholinergic effects.

The analysis showed that 78 percent of participants used anticholinergics at least once in 10 years. Nearly 800 participants (23 percent) developed dementia, usually Alzheimer's. The higher the use of anticholinergics, the higher the risk of dementia, researchers found, whether the drugs had been taken recently or years ago.

Another NIH-funded study was one of the first to use brain imaging to examine the link between this class of drugs and changes in brain structure and function ([Risacher et al., 2016](#)). Researchers analyzed measures of cognition and brain images showing brain metabolism and atrophy in 451 cognitively normal participants. They compared these measures between people who used anticholinergic drugs and those who did not. They also considered how often the drugs were used and their respective levels of anticholinergic activity—defined as low, medium, or high by an [Anticholinergic Burden Scale](#).

Cognitive testing and brain imaging showed that participants using the medications exhibited poorer memory and executive function, reduced brain metabolism, increased brain atrophy, and increased risk for developing cognitive impairment. These declines were greatest among those taking greater amounts of drugs with medium to high anticholinergic activity.

These findings suggest that physicians treating older people should prescribe alternatives to anticholinergics, when possible, or lower doses of the drugs. More studies are needed to discover the mechanisms that underlie the harmful effect of the medications, and to what extent stopping use of anticholinergics can reduce the risk of developing dementia.

## 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.

### *Cognitive reserve, education, and racial differences*

Cognitive reserve, or the ability to maintain cognitive function despite Alzheimer's-related brain changes, seems to depend on similar sets of lifestyle factors in older black and white adults ([Kaup et al., 2015](#)). Scientists studied data from 670 older adults, age 69 to 80 years at baseline, who had received followup with cognitive tests over the course of 11 years while volunteering in the NIH Health, Aging, and Body Composition (Health ABC) study. The black and white volunteers carried at least one copy of the APOE ε4 allele and were at high genetic risk of cognitive decline and dementia. The investigators looked for factors associated with high cognitive resilience (defined as maintaining cognitive performance within the upper 33<sup>rd</sup> percentile relative to their peers).

For both groups, higher education and literacy level were the strongest predictors of cognitive resilience in old age. Lack of recent negative life events was also a predictor of cognitive resilience in whites, while in blacks, greater cognitive reserve was found in those free of diabetes. These findings suggest that intervention targets may vary by groups: white APOE ε4 carriers may benefit from stress reduction and management, and black APOE ε4 carriers may benefit from efforts to improve cardiovascular health. Enhancing cognitive reserve and improving overall health in both groups are possible intervention targets, researchers noted.

### *Early-life education may affect late-life cognition*

Researchers examining racial differences in cognitive aging found that the quality as well as length of early-life education are key factors in successful aging ([Sisco et al., 2015](#)). Scientists looked at cognitive test data for 1,679 non-Hispanic adults age 65 to 102 (71 percent black, 29 percent white, 70 percent women) participating in the NIH-funded Washington Heights-Inwood Columbia Aging Project.

As has been found in other studies, older black participants performed significantly worse on tests of general cognitive performance, memory, and executive function than did older white participants. However, accounting for quality of education and literacy in late life reduced these disparities by up to 32 percent. The findings suggest that early-life educational quality and literacy in late life explain a substantial portion of race-related disparities in late-life cognitive function.

### ***Comorbid depression and diabetes increase MCI risk in Mexican Americans***

Mexican Americans on average develop MCI and Alzheimer's disease 10 years earlier than non-Hispanic whites. Their risk factors for cognitive decline also seem to differ. Researchers looked at the association of comorbid depression and diabetes with MCI and Alzheimer's disease in data gathered from 2,435 older Mexican Americans and non-Hispanic whites ([Johnson et al., 2015](#)). Among the Mexican Americans, those diagnosed with both depression and diabetes were two to eight times more likely to develop MCI than those who did not have these conditions. In contrast, the combination of depression and diabetes did not significantly increase MCI risk among the non-Hispanic whites in this study group.

Depressive symptoms are more prevalent among aging Mexican Americans than among aging non-Hispanic whites, and Mexican Americans also have an average earlier age of onset of diabetes. This study indicates a strong link of comorbid depression and diabetes to cognitive decline in Mexican Americans—a link that may help guide preventive interventions for this ethnic group.

### **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 than other groups? Additional funds would expand population and health disparity investments by:

- 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 studies examining the molecular characteristics (genomic, epigenomic, proteomic) of Alzheimer's and related dementias, and incorporating the collection of nontraditional data using wearable sensors and mobile health technology

Please see the [list of milestones](#) to which additional funding in FY 2018 would apply. Also see the [full list of milestones](#) aimed at Alzheimer's disease research by 2025.

## 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 homes, 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.*

Caring for a loved one with dementia places tremendous financial, emotional, and physical demands on caregivers. 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 not only deepening our understanding of the scope and specific challenges of caregiving, but also identifying ways to alleviate some of the burden.

### **Progress in Research on Caregiving and Quality of Life**

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

#### ***Dementia caregivers number in the millions***

The growing number of aging people with dementia raises concerns about how their care affects family members and other caregivers. To assess the magnitude of this issue, researchers examined data from two NIH-supported studies involving Medicare beneficiaries age 65 years and older: the [National Health and Aging Trends Study](#) and a companion study, the [National Study of Caregiving](#). The study participants included 2,423 adults who were not living in nursing homes, and their 1,924 family and other unpaid caregivers ([Kasper et al., 2015](#)). About 10 percent of the cared-for adults had dementia, and one-third of the caregivers assisted people with dementia.

About 80 percent or more of the older adults (regardless of their dementia status) received care from family members and other unpaid caregivers. However, the intensity of caregiving was much greater for older adults with dementia, and the burden of their care fell more on spouses, daughters, and others who resided with them. The length of time the older people with dementia required care was also longer than for those without dementia. All told, 5.8 million caregivers were assisting older adults with dementia and devoted a total of 6 billion hours per year in care.

These huge numbers highlight the need to better support and monitor older adults with dementia and their caregivers.

### ***Relief for caregiver depression may be a phone 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 low-cost and readily accessible interventions for caregivers of people with dementia in the community, a goal of the FY 2018 research agenda.

### ***Counseling may reduce stress experienced by children caring for parents***

Adult children caring for a parent with dementia often juggle caregiving with midlife demands of work and family, which can lead to depression and dissatisfaction with their quality of life. Researchers wondered whether an intervention previously shown to reduce depression among caregivers of spouses with dementia might also prove effective for adult children. The protocol combined one-on-one counseling and support groups.

In a study of 107 adult-children caregivers, about half received individual and family counseling, with a focus on improving support from family and friends and problem-solving; the other half were the control group ([Gaugler et al., 2015](#)). All participants filled out questionnaires about their levels of stress and depression, including feelings of exhaustion or of being trapped in the caregiving role, from the study start and every 4 to 6 months over a nearly 4-year timeframe.

Participants receiving the intervention showed significant decreases in symptoms of depression, such as feelings of apathy and withdrawal, and reported improved quality of life.

The findings suggest that development of counseling and group support programs may be a viable way to improve the lives of adult children caring for parents with dementia.

### ***Respite programs influence sleep, stress of caregivers***

Disrupted sleep is a common complaint among those who live with and care for people with dementia, and it may increase a caregiver's risk for health problems. Researchers wanted to know how caregiver sleep might be influenced by their levels of cortisol—a hormone that responds to stress, mobilizes energy, and has anti-inflammatory effects—and by the time their charges spend away from home in adult day services (ADS), which offer respite for caregivers ([Leggett et al., 2015](#)).

The researchers collected saliva samples from 158 caregivers over 8 days to measure cortisol levels within a half-hour of waking. Primarily women in their 60s who used ADS at least twice a week, the participants also wrote daily diaries about their health, well-being, and activities.

The researchers reported that on ADS days, caregivers had higher cortisol levels within a half-hour of waking—a sign of increased energy levels and anticipation—regardless of how many hours they slept the night before. On non-ADS days, the participants had higher cortisol levels only if they slept fewer hours than usual. Sleeping longer than usual on non-ADS days resulted in low cortisol levels, a state associated with exhaustion and burnout in adults.

While more research is needed on the mechanisms by which respite programs influence sleep and cortisol regulation, this research suggests that ADS offers caregivers relief from chronic stress and has the potential to improve their mental and physical health.

### **Promising Research Opportunities**

Additional FY 2018 funding directed at [NIH research milestones](#) would build on these critical insights into the scope and scale of dementia caregiving. These efforts to improve the lives of those living with dementia and their caregivers include:

- Developing and validating assessments to determine the impact of caregiving on psychological, financial, and physical health in observational, interventional, and longitudinal population-based studies
- Developing a project to inform the design of cost-effective, community-based caregiving interventions that enable people with Alzheimer's to remain in their homes
- Developing effective intervention programs to support caregiver well-being at different stages of the care continuum
- Establishing 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.** The 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, 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](#). These centers 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 the ADCS in 1991 to develop and test new interventions and treatments for Alzheimer's disease that might not otherwise be developed by industry. 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 research studies at 29 NIH-funded ADCs. It stores detailed longitudinal data from 26,500 participants and 2,100 brain autopsies collected over 35 years and makes them available to Alzheimer's researchers worldwide. 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. Now celebrating its 25<sup>th</sup> anniversary, NCRAD has sent nearly 200,000 biological samples to more than 125 researchers around the world. Most recently, specimens from NCRAD and accompanying data have been utilized in genetic sequencing projects, resulting in the discovery of several new gene loci previously unknown to be related to Alzheimer's disease.

**[NIA Genetics of Alzheimer's Disease Data Storage Site \(NIAGADS\)](#)**. NIAGADS is a Web-based warehouse for Alzheimer's disease genetics data that currently houses 22 data sets with nearly 44,000 subjects and more than 24 billion genotypes. In 2015, to facilitate the sharing of sequence data with the genetics community, NIAGADS released genotypic data generated on more than 11,500 subjects and responded to data requests from 30 labs at 26 institutions.

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 primary Federal Government resource for information about Alzheimer's disease and related dementias, research, and caregiving, the ADEAR Center educates the public about the latest research findings and provides evidence-based information online, in print, and via a call center. Information about Alzheimer's and other dementias, participation in clinical trials, and caregiving is freely available. ADEAR Center outreach to the research and care communities, media, and advocacy organizations is supported via weekly e-alerts to more than 50,000 subscribers and by social media outreach.

**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.

Since late 2014, NIH investments totaling \$85 million have supported more than 130 investigators at 125 institutions in the United States and eight other countries who are developing new tools and technologies to understand neural circuit function and capture a dynamic view of the brain in action. These new tools and this deeper understanding will ultimately catalyze new treatments and cures for devastating brain disorders such as Alzheimer's and related dementias.

### **Promising Research Opportunities**

Additional funding would accelerate efforts to build an infrastructure for translational studies, as well as improve and standardize data collection and sharing among scientists and clinicians focused on developing effective treatments for Alzheimer's disease and related dementias. The focus of such efforts would be to:

#### ***Translational infrastructure and capabilities***

- Develop and standardize high-throughput methods for profiling of different types of brain cells for research
- Develop standardized protocols for generations of stem cells derived from skin that can be used in dementia research
- Create a network of translational centers that will apply the new research technologies 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

Please see the [list of milestones](#) to which additional funding in FY 2018 would apply. Also see the [full list of milestones](#) aimed at Alzheimer's disease research by 2025.

## CATEGORY G. CONSORTIA AND PUBLIC-PRIVATE 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 fully engaged with the public and private sectors to leverage financial and human resources to move science forward. Alzheimer's disease is a particular focus in this groundbreaking approach that brings together government agencies, academic institutions, industry, and professional and advocacy organizations. These ongoing efforts include:

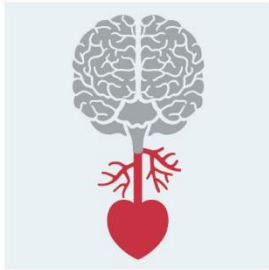
- NIH spearheads initiatives aimed at speeding discovery and overcoming obstacles in translational research. Working with biopharmaceutical companies and several nonprofit organizations, NIH established the [Accelerating Medicines Partnership](#) (AMP) to identify and validate the most promising biological 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, 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.
- The [Alzheimer's Disease Neuroimaging Initiative](#) (ADNI) is a landmark, public-private study that has advanced our understanding of who is at risk of Alzheimer's and ways to detect disease onset and progression. It has identified and developed 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.  
Expanded several times since its 2004 launch, ADNI continues to recruit volunteers at 55 sites in the United States and Canada. 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. The PMI is gearing up in 2016 to launch a national cohort study of a million or more Americans to propel our understanding of many diseases, including Alzheimer's. Many factors have converged to make this the right time to begin a program of this scale and scope. Americans are more engaged than ever in improving their health and participating in health research. In addition, electronic health records have been widely adopted, genomic analysis costs have dropped significantly, data science has become increasingly sophisticated, and health technologies have become mobile.
- The [NIH Biomarkers of Alzheimer's Disease in Adults with Down Syndrome Initiative](#) is focused on identifying and tracking the progression of Alzheimer's in people with Down syndrome. Launched in 2015, the Initiative's goal is to develop biomarker measures that signal the onset and progression of Alzheimer's in this vulnerable population. Costing an estimated \$37 million over 5 years, it funds two research teams working collaboratively to image and track Alzheimer's-related changes in the brain and cognition of more than 500 volunteers with Down syndrome, age 25 years and older.
- NIH funded the [Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease \(M<sup>2</sup>OVE-AD\) Consortium](#) in early 2016 to advance our understanding of vascular contributions to Alzheimer's disease. The 5-year, \$30 million program brings together more than a dozen research teams working on five complementary projects. Scientists from diverse fields using the latest methodologies will work collaboratively toward shared goals: to dissect the complex molecular mechanisms by which vascular risk factors influence Alzheimer's disease and to identify new targets for treatment and prevention.

## CATEGORY H. ALZHEIMER'S DISEASE-RELATED DEMENTIAS (ADRD) RESEARCH



*Topics under the ADRD category include frontotemporal degeneration, Lewy body dementia, vascular dementia, and mixed dementia.*

While Alzheimer's disease is the most common form of dementia, an estimated 20 to 40 percent of older people have [Alzheimer's disease-related dementias](#) (ADRD), such as frontotemporal degeneration (FTD), Lewy body dementia (LBD), 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.

The National Institutes of Health (NIH) funds a broad range of research to better understand the underlying causes of ADRD that may lead to new prevention and treatment strategies. For example, dementia driven by cerebrovascular disease may be preventable with current treatments for cardiovascular disease. Toward that end, researchers are developing biomarkers that can accurately determine and distinguish different types of brain pathologies in people living with dementia, as well as biomarkers that can detect and track disease onset and progression. At the molecular and cellular level, researchers are investigating the genetics and mechanisms involved in ADRD.

Additional funds appropriated for dementia research in FY 2016 enabled NIH to support new research opportunities in biomarker discovery and development, including the [Small Vessel Vascular Contributions to Cognitive Impairment and Dementia Biomarkers Consortium](#) and the [Biomarkers for the Lewy Body Dementias](#). The additional funding is also spurring discovery by stimulating research on how vascular changes can contribute to brain white matter disease; creating a multicenter, interdisciplinary "[Center without Walls](#)" to investigate the molecular mechanisms of tau toxicity in frontotemporal degeneration; and supporting [health disparities research](#). Expanded funding in FY 2018 would continue to build on these efforts and other programs targeting mixed dementias.

These efforts are informed by the research agenda recommendations resulting from the NIH-hosted [Alzheimer's Disease-Related Dementias 2016 Summit](#). Final recommendations from the Summit will be released later in 2016.

## 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 dementia*

Numerous studies over several decades have linked risk for Alzheimer's disease with cardiovascular conditions such as arteriosclerosis (hardening of the arteries), microinfarcts (tiny brain lesions), silent stroke, and diffuse white matter disease (fibers that connect brain regions are compromised by disease in small blood vessels).

Recently, investigators discovered a shared genetic contribution between small vessel stroke and Alzheimer's disease by analyzing the combined data of large genetic studies in Alzheimer's disease and stroke. They suspect that genetic variations in cholesterol metabolism and/or immune response may be causal in both conditions ([Traylor et al., 2016](#)).

NIH-funded researchers are investigating how brain damage from multiple strokes or diseased blood vessels can contribute to cognitive impairment and dementia, known as vascular contributions to cognitive impairment and dementia (VCID). Emerging evidence suggests that modifiable vascular risk factors that increase the risk for stroke—such as hypertension, atrial fibrillation, diabetes, and atherosclerosis—may also play a role in VCID. Indeed, as stroke risk has decreased in the United States and other developed countries, investigators have found decreases in dementia risk ([Satizabal et al., 2016](#)).

To learn more about the complex molecular mechanisms by which vascular risk factors influence Alzheimer's and to identify new targets for treatment and prevention, NIH launched the [Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease \(M<sup>2</sup>OVE-AD\) Consortium](#) in early 2016. Expanded research in FY 2018 would further support such basic research investigating VCID cellular and molecular mechanisms, lead to development of new VCID models and biomarkers, and stimulate research on how vascular changes can contribute to white matter disease and Alzheimer's.

### *Frontotemporal degeneration*

Frontotemporal degeneration (FTD), the second most common cause of dementia in those younger than age 65, causes progressive degeneration in areas of the brain important for decision making, behavioral control, emotion, and language. The brains of people with FTD have abnormal forms of two proteins known to play a role in Alzheimer's: tau and TDP-43. NIH-funded studies examining the roles played by these proteins will inform the search for effective therapies to treat both FTD and Alzheimer's disease.

### ***FTD mutation jams cell trafficking***

Some people with FTD also develop amyotrophic lateral sclerosis (ALS) with severe muscle weakness. Scientists are now learning that features of these two diseases often occur together in a syndrome is called FTD with ALS (FTD/ALS).

Scientists have discovered that mutations in the gene for C9ORF72, a protein found in the nuclear envelope (the membrane that surrounds the nucleus and separates it from the cytoplasm) can lead to FTD/ALS. The disease mutations are “repeat expansions,” in which specific DNA sequences are repeated hundreds or thousands of times. Three studies in 2015 suggest that C9ORF72 mutations wreak havoc in neurons by blocking the normal trafficking of molecules in and out of the cell nucleus ([Freibaum et al., 2015](#); [Jovićić et al., 2015](#); and [Zhang et al., 2015](#)). The researchers used a combination of animal models, human tissue, and cells to identify specific transport mechanisms that are disrupted by mutated C9ORF72 and that could be potential targets for therapies to treat some forms of FTD/ALS.

Based on improved understanding of the C9ORF72 mutation, scientists created a new mouse model of familial FTD/ALS that has DNA for 66 copies of the disease-associated gene repeat sequence ([Chew et al., 2015](#)). The mice developed normally, but by 6 months of age their brains and spinal cords had FTD/ALS-related changes. The mice also had pathological and behavioral signs similar to those seen in human FTD/ALS. This new mouse model will facilitate preclinical studies and drug testing for FTD/ALS.

### ***Natural history studies and biomarker development in FTD***

[Three NIH-funded research teams](#) are continuing longitudinal studies of familial and sporadic FTD to understand progression of FTD both before and after symptom onset; identify new biomarkers for diagnosis, progression, and prognosis; and establish a clinical research consortium to support FTD therapy development.

Expanded funding in FY 2018 would support new and ongoing genetic and biomarker studies that may lead to promising interventions for FTD.

### ***Lewy body dementia***

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, it is thought that the spread of Lewy bodies in the brain contributes to the cognitive problems that occur in the later stages of Parkinson’s disease.

### ***Lewy bodies may be toxic to neurons***

Scientists have questioned whether Lewy bodies themselves are toxic or whether they form to protect neurons by sequestering misfolded alpha-synuclein. To answer this question, scientists developed a fluorescence microscope system and genetically engineered mice that allowed them to image neurons in living mice over time ([Osterberg et al., 2015](#)). They injected misfolded alpha-synuclein into mice genetically engineered to have a normal form of the protein, which can be viewed in the brain during several weeks.

They discovered that the misfolded alpha-synuclein protein aggregated with the normal, tagged form in the mice. The normal protein started converting into an abnormal form called fibrils, which then became very compact and formed Lewy bodies. At the same time, the neurons containing these newly formed Lewy bodies began dying, while those free of Lewy bodies remained healthy. This finding suggests that Lewy bodies may cause neuronal death and thus neurodegenerative disease, providing a promising target for therapies.

### ***Lewy bodies occur in later stages of cognitive decline***

The trajectory of cognitive decline in older people with neurodegenerative disease typically occurs in three stages: a symptom-free stage, an intermediate stage of slow decline, and a final stage of more rapid decline. To understand how different pathologies contribute to each stage, scientists studied brain tissue and clinical data from 653 volunteers ([Yu et al., 2015](#)). Cognitively normal when they entered the study at an average of age of 79, a little more than half of the volunteers' brains showed signs of Alzheimer's at autopsy. In addition, sometimes co-occurring with Alzheimer's pathology and sometimes not, 32 percent had infarcts (areas of dead brain tissue due to stroke), and 22 percent had Lewy bodies. Overall, 42 percent showed more than one type of pathology in the same brain.

The researchers found that the presence of Alzheimer's pathology or infarcts was associated with higher risk of progression from normal cognition to mild impairment and from mild to moderate impairment. In contrast, Lewy bodies were associated only with progression from mild to moderate impairment. These findings suggest that early stages of cognitive decline are typically associated with Alzheimer's and/or cerebrovascular disease, whereas the impact of Lewy body pathology on cognition may be more potent during later stages.

Expanded FY 2018 funding would continue efforts to develop LBD biomarkers and support studies to better understand genetic causes of LBD and guide therapeutic development.

### **Promising Research Opportunities**

The NIH research program will continue to expand our understanding of ADRD. To help chart that discovery, research milestones are currently being updated based on expert and public input from the [Alzheimer's Disease-Related Dementias 2016 Summit](#). (This meeting builds on



recommendations from the [Alzheimer's Disease-Related Dementias \(ADRD\): Research Challenges and Opportunities 2013 Summit.](#) The updated list of milestones aimed at related dementias research for 2025 will be finalized and publicly available later in 2016; see the [draft recommendations](#).

In FY 2018, expanded funding would focus on:

- Achieving consensus on clinical diagnostic criteria and developing diagnostic tools to help primary care physicians and clinical researchers detect cognitive impairment and dementia, and discern among different types of dementias, including criteria and tools that can be used in ethnically and culturally diverse populations
- Discovering and validating neuroimaging, physiological, and molecular biomarkers that will enhance diagnostic accuracy and improve assessments of disease progression in people with ADRD, especially in mixed Alzheimer's/vascular dementia
- Supplementing ongoing clinical trials and studies to maximize representation of diverse populations in dementia research
- 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, including genetic differences in health disparities populations, that cause or contribute to ADRD and studying the molecular and cellular mechanisms by which they contribute to the disease process

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