

SUSTAINING MOMENTUM: *NIH Takes Aim at Alzheimer's Disease & Related Dementias*

NIH BYPASS BUDGET PROPOSAL
FOR FISCAL YEAR 2019



National Institutes of Health

CONTENTS

SUSTAINING MOMENTUM: NIH TAKES AIM AT ALZHEIMER’S DISEASE & RELATED DEMENTIAS..	2
INTRODUCTION.....	4
A National Imperative.....	5
Capitalizing on Expanded Research Funding.....	6
Budgeting to Fight the Threat of Dementia.....	7
The Path to Cures.....	10
FISCAL YEAR 2019 PROFESSIONAL JUDGMENT BUDGET: ALZHEIMER’S DISEASE AND RELATED DEMENTIAS	11
MAKING PROGRESS, ADVANCING RESEARCH IN ALZHEIMER’S DISEASE AND RELATED DEMENTIAS	13
Harnessing the Power of Big Data to Discover Next-Generation Therapeutic Targets.....	13
Technology Enables a Radical Rethinking of Tools, Translational Infrastructure.....	16
Creating a Pipeline of New Candidate Therapeutics for All Stages of Disease	18
Learning About Alzheimer’s Complexity from Down Syndrome	19
Detecting Disease Progression with Neuroimaging and Novel Biomarkers.....	21
Monitoring Elders and Tracking Disease with Digital Technologies.....	24
Advancing Understanding of Alzheimer’s Disease-Related Dementias	25
Improving Quality of Clinical, Long-Term Care.....	26
Making Progress on Alzheimer’s Health Disparities	28
Leaning Forward	31
REFERENCES.....	34

SUSTAINING MOMENTUM: NIH TAKES AIM AT ALZHEIMER'S DISEASE & RELATED DEMENTIAS

July 28, 2017

On behalf of the National Institutes of Health (NIH), I am pleased to present our Fiscal Year (FY) 2019 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 capitalize on and accelerate the important scientific advances we are making against these devastating disorders.

You have perhaps before heard me refer to the NIH as the National Institutes of Hope. Nowhere is this more evident than when it comes to our investment in Alzheimer's disease and related dementias. At universities and in laboratories, including our own intramural programs, across the United States, teams of dedicated investigators are making great strides every day. Recent advances have, for example:

- Helped map the brain's innermost connections and the molecular fabric of Alzheimer's
- Deepened understanding of metabolic changes at the heart of the disease
- Detected disease progression through neuroimaging and discovery of novel biomarkers
- Used new technologies, through unprecedented multidisciplinary collaborations, to make large data sets available with greater accuracy and speed to the research community
- Looked at health disparities in new ways, with studies of genetics and risk factors that may be contributing to higher dementia rates among certain groups
- Begun testing technological innovations in the home that aim to increase the ability of older adults to age in place

Through this professional judgment budget for FY 2019, NIH hopes to continue to build the scientific foundation for the future. Increased investments in research will allow us to further expand our knowledge base and provide vital support for the scientific infrastructure of people and technology for the Alzheimer's and related dementias research enterprise. Some of the sharpest and most creative scientific minds are at work to fight these conditions, and we must do everything we can to maintain their focus.

This professional judgment budget for Alzheimer's disease and related dementias was prepared at the request of the U.S. Congress. It was developed from a planned, comprehensive research

agenda of targeted and specific milestones, constructed with the crucial input of the scientific and advocacy communities.

To build the professional judgement budget estimate for FY 2019, we began with consideration of the estimated funding level for Alzheimer’s and related dementias research from FY 2017—\$1,414 million. The FY 2018 President’s budget has proposed to reduce this level of funding by \$577 million. The FY 2019 professional judgment budget includes funding to compensate for this reduction, as well as an additional increase of \$597 million (for new research)—yielding a total needed for FY 2019 of \$2,011 million. This total would represent an increase of \$1,174 million in additional funds relative to the FY 2018 President’s budget proposal to sustain momentum in Alzheimer’s and related dementias research. This Bypass Budget will be updated annually through FY 2025.

This is a critical time in Alzheimer’s research. The path toward a cure remains very difficult, even with everything we have learned. But we are beginning to see a way forward, where we can now dare to think in terms of true precision medicine in the realm of Alzheimer’s disease—the possibility of treating the right person with the right intervention at the right time. With sustained momentum, we have the best hope of realizing that vision.

A handwritten signature in black ink, appearing to read "Francis S. Collins". The signature is fluid and cursive, with a large initial "F" and "C".

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

INTRODUCTION

On November 25, 1901, a woman named Auguste Deter came to Frankfurt Hospital, complaining of progressive confusion, paranoia, agitation, and memory loss. She could no longer identify familiar objects or even her husband and loved ones. She was ultimately identified as the first person to be diagnosed with Alzheimer's disease.

"I have lost myself," she said—a powerful statement that resonates today amid the growing transcontinental tragedy of Alzheimer's for patients and their loved ones (Maurer et al., 1997).

Alzheimer's disease and related dementias are progressive, irreversible brain disorders that slowly destroy memory, thinking skills, and the ability to live independently. We have not yet found a cure for these devastating disorders. And 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 onset or slow progression.

Today, however, there is new hope. Progress in a growing number of scientific areas is converging to give us a much better understanding of Alzheimer's disease and how to attack it. Significant boosts in funding have already accelerated research, and it is clear that sustained financial support in the future will be essential to continuing the momentum of research programs that promise to find effective treatments for the disease.

It is estimated that as many as 5.3 million Americans age 65 and older are living with Alzheimer's disease, the most common form of dementia, with additional, significant numbers developing the disease earlier than age 65 (Hebert et al., 2013). Many thousands more are diagnosed with Alzheimer's disease-related dementias (ADRD), such as vascular cognitive impairment/dementia, Lewy body dementia, or frontotemporal dementia. Further, results of a recent meta-analysis indicated that 35.6 million people lived with dementia worldwide in 2010, a number expected to nearly double almost every 20 years—to 65.7 million people in 2030 and to 115.4 million in 2050 (Prince et al., 2013). Age is the greatest risk factor for Alzheimer's disease, fueling this global epidemic.

The costs of dementia are tremendous. National Institute of Health (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 tallied direct costs of dementia care at \$109 billion. 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 (Hurd et al, 2013).

In 2015, NIH-supported research focused on analyzing the staggering 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.

But the current demography of Alzheimer's does not have to be its destiny. 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 aimed at prevention and treatment of Alzheimer's and related disorders, supporting scientists in the United States and worldwide, many of whom are devoting their entire careers to this noble cause.

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 changing the course of Alzheimer's and related dementias and calculates the additional funding needed to ultimately 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, heightened interest in Alzheimer's resulted in passage of the National Alzheimer's Project Act (NAPA). Signed into law in January 2011, the Act calls for an aggressive and coordinated national plan to intensify research, and to provide better clinical care and community and long-term care and services for people with dementia and their families.

Shortly after the law took effect, the Secretary of the U.S. Department of Health and Human Services appointed a Federal Advisory Council on Alzheimer's Research, Care, and Services, consisting of some of the Nation's foremost experts and advocates. 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 these disorders. In support of the research goals of the National Plan, NIH embarked on an ambitious strategic planning process that engaged key stakeholders and resulted in the development of a broad set of research implementation milestones and success criteria.

As the world's leading funder of dementia research, NIH plays a vital leadership role in an effort that involves multiple stakeholders, including government, academia, industry, advocacy

groups, and the general public. Funding directed to NIH enables not only greater investment in innovative investigator-initiated studies and research infrastructure, 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. These investments spur innovation throughout our country. NIH spends more than 80 percent of its total funding on research grants at institutions and small businesses across the nation. None of this work would be possible, however, without the critical support of the American public, including and especially their generous participation in clinical studies and trials.

Capitalizing on Expanded Research Funding

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

- NIH redirected funds from other programs by \$50 million in fiscal year (FY) 2012 and by \$40 million in FY 2013 to support promising research on 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.
- The biggest increases in funding came in FY 2016 and FY 2017, following congressional passage of the Consolidated Appropriations Act of 2016 (P.L. 114-113) and the Consolidated Appropriations Act of 2017 (P.L. 115-31). The FY 2016 appropriations directed an unprecedented additional \$350 million toward Alzheimer's and related dementias research, with an additional \$400 million provided in FY 2017. This infusion of resources enabled the launch and expansion of research programs and invigorated investigator-initiated research. In the current fiscal year, FY 2017, with appropriations finalized on May 5, 2017, NIH is now implementing plans for spending these just-allocated funds.
- Overall, NIH spending on Alzheimer's disease and related dementias research has increased by \$912 million from FY 2012 to FY 2017.

The boost in funding has moved research forward in these critical areas:

- Decoding the genetics of Alzheimer's and related dementias and understanding the complex biology of disease and resilience to disease
- Discovering therapeutic targets and biomarkers for treatment and prevention

- Building a new translational infrastructure and public-private partnerships that address key challenges in therapy development
- Developing pharmacologic and non-drug interventions
- Innovating disease monitoring, assessment, and care

Progress in these areas is described in the Making Progress section of this report, where we discuss the momentum in research and opportunities to build on what we have learned.

Budgeting to Fight the Threat of Dementia

In summer 2015, NIH prepared its first-ever professional judgment budget for Alzheimer’s and related dementias, as required in Public Law No. 113-235, the Consolidated and Further Appropriations Act, 2015, SEC. 230, which states:

Hereafter, for each fiscal year through fiscal year 2025, the Director of the National Institutes of Health shall prepare and submit directly to the President for review and transmittal to Congress, after reasonable opportunity for comment, but without change, by the Secretary of Health and Human Services and the Advisory Council on Alzheimer’s Research, Care, and Services, an annual budget estimate (including an estimate of the number and type of personnel needs for the Institutes) for the initiatives of the National Institutes of Health pursuant to the National Alzheimer’s Plan, as required under section 2(d)(2) of Public Law 111–375.

That first professional judgment budget estimate outlined the additional funding needed during FY 2017 to help reach the ultimate research goal of the Alzheimer’s National Plan—to effectively treat and prevent Alzheimer’s and related dementias by 2025. 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 to Congress without modification through the traditional Federal budget process.

This year, the professional judgment budget estimates the additional funding required in FY 2019 to enhance investigator-initiated research grants and initiatives beyond NIH’s current base budget to meet the 2025 treatment/prevention goal. It takes into account the past three years of Alzheimer’s disease and related dementias research funding, as follows: The estimated funding level for this research for FY 2017 is \$1,414 million, based on the Consolidated Appropriations Act, 2017 (P.L. 115-31), and the FY 2018 President’s budget has proposed to reduce this level by \$577 million (a 41 percent cut). The FY 2019 professional judgment budget

includes funding to compensate for this reduction, as well as an additional increase of \$597 million (for new research)—yielding a total professional judgment budget estimate for FY 2019 of \$2,011 million. This total would represent an increase of \$1,174 million in additional funds relative to the FY 2018 President’s budget proposal to sustain momentum in Alzheimer’s and related dementias research.

This estimate is large, but these funds will enable NIH to focus intensively on better understanding the basic biology underlying dementia; characterizing novel biomarkers; translating findings into innovative targets; supporting clinical trials testing promising treatments; and improving the diagnosis, care, and support of those living with dementia. The estimate also includes \$3.8 million for the additional staffing and administrative support needed to develop, implement, and oversee new research programs and projects in these areas. It is difficult to envision a scenario in which this progress will not be slowed if funding levels are not sustained.

Strategic planning for this research

In the last 5 years, NIH has undertaken a rigorous strategic planning process to assess the status of our knowledge and where research should be directed. The process is complex and inclusive, resulting in the development of the [implementation research milestones](#) referenced above. The NIH strategic planning process for Alzheimer’s and related dementias is led by [NIA](#), with collaboration from the [National Institute of Neurological Disorders and Stroke](#) (NINDS) and other NIH Institutes and Centers, including the [National Institute of Mental Health](#); [National Institute of Nursing Research](#); [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](#); and [National Heart, Lung, and Blood Institute](#). This strategic framework serves as the basis for developing NIH’s research plan and for preparing the annual bypass budget.

Thought leaders lend voices to goal-setting

The research implementation milestones are the result of extensive input from a variety of sources and perspectives outside of NIH. Central to this process has been 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 to update and enhance our research agenda, as well as contribute to a series of [recommendations](#) that were the basis for the implementation milestones detailed in this FY 2019 budget proposal.

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

Looking ahead, an important research summit focusing on care and services for people with dementia and their caregivers will occur in October 2017. This meeting will take place on the NIH campus under the auspices of the Office of the Assistant Secretary for Planning and Evaluation at HHS. Research recommendations from this meeting will augment future planning efforts.

These meetings have and will continue to draw hundreds of experts across diverse fields of dementia and other research, as well as patients, caregivers, advocates, and policymakers. Their goal is a common one: 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 other public and private organizations can most effectively collaborate to address these research priorities. The bottom line: NIH's goals are the shared goals of researchers and stakeholders nationwide.

How NIH prioritizes its research investment

The bulk of NIH's research funding goes to investigator-initiated projects from researchers around the country. 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 Alzheimer's and related dementias.

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. Between October 2015 and January 2017, more than [40 Funding Opportunity Announcements \(FOAs\)](#) were issued by NIH, soliciting creative and cutting-edge proposals that could be supported if additional funds became available in the FY 2016 and FY 2017 budgets. These initiatives solicit Alzheimer's and Alzheimer's-related dementias research covering a range of topics to address multiple research priorities and their implementation milestones. Research areas include: training, health disparities, data mining to leverage existing resources, clinical trials, caregiving,

and clinical care, as well as basic and translational research.

How to navigate the bypass budget

This bypass budget proposal outlines the additional FY 2019 funding needed to advance NIH-supported research on Alzheimer’s and related dementias aimed at the key research goal of the National Plan: to prevent and effectively treat these disorders by 2025.

Beyond dollar estimates, we provide a narrative in this document that highlights key areas of recent progress upon which NIH would build with such increased funding. The document also includes a subset of Alzheimer’s disease and related dementias research milestones that could be started or accelerated specifically in FY 2019, upon which the current bypass budget estimates are based.

The Path to Cures

Our Nation faces many challenges as we work together to find effective therapies as soon as possible to prevent and treat Alzheimer’s disease and related dementias. At the same time, we believe 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 support in FY 2016 and FY 2017.

The words of Auguste Deter resonate in our minds and hearts. We remember those “lost” to Alzheimer’s and related dementias as we navigate the path forward toward a cure.

FISCAL YEAR 2019 PROFESSIONAL JUDGMENT BUDGET: ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Baseline Estimate, President's Budget, Fiscal Year 2018

(dollars in thousands)

Alzheimer's Disease, Including Alzheimer's Disease-Related Dementias (AD/ADRD) \$837,000

Professional Judgment Budget FY 2019 Additional Resources Needed

(dollars in thousands)

Molecular Pathogenesis and Pathophysiology of Alzheimer's Disease	\$110,000
Diagnosis, Assessment, and Disease Monitoring	\$70,100
Translational Research and Clinical Interventions	\$191,000
Epidemiology	\$58,025
Care and Caregiver Support	\$32,800
Research Resources	\$76,375
Alzheimer's Disease-Related Dementias	\$55,000
Staffing Needs and Administrative Support	\$3,800
Resources Needed for New AD/ADRD Research	\$597,100

Difference Between FY18 President's Budget Request and FY17 Omnibus Appropriation* (dollars in thousands)	\$577,000**
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*P.L. 115-31, the Consolidated Appropriations Act, 2017

**Est. \$1,414 million (FY17 Omnibus) - \$837 million (FY18 President's Budget) = \$577 million

Professional Judgment Budget FY 2019 Additional Resources Needed, Above the FY 2018 President's Budget Request

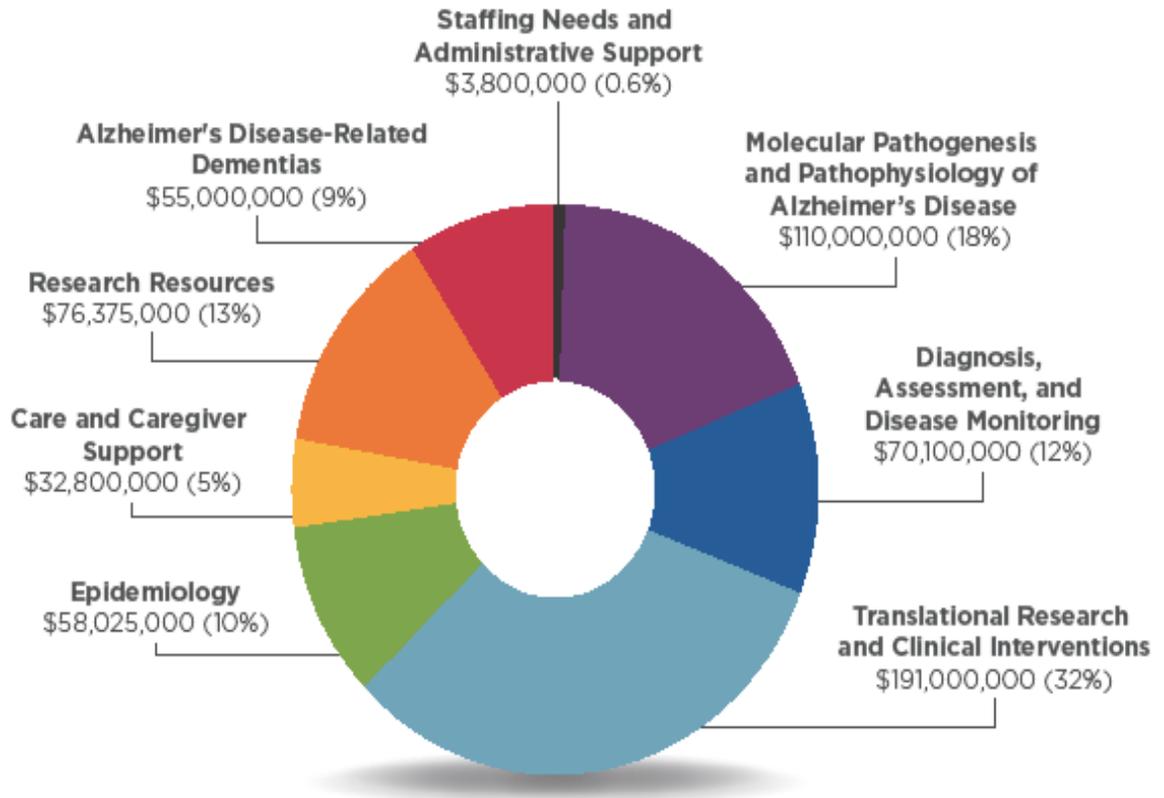
(dollars in thousands)

Resources Needed for New AD/ADRD Research	\$597,100
Difference Between FY18 President's Budget Request and FY17 Omnibus Appropriation	\$577,000
TOTAL ADDITIONAL RESOURCES NEEDED	\$1,174,100

TOTAL RESOURCES NEEDED (dollars in thousands)	\$2,011,100***
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***Est. \$837 million (FY18 President's Budget) + \$597.1 million (new research resources needed) + \$577 million (difference between FY18 President's Budget request and FY17 Omnibus) = \$2,011.1 million

Distribution of Additional Budget Funding Across Research Areas, FY 2019
Total: \$597,100,000



MAKING PROGRESS, ADVANCING RESEARCH IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

In this narrative for the Fiscal Year (FY) 2019 Professional Judgment Budget for Alzheimer's Disease and Related Dementias, we highlight nine key areas of focus, featuring new initiatives that together are laying the foundation for precision medicine for these disorders. These initiatives are central to the development of an integrated, multidisciplinary research agenda. Such an agenda is necessary to address critical knowledge gaps and accelerate the discovery and delivery of successful treatments for people with Alzheimer's at all stages of the disease, as well as to improve care and services.

The programs featured below span the spectrum of research, from basic discovery science to the development of therapeutic interventions and early disease detection and disease monitoring. They bring forward cutting-edge technologies, innovations in data science, development of research tools, and new infrastructure for translational and clinical research.

Harnessing the Power of Big Data to Discover Next-Generation Therapeutic Targets

The transformation of biology into a data-intensive science and the availability of large-scale molecular, clinicopathological, and other types of patient data offer unprecedented opportunities for:

- Understanding the complexity of the disease process
- Discovering new, disease-relevant therapeutic targets
- Advancing diagnostics

National Institutes of Health (NIH)-supported studies are mapping the molecular fabric of Alzheimer's and related dementias using the most advanced profiling technologies and computational approaches in a team-science framework.

Partnering to amplify the search for novel drug targets

The [Accelerating Medicines Partnership-Alzheimer's Disease \(AMP-AD\) Target Discovery and Preclinical Validation Project](#) is a new discovery engine for Alzheimer's research. Its key goal is to shorten the time between the discovery of potential drug targets and the development of new drugs to treat and prevent Alzheimer's disease.

The program was established in 2014 as a bold, public-private partnership that brings together the government, industry, and nonprofit sectors and provides support for a consortium of six

multi-institutional, multidisciplinary academic teams. The teams are applying pioneering systems and network biology approaches to integrate multidimensional human “omic” (genomic, proteomic, metabolomic) data from more than 2,000 human brains at all stages of Alzheimer’s with clinical and pathological data. These efforts are paired with experimental validation studies in a variety of cell-based and animal models.

The key feature of the program is the broad and rapid sharing of biological data and analytical results. This is made possible via the [AMP-AD Knowledge Portal](#). Launched in 2015, the portal is a big-data hub that allows researchers in this program, as well as the research community at large, to access and analyze data on a scale that would not be possible by individual research teams, academic institutions, or pharmaceutical companies. Using the data from the AMP-AD Knowledge Portal, consortium members and researchers at large are making methodological advances and gaining new understanding of:

- **Molecular changes at the heart of Alzheimer’s.** Recently reported findings of a large-scale analysis of Alzheimer’s-related proteins in the brain are providing new insights into the molecular changes at the heart of the onset and progression of the disease. The NIH-supported research team ([Seyfried et al., 2017](#)) tracked alterations in how individual proteins and networks of proteins were turned on or off in brain tissue from volunteers who progressed from symptom-free to the earliest and later stages of Alzheimer’s. Using network modeling approaches to analyze large-scale data, they identified changes that may influence Alzheimer’s before symptoms appear, such as increased activity of protein networks linked to inflammation.
- **Vulnerability of brain regions.** Another team ([Wang et al., 2016](#)) used RNA profiling to look for clues about why some brain regions are especially vulnerable to Alzheimer’s. The team mapped gene expression changes associated with the severity of dementia symptoms and the plaques and tangles characteristic of Alzheimer’s. Scientists analyzed the activity of 44,692 genes in 19 different regions of the cortex, then sorted the genes into 1,558 “modules” (groups of genes that operate in common biological pathways). The modules were ranked for how well their changes in expression correlated with disease severity. The team identified key neurobiological pathways and genetic signatures, many occurring early in the progression of disease, as possible treatment development targets.

One of the key achievements of the AMP-AD consortium is the discovery of more than 100 novel candidate targets. These targets are now being evaluated in collaboration with industry partners. Many of the candidate targets hold promise for further discovery and development of Alzheimer’s drugs.

A mission to MOVE Alzheimer's science forward

Big-data approaches also may help scientists decode the molecular ties between vascular disease and Alzheimer's. Launched by NIH in March 2016, the [Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease \(M²OVE-AD\) Consortium](#) aims to build a more nuanced and accurate understanding of how the vascular system—the body's network of large and small blood vessels—may be involved in the onset and progression of Alzheimer's and related dementias.

Using a team-science approach, scientists from diverse fields are employing the latest technologies to better understand the complex molecular components by which vascular risk factors may influence Alzheimer's and to identify new targets for treatment and prevention. M²OVE-AD builds on the investments made in the open-science approach and big-data infrastructure established by AMP-AD.

The M²OVE-AD Consortium is already providing a path for identifying the molecular signatures—sets of genes, proteins, and metabolites—that might be used as markers for disease risk or to track the effectiveness of promising therapies.

- **Associating metabolic changes with different stages of disease.** In March 2017, a team of researchers ([Toledo et al., 2017](#)) supported by M²OVE-AD and AMP-AD reported initial findings from the most comprehensive study to date aimed at identifying metabolic changes associated with the progression of Alzheimer's. The research team measured more than 180 metabolites in blood samples from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a global research effort that actively supports the investigation and development of treatments that slow or stop the progression of Alzheimer's. They then tracked how changes in metabolite levels correlated with changes in protein markers of the disease process found in cerebrospinal fluid (CSF), changes in imaging markers, and changes in cognition.

The researchers found that metabolic changes reflecting errors or alterations in lipid metabolism, mitochondrial function, and energy utilization were associated with different stages of the disease, from no symptoms to mild cognitive impairment (MCI) and full-blown Alzheimer's. A subset of lipid metabolites was tied to changes in cognition and brain volume measured during a 5-year period, as MCI progressed to Alzheimer's, suggesting a dynamic relationship between peripheral organ systems and the brain.

This is just the first step of a large multiyear effort that aims to generate a biochemical

roadmap, which can become part of a new, detailed model of Alzheimer's disease that better reflects its heterogeneity and complex biology. In addition, these efforts will serve as a basis for the discovery of blood-based biomarkers that are critically needed for accelerating clinical trials.

- **Understanding the impact of sex differences on disease progression.** Approximately two-thirds of all Alzheimer's disease cases are female ([Mazure and Swendsen, 2016](#)). The greater prevalence of the disease is due in part to the higher incidence of Alzheimer's disease in women than men after age 78 ([Chêne et al., 2015](#); [Mazure and Swendsen, 2016](#); [Miech et al., 2002](#); [Mielke et al., 2014](#); [Roberts et al., 2014](#); [Ott et al., 1998](#); [Toledo et al., 2017](#)). In addition, the strongest genetic risk factor for Alzheimer's disease, the apolipoprotein E gene ε4 allele, has a 1.5 times stronger association with the clinical symptoms of the disease among females compared with males ([Farrer et al., 1997](#)). Despite this finding, little is known about how genes and the environment interact to result in sex differences in disease incidence and disease progression.

In 2016, NIH added a new team to the M²OVE-AD Consortium to zero in on the how sex differences impact the trajectory of the disease with the largest current study of gene expression mechanisms in postmortem human brains in Alzheimer's. It is hoped that this closer look at sex differences in disease progression can provide major insights related to the overall understanding of Alzheimer's biology and help direct us toward new drugs targeted specifically at women or men at risk for dementia.

Technology Enables a Radical Rethinking of Tools, Translational Infrastructure

One of the major challenges to the successful development of therapies for Alzheimer's disease has been poor translation of preclinical efficacy in animal models to humans. Positive test results in animal models often do not translate successfully into positive outcomes in clinical studies for a number of potential reasons—for example, animal models that do not fully mimic Alzheimer's disease in humans, challenges with study design and data analysis, and insufficient characterization of animal models relative to the human disease.

Increased resources in the last few years have allowed NIH to step up efforts to improve the predictive power of preclinical testing in animal models.

AlzPED: Improving transparency, reproducibility, and translation of preclinical data

In November 2016, NIH launched the [Alzheimer's Disease Preclinical Efficacy Database](#), or AlzPED. AlzPED serves as a knowledge platform for the dissemination of data and analysis to scientists from academic centers, industry, and disease-focused foundations in a way that

promotes efficiency, transparency, reproducibility, and accuracy of research aimed at preclinical therapy development for Alzheimer's. Currently, AlzPED provides quick access and visibility to integrated preclinical efficacy data from close to 300 published studies. It will soon provide a platform for researchers to share findings and data from unpublished studies.

Of vital importance, AlzPED is designed to help identify the critical data, design elements, and methodology missing from studies. This missing information can make studies susceptible to misinterpretation and less likely to be reproduced, reducing their translational value. By providing this comprehensive preclinical data in one platform, AlzPED helps researchers develop and implement reproducibility strategies, including guidelines for standardized best practices for the rigorous preclinical testing of promising Alzheimer's therapeutics.

Building better mouse models to bridge the preclinical-to-clinical development gap

A major reason for the high failure rate of Alzheimer's drugs in the clinic is the poor predictive power of studies testing candidate therapeutics in Alzheimer's transgenic mouse models. To remove this roadblock, NIH is moving ahead to build better mouse models for the disease. Capitalizing on recent advances in gene sequencing and genome editing technologies, NIH in 2017 launched the [Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease](#) (MODEL-AD), an initiative expected to create the next generation of mouse models for preclinical efficacy testing of candidate therapeutics. The new models will be based on newly identified late-onset Alzheimer's disease risk genes and will undergo extensive molecular, pathological, and clinical staging to align the pathological features in mice with corresponding stages of human disease.

MODEL-AD aims to produce multiple models annually for the next 5 years, selecting and advancing the most promising lines as they go. All data and models generated will be made freely available to researchers in academia, industry, and other institutions, with the ultimate goal of speeding up the development of Alzheimer's treatments.

Reprogramming human cells to stem cells and beyond

An exciting new addition to the Alzheimer's research toolbox builds on breakthrough findings several years ago showing that adult human skin cells can be converted, or "reprogrammed," to a type of stem cell called induced pluripotent stem cells (iPSCs). The iPSCs can, in turn, be converted to make other cells, like neurons, in order to directly study human cell biology and disease processes in living human cells, something not previously possible for brain cells.

The National Institute on Aging (NIA) pursued this extraordinary technology by issuing requests for applications for iPSCs that can help improve the grasp of Alzheimer's disease processes, identify new therapeutic pathways, and screen potential new drugs.

This program seeks to stimulate research on human cell models of Alzheimer's in three areas:

- Develop human iPSCs as cell models to study Alzheimer's pathophysiology
- Explore the impact of age on the development of Alzheimer's in iPSC models to potentially investigate early disease events and late-stage features of Alzheimer's
- Establish functional genotype-phenotype relationships of genes or genetic variants suspected of altering the risk of Alzheimer's

Proof-of-concept results hold promise that these modified cells can help investigate the pathological processes involved in Alzheimer's. For example, researchers ([Muffat et al., 2016](#)) derived microglia, the brain's resident immune cells, from cultured human iPSCs. These microglia looked like their brain-residing counterparts. Having these cells available will permit their role in Alzheimer's and other neurodegenerative diseases to be defined. Moreover, it is now possible to recapitulate Alzheimer's-like pathology in three-dimensional neural cell culture systems ([Choi et al., 2016](#)), which could be used for disease mechanism discovery and drug screening. Such human cell-based systems will be critical to define cell-to-cell interactions in the development of Alzheimer's, such as the microglia-mediated loss of neuronal connections reported in animal models ([Hong et al., 2016](#)).

Our understanding of the genetic, molecular, and cellular mechanisms underlying Alzheimer's will be enhanced by studying Alzheimer's, unique to humans, in human cells. This reprogramming of human cells to model Alzheimer's and aging holds great promise, as well as many unknowns, and is an example of scientific advances with the capacity to produce dramatic breakthroughs.

Creating a Pipeline of New Candidate Therapeutics for All Stages of Disease

To bridge the funding gap between discovery science and early-phase clinical trials, when a candidate drug for Alzheimer's disease becomes potentially attractive for investment by the pharmaceutical industry, NIH continues to invest in robust translational programs. These programs include the NIA Alzheimer's Disease Drug Development program, the NIH-wide [Blueprint Neurotherapeutics Program](#), and the NIH Small Business Innovation Research program.

Cumulatively, these programs tap into the creativity of academic and biotech researchers and provide a lifeline for sustaining and growing innovation in academia, the biotech industry, and small businesses. With NIH support, the small-business community creates jobs while testing and designing breakthrough technologies and therapies for both early- and late-stage Alzheimer's disease.

Translational studies moving research forward include:

- **Activating neural stem cells for brain repair.** Allopregnanolone (“Allo”) is a natural neurosteroid. NIH-supported scientists conducted preclinical studies that demonstrated the ability of the drug to stimulate regeneration of the brain’s own stem cells, illuminated relevant molecular mechanisms, and developed a special formulation that can be used for testing in humans. Additional NIH support enabled the first-in-human safety testing of this promising neuroregenerative compound. This new Allo formulation is now ready to be evaluated for efficacy in people with Alzheimer’s disease.
- **Insulating brain cell connections from harm.** NIH support enabled the development of the candidate therapeutic LM11A-31, one of the first compounds able to activate the brain’s own defense mechanisms, thereby protecting neural connections in the brain from brain degeneration and the ravages of Alzheimer’s. LM11A-31 works by changing the way certain proteins on the outer surface of nerve cells send molecular signals. This candidate drug is expected to prevent the start of the domino effect of Alzheimer’s damage by protecting nerve cells and their networks. A clinical trial testing the safety of LM11A-31 in people with Alzheimer’s and exploring its ability to alter various indicators of the disease process has been initiated with NIH support.
- **Boosting declining cognition.** Other NIH-supported projects focus on boosting the neural connections essential to memory and cognition. Through a unique mechanism of action, the compound BPN14770 has been shown to alter one of the brain’s own cognition enhancers. This therapeutic candidate has promise to treat not only Alzheimer’s but also schizophrenia, Fragile X syndrome, and other learning or developmental disabilities. Through the NIH small-business program, a biotech company conducted Phase I safety testing and is now poised to start efficacy testing in people with Alzheimer’s.
- **Neutralizing the toxic effects of harmful proteins.** Another compound, CT1812, developed with support from NIH translational programs and the small-business program, is currently in Phase I safety testing. CT1812 is a unique drug candidate with the potential to prevent the ripple effect of neurotoxicity elicited by beta-amyloid oligomers.

Learning About Alzheimer’s Complexity from Down Syndrome

Down syndrome and Alzheimer’s disease are closely connected. Almost all people with Down syndrome develop brain changes associated with Alzheimer’s by age 40, and a high percentage of them go on to develop dementia. Scientists are keen to learn why that is so, both to help

people with Down syndrome and to see if more can be learned for everyone about the development of Alzheimer's.

Chromosome 21 is an important part of the human genome, linked to Alzheimer's, Down syndrome, and amyotrophic lateral sclerosis. People with Down syndrome are born with an extra copy of this chromosome, which also contains the amyloid precursor protein gene, which is related to the signature amyloid plaques of Alzheimer's and, in people with three copies of this gene, an increased risk of early-onset Alzheimer's.

As medical advances have helped extend the lifespan of adults with Down syndrome, many face an increased chance of developing signs of Alzheimer's by middle age. The National Plan to Address Alzheimer's Disease calls for improved care for specific populations that are unequally burdened by the disease, including people with Down syndrome. Research is moving knowledge forward in important ways:

- **Using biomarkers to track Alzheimer's progression in people with Down syndrome.** As part of its commitment to address Down syndrome and Alzheimer's disease, NIH recently launched the [Alzheimer's Biomarkers Consortium–Down Syndrome](#). The initiative seeks to identify biomarkers and track the progression of Alzheimer's in people with Down syndrome, using brain imaging and fluid and tissue biomarkers to help understand the progression of the disease. These studies, by two teams of researchers, will include positron emission tomography (PET) brain scans that detect levels of tau, to be tested for the first time in people with Down syndrome. The teams will make their data and samples available to qualified researchers worldwide, with the goal of improved testing of interventions.
- **Testing immunotherapy.** NIH is currently funding a Phase I clinical trial to investigate an immunotherapy vaccine to treat Alzheimer's in adults with Down syndrome. The experimental vaccine, developed through a partnership between an American university and a Swedish biotech firm, induces antibodies against beta-amyloid, which comprise plaques in the Alzheimer's-affected brain. This early-phase trial will involve 24 adults with Down syndrome between ages 35 and 45. Future steps include testing the vaccine candidate's effects on cognitive function and Alzheimer's biomarkers.
- **Tracking Alzheimer's progression in adults with Down syndrome.** NIH also funds a project investigating the natural history of amyloid deposition in adults over age 30 with Down syndrome. The buildup of amyloid protein fragments in the brain is a hallmark of Alzheimer's. This longitudinal study investigates the progression of amyloid deposition using brain imaging with a noninvasive, in vivo PET tracer (Pittsburgh Compound B) in 24-month intervals. Cognitive function of study participants, at the time of imaging, is

also assessed to determine if there is a predictable trajectory toward clinical Alzheimer's.

- **Examining defects in the body's abnormal protein disposal system.** Researchers ([Tramutola et al., 2017](#)) have zeroed in on a failure in how cells dispose of damaged or misfolded proteins as a possible mechanism in Down syndrome and possibly Alzheimer's disease. Cells target damaged or misfolded proteins for disposal by tagging them with a small protein called ubiquitin. Cell mechanisms that route ubiquitinated proteins for disposal often wear out with age or disease. Comparing ubiquitinated proteins after death in brain samples before and after the onset of Alzheimer's, the team found that people with Down syndrome showed higher levels of certain ubiquitinated proteins. People with both Down syndrome and Alzheimer's showed even greater increases in these levels. These results suggest that defects in this protein disposal system may impact both Down syndrome and Alzheimer's.

Detecting Disease Progression with Neuroimaging and Novel Biomarkers

Biomarkers—changes in the quantities of genes, proteins, or metabolites, whose presence in a living organism can be measured to indicate disease or environmental exposure—are essential for developing diagnostics and treatments. For example, plasma cholesterol is probably the best recognized biomarker for cardiovascular disease risk.

As recently as 2004, there were no established biomarkers for Alzheimer's. In 2017, we can image both amyloid plaques and tau neurofibrillary tangles, the two neuropathological hallmarks of Alzheimer's, in the brains of living humans. In addition, scientists have identified many other potentially promising biomarkers, from blood proteins to early changes in smell. Validating these biomarkers for use in research continues, as examining their utility for widespread clinical use is getting underway. The discovery of biomarkers for Alzheimer's disease has transformed how we think about disease progression. It has fostered hope that, by detecting signs of disease-related change years before clinical symptoms such as memory loss appear, we will know who is at risk for developing Alzheimer's and can then intervene at the earliest possible time. Additionally, knowledge of the normal trajectory of changes in brain structure and function is critical in differentiating normal aging from Alzheimer's and in detecting the disease at its earliest stages.

A landmark initiative continues to innovate

The [Alzheimer's Disease Neuroimaging Initiative](#) (ADNI) has contributed to much of this progress, particularly in neuroimaging. ADNI, a long-running, NIH-supported study, was designed to develop tools for clinical trials by tracking how neuroimaging and fluid biomarkers

change with disease onset and progression. Launched by NIH in 2004, this landmark public-private partnership looks at how the evolution of clinical symptoms and neurocognitive testing in healthy controls, people with MCI, and people with mild Alzheimer's correlates with changes in multiple biomarkers reflecting disease development. Participants have their blood, cerebrospinal fluid, and DNA collected at multiple timepoints, and they undergo multiple neuroimaging procedures that examine changes in brain structure and volume, white matter integrity, functional connectivity, glucose metabolism, and the amount and location of amyloid protein plaques, one of the hallmarks of Alzheimer's disease. The biomarkers developed and validated in ADNI are being used more and more in clinical trials.

In 2016, ADNI moved into a critical new phase of discovery with ADNI3, with \$40 million in NIH support over the next 5 years and at least \$16 million in private-sector investment secured by the Foundation for the National Institutes of Health. The new effort will add brain scans that detect the amount and location of tau protein tangles—a second hallmark of Alzheimer's disease—to the ongoing collection of neuroimaging and biofluid biomarkers. People already participating in ADNI—some have been volunteering for more than 8 years—and replacements for those no longer participating will be followed as their status moves from cognitively healthy through development of mild Alzheimer's.

ADNI3 will also explore the use of tablet and Web-based assessment to track the cognitive health of volunteers. Changes in the ability to do real-life tasks are often a harbinger of Alzheimer's. This phase of ADNI will use an innovative test, the Financial Capacity Instrument, to measure how well participants manage standard financial tasks involving bills and money as a possible indicator of early disease.

ADNI has also pioneered rapid, transparent data sharing while protecting participants' privacy. Qualified researchers across the world can access ADNI brain scan images and biomarker data through a Web-based portal as soon as data are quality-controlled and added to the database. ADNI also shares the blood, cerebrospinal fluid, and DNA it has collected with other investigators who are developing novel biomarkers. To date, more than 8,500 researchers have sought access, and ADNI data have been a part of more than 1,200 research papers. Additionally, ADNI has spawned numerous similar efforts across the globe.

New biomarker in Alzheimer's clinical trials

The [AMP-AD Biomarkers Project](#) is exploring the utility of tau PET imaging and novel fluid biomarkers for tracking response to treatment and/or disease progression. Tau PET scans reveal tau tangles in the living brain, allowing researchers to learn more about how and where this protein builds up in the brain and how its interactions with amyloid plaques could impact disease progression and response to treatments.

Under the Biomarkers Project, NIA-supported, Phase II/III secondary prevention trials are testing several anti-amyloid therapies. Through the AMP-AD partnership, imaging and fluid biomarker tests already included in these trials will be supplemented with tau PET imaging and novel fluid biomarkers. Screening and baseline data from the trials will be made broadly available through the [Global Alzheimer's Association Interactive Network collaborative platform](#). Trial data and biological samples will also be shared after the trials are completed.

Mapping aging brain connectivity will tell us more

As scientists seek to learn more about what the brain looks like and the changes associated with advancing dementia, they also want to develop a clearer picture of normal brain connectivity with aging. Surprisingly little is understood about how different areas of the brain connect and work together as a system, yet connectivity is critical to understanding, diagnosing, and treating certain neurological and psychiatric disorders. Problems in connectivity are now suspected in several disorders, including Alzheimer's disease, which was previously thought not to be affected by these changes.

To explore these important questions, NIH supports the Lifespan Human Connectome Project (LHCP) to map structural and functional connectivity in the developing, adult, and aging human brain. An extension of the groundbreaking [Human Connectome Project](#) (HCP), the LHCP's goal, as it applies to aging and dementia, is to capture changes in later-lifespan brain connectivity, expand understanding of the fundamental organization and operation of the brain and behavior, and provide data to support research examining the role of aging in brain disorders.

The HCP data are already providing new insights into the organization of the human brain. One research team ([Glasser et al., 2016](#)) has made great progress toward a century-old goal of neuroscience: more precise mapping of the human cerebral cortex. Using brain images from the HCP, the investigators defined 180 cortical regions, of which 83 correspond to known areas and 97 appeared to be newly identified regions. This vastly improved topography of the brain has implications for better understanding of cognition, lifespan, and disease.

Complementing this macroscale mapping of the brain by the LHCP is new scanning that can detect age-related changes in brain microstructure. Increasingly sophisticated techniques are helping scientists zoom in on age- and disease-related changes in the brain's microarchitecture. Scientists recently used a new technique called Neurite Orientation Dispersion and Density Imaging (NODDI) to study the brains of 116 cognitively healthy older individuals ([Merluzzi et al., 2016](#)). The participants also underwent cognitive testing.

The team found that increasing age was associated with reductions in the density of neurites (dendrites and axons) in specific regions of the prefrontal cortex, an area involved in memory,

attention, and executive function. Decreased neurite density was related to significantly worse performance on tests of verbal memory and executive function. NODDI offers a new method for identifying changes in neuronal structure that could help differentiate normal aging from Alzheimer's.

Monitoring Elders and Tracking Disease with Digital Technologies

Digital technologies provide new flexibility to assess seniors in their homes and in office and study settings. NIH support for one major new initiative is developing and testing technologies to help older adults age in place. Another effort is aiding researchers' ability to assess older adults' cognition through a portable tablet app, expanding opportunities for participation in research, with potential for clinical application.

Transformational technology to help older adults age in place

An overwhelming majority of seniors want to continue living at home as they grow older. In recognition, the [Collaborative Aging \(in Place\) Research Using Technology \(CART\) Initiative](#) unites NIH, other government agencies, academic, and industry experts to develop and test tools that track changes in older adults' health status and activities unobtrusively in real time. Launched in October 2016, the \$9 million, 4-year project, which includes contributions from a number of NIH institutes and the Department of Veterans Affairs, will start with a pilot project in more than 200 homes in rural and urban communities across the United States.

CART collaborators are looking at existing and innovative technologies to detect signs of depression, evaluate falls risks, and even monitor common safety hazards like leaving the stove on. The hope is that technology implemented in the CART infrastructure will provide early detection of changes in key health- and independence-related activities, such as driving, body composition, mobility, and sleep, as well as measure aspects of cognition and socialization. Subtle changes in these patterns of health and home often are early warning signals of cognitive or physical obstacles to independent and safe aging in place. Scientists hope CART will help elders remain independent while avoiding hospitalizations and transitions into care facilities.

CART scientists believe the project could be transformative for the field of aging research and for care. It might one day, for example, help clinical trials collect real-time data that might otherwise be collected only once or twice a year. The potential benefits for older adults and their families and/or caregivers are most important, as more seniors could stay in their own homes as they age, comfortably and safely.

There's an app for that—detecting cognitive changes

Pen-and-paper tests have traditionally been the standard way to assess cognitive decline in research, but most of these tests were designed for a later stage of disease than most studies are focusing on now. One new project hopes to make such measures more sensitive and reliable using a digital platform. Through a Small Business Innovation Research grant from NIA, one company is tailoring its computerized cognitive assessment battery, administered via iPad, to detect cognitive decline earlier in older adults, while making sure that the iPad results match the pen-and-paper results. This iPad-based application, or “app,” can serve as a screening tool for clinicians and outcome measures in clinical trials. The approach will be part of a study that will test its ability to discern healthy participants from those experiencing the very earliest stages of cognitive decline.

Advancing Understanding of Alzheimer’s Disease-Related Dementias

Alzheimer’s disease is only one of many dementia disorders. An estimated 20 to 40 percent of people with dementia have some other form, such as Lewy body dementia, vascular dementia, or frontotemporal degeneration. Among all people with dementia, many are believed to have mixed dementia, which involves more than one dementia disorder.

NIA and the National Institute of Neurological Disorders and Stroke lead NIH’s effort in Alzheimer’s disease-related dementias (ADRD) research. Important efforts are underway to better understand the origins, genetics, and mechanisms of ADRD, which may lead to new prevention and treatment approaches.

Consortiums build progress in biomarker discovery, development

Biomarker discovery and development remain a priority for NIH research on vascular and Lewy body dementia. In 2017, NIH launched a new center focused on small vessel disease in the brain and its role in vascular contributions to cognitive impairment and dementia (VCID). The [MarkVCID Consortium](#) is designed to accelerate the development of new and existing biomarkers for small vessel VCID.

The 5-year program consists of seven research groups across the United States working together, along with a coordinating center. A kickoff meeting for the consortium was held immediately prior to the 2017 International Stroke Conference.

Current VCID research centers on several noninvasive biomarker candidates based on magnetic resonance imaging scans, fluid analysis, and other measurements. These candidates must be standardized and validated before they can be used in clinical trials. Consortium scientists’ ultimate goal is to develop a gold standard for early identification and intervention for VCID.

A planned second phase of the project will begin disseminating biomarker candidates with the most potential to all consortium sites, in hopes of providing small vessel VCID biomarkers that are ready for Phase II and Phase III clinical trials.

Science collaboration, walls optional

Support for ADRD research has allowed scientists from across the United States to catalyze research via a multicenter, interdisciplinary “Center Without Walls” (CWOW). CWOWs unite interdisciplinary teams from top universities and labs to coordinate and cross-pollinate scientific resources, data, and findings to speed up dementia discoveries.

CWOW members are currently examining how vascular changes can contribute to brain white matter disease, investigating the molecular mechanisms of tau toxicity in frontotemporal degeneration, and supporting health disparities research. CWOWs focused on tau and frontotemporal degeneration have begun ramping up in-person and Web-based collaborations to share cell data. CWOW projects will examine the underlying biochemical and genetic mechanisms of how tau is released in the body and affected by neuronal activity.

Improving Quality of Clinical, Long-Term Care

As we seek ways to treat and prevent dementia, providing the best clinical and long-term care for people living with dementia is paramount. How can clinicians better attend to those at risk or who are just beginning to exhibit signs of cognitive distress? How can they help patients further along in the disease process, who may be beset by behavioral issues? Can the stresses and practical challenges of caregiving be better managed to help support loved ones and health professionals caring for people with Alzheimer’s?

Looking for systemic changes in care delivery, management

Continuity of care—consistent treatment over time by the same healthcare professional or small healthcare team—is considered the ideal for Alzheimer’s patients and can help bridge transitions between informal, community, and formal care settings. But the reality is often very different, affecting both patients and communities. In one recent study ([Amjad et al., 2016](#)), lack of continuity in care was linked to higher rates of hospitalization, emergency department visits, testing, and healthcare spending for fee-for-service Medicare beneficiaries. Studying and defining a continuum of care, including potentially relevant clinical, provider, and systems factors, should inform ways to improve care for patients, their families, and the healthcare system.

Innovation in such research is already underway. In 2016, for example, NIH awarded funds for the development of an interactive mobile app that guides individuals from the time they are

first concerned about memory loss through each phase of progressive disease. The tool teams up patients and families with dementia specialists, who can share best practices and help families achieve early, high-quality, cost-effective care, improving quality of life and avoiding expensive and unnecessary care crises.

Activities reduce behavioral symptoms in hospitalized dementia patients

Behavioral problems, such as agitation, aggression, and apathy, are common among Alzheimer's patients in hospital settings. They are disabling for patients and among the most troubling behaviors for caregivers. Researchers ([Gitlin et al., 2016](#)) who previously developed a Tailored Activity Program that improved behavioral symptoms in dementia patients being cared for at home have since tested the program in hospital settings. In this program, occupational therapists design enjoyable activities tailored to the individual patient's skills, desires, and interests, including games, singing, and crafts.

In the study, hospitalized people with dementia met with an occupational therapist to develop a personalized activity program. Over the course of an average of eight 40-minute sessions, study participants showed increased pleasure and less anxiety, anger, and other negative behaviors. Families who continued with the prescribed activities after the patient returned home expressed high satisfaction with the program. Such programs have the potential to use activities rather than drugs to help people with dementia be calmer, happier, and more engaged.

Finding new ways to support caregivers

Caregivers of people with dementia cite important emotional rewards, but many are also burdened with the significant emotional, physical, and financial toll of caregiving.

Caring for a loved one at home is particularly challenging, with additional emotional strains that can lead to caregiver fatigue, depression, and anxiety. In addition, caregivers can face economic stress from lost income and the expense of attending to someone with dementia. Eventually, families can be forced to seek institutional care, which may be more manageable, although likely more expensive, when care at home becomes too difficult to continue.

We have learned a great deal about dementia caregivers' multifaceted challenges and have discovered some effective strategies that help. Family and professional caregivers are counting on research to help lessen their burden. Recent study results include the following:

- **The intensity of effort for unpaid caregivers.** Scientists frequently use the National Health and Aging Trends Study and its companion, the National Study of Caregiving, to investigate the role of dementia in caregiving. In one recent look at national trends,

researchers ([Kasper et al., 2015](#)) found that among family and unpaid caregivers of older, noninstitutionalized adults, one-third of caregivers, and 41 percent of the hours of help they provided, were devoted to people with dementia. However, people receiving such care make up only about 10 percent of older, noninstitutionalized adults.

- **A video-based tool for families of people with advanced dementia.** More than 1 million Americans have advanced dementia ([Hebert et al., 2003](#)) and experience loss of meaningful communication, total functional dependency, and a median survival rate of 1.3 years ([Mitchell et al., 2009](#)). Their families face difficult care choices on issues such as tube feeding, infections, and falls. These wrenching choices are usually made in nursing homes, often with a limited amount of time to discuss and decide.

To address this gap, NIH-supported researchers ([Hanson et al., 2017](#)) developed a Goals of Care intervention, which combined a video decision aid and a structured care plan meeting for family decision makers of people with advanced dementia. The study showed that the intervention improved end-of-life communication, enhanced palliative care plans, and reduced hospital transfers for nursing home residents with advanced dementia.

Using next-generation strategies—robots

We are continuing to learn more about the role that new technologies may play in caregiving. To build on new technological capabilities, in March 2017, NIH invited small businesses to submit [applications](#) for a wholly new approach to caregiving—the use of socially-assistive robots, or SARs, to address the needs and conditions of caregivers of older people with Alzheimer’s disease or related dementias.

These robots, it is envisioned, could function as companions, reducing the effects of loneliness or offering psychosocial support by enhancing social connections and communications. The SARs might also provide physiological support through techniques such as biofeedback and assist with care management and activities of daily living. The devices might also help caregivers with difficult or physically stressful tasks. Key elements to be addressed include developing SARs that are affordable and culturally acceptable in diverse populations.

Making Progress on Alzheimer’s Health Disparities

Population-based research points to differences in the prevalence of cognitive decline and Alzheimer’s disease among racial and ethnic groups, with African Americans and Hispanics showing rates higher than non-Hispanic whites, for example. NIH is examining a range of possible causes of these disparities, including the impact of comorbidities, such as

hypertension, cardiovascular disease, and diabetes; health behaviors; and disease processes. In these investigations, it is important that research draws on culturally appropriate and standardized measures to better understand differences and to suggest appropriate interventions.

At NIA, which leads the NIH Alzheimer's disease and related dementias research program, health disparities studies are guided by recommendations from the NIH dementia summits and the [NIA Health Disparities Research Framework](#), which outlines four key levels of analysis for health disparities research: environmental, sociocultural, behavioral, and biological.

African Americans, genetics, and Alzheimer's risk

One recent study ([Cukier et al., 2016](#)) looked at possible genetic influences that might explain differences in prevalence between African Americans and non-Hispanic whites. The exact mechanisms are unknown, but in this study increased genetic risk appeared related to DNA sequence variations in the gene for ATP-binding cassette sub-family A member 7 (ABCA7), a cell membrane transporter involved in the brain's system for clearing out the beta-amyloid protein fragments involved in Alzheimer's.

Scientists zeroed in on a small chromosomal region containing the ABCA7 gene in 40 African Americans with Alzheimer's and 37 cognitively healthy African Americans (age, 67 years or more), all of whom carried the high-risk allele of the gene. In all 77 individuals, a 44 base-pair piece was missing from the gene sequence, a mutation predicted to remove almost three-fourths of the ABCA7 protein. The team confirmed that this deletion mutation was associated with increased Alzheimer's risk in two large African-American populations, but it found the mutation virtually absent in samples from more than 3,000 non-Hispanic whites. This study highlighted the importance of including diverse populations in genetic research and points to new possibilities for personalized therapeutics for Alzheimer's.

Funding opportunities seek studies to address challenges

Recent Alzheimer's research recommendations from several scientific meetings have underscored the need for diverse study cohorts and improved methods and tools for Alzheimer's-related health disparities research. To address these recommendations, NIH is [seeking applications for research](#) that address these issues directly. Priorities include improving recruitment and retention of under-represented populations in dementia research; mapping and analyzing pathways through NIA's Health Disparities Research Framework that create and sustain Alzheimer's health disparities; tackling challenges faced by informal caregivers from diverse backgrounds; and understanding disparities in access and use of more formal, long-term support systems and services for people with dementia and their families.

Connections on cardiovascular, dementia risk in the Hispanic community

Another recent project focuses on the Hispanic/Latino population to explore disparities in dementia's impact. Recently, an NIH-led study was expanded to examine links between risk factors for cardiovascular disease and dementia. The [Hispanic Community Health Study/Study of Latinos \(HCHS/SOL\)](#), which began in 2006, is a multicenter, community-based cohort study of more than 16,000 Latino adults in New York, Chicago, Miami, and San Diego. HCHS/SOL has focused on the high rates of prediabetes, diabetes, and obesity in these Latino communities, along with related sleep disturbances and high blood pressure that contribute to these conditions.

The Study of Latinos–Investigation of Neurocognitive Aging (SOL-INCA) ancillary project is analyzing SOL's wealth of data to examine how genetics and cardiovascular disease risk factors impact the prevalence of neurocognitive disorders among middle-aged and older participants. SOL-INCA scientists hope to find sociocultural risk and protective factors that may contribute to observed differences in dementia rates in Latinos. Its long-term goal is to look for targets that can be tested for actionable, culturally appropriate strategies for preventing or delaying the progression of dementia.

Building infrastructure, expanding inclusion in research

NIH is strongly committed to connecting researchers across the country who are focused on diversity in Alzheimer's science. These efforts focus on national and local initiatives to improve recruitment into clinical studies overall and targeted efforts to engage under-represented groups, not just into studies but into the ranks of research scientists. Several collaborative and creative efforts in this area are underway.

- **Minority Aging Research Centers focus on health, workforce disparities.** Seven NIA-supported [Resource Centers for Minority Aging Research \(RCMARs\)](#) across the United States are working to reduce health disparities in aging while increasing diversity among scientists conducting aging research and the populations they study. These Centers mentor minority academic researchers in careers specializing in minority elder health research, work to create culturally sensitive health measures to better assess minority elders' health, and seek to provide minority seniors with more effective health and well-being interventions.
- The [Diversity and Cognitive Aging: Progress and Future Challenges meeting](#) was held March 16, 2016, at the University of California, Davis, Latino Aging Research Resource Center, a RCMAR focused on Hispanic aging and health. The conference highlighted NIA-funded research in northern California and brought together nearly 100 leading national experts, including leadership from NIA's Office of Special Populations, to discuss building

a collaborative, nationwide framework for disparities research. Among the topics of interest were social determinants of aging; metabolic, cardiovascular, and inflammatory predictors of cognitive aging and dementia in diverse populations; and genetic and socioeconomic impacts on cognitive decline in these populations.

- **Alzheimer’s Centers step up outreach to under-represented groups.** Several NIA-supported Alzheimer’s Disease Research Centers across the country are stepping up coordination and collaboration of their efforts to reach out to under-represented groups. For example, the University of Washington Center continues to work with Native American communities in the Pacific Northwest, while Centers in African-American communities with a long history of connecting with families facing Alzheimer’s are more widely sharing strategies and best practices. A recently established listserv aims to connect scientists and staff who are passionate about helping the Latino community. The listserv connects bilingual professionals who do assessments, coordinate outreach, and treat people with dementia in clinics across the United States.
- **A creative approach.** The [Alzheimer’s Disease Cooperative Study](#) has partnered with Garrett Davis, an African-American playwright who has written about the experience of Alzheimer’s disease in a black family. Davis heads the [Forget Me Not Project](#), which aims to use a play as a medium to raise awareness among the African-American community and the general public on issues related to caregiving and wellness in families dealing with Alzheimer’s, diabetes, attention deficit hyperactivity disorder, and bipolar disorder.
- **Building a cadre of diverse scientists.** The [NIH Diversity Supplement Program](#) focuses on increasing the number of minority scientists focused on health disparities research. Studies have shown increased comfort and satisfaction levels among minority volunteers who participate in health research projects led by scientists from similar cultural backgrounds. NIA’s [Butler-Williams Scholars Program](#) aims to recruit and support new investigators into research, with a focus on ethnic and racial minorities and aging.

Leaning Forward

Today, thanks to recent, historic levels of investment in Alzheimer’s disease and related dementias, the Nation has been able to provide more robust support for the army of researchers committed to fighting for a world without dementia. Moving forward, the foundation built with that increased funding needs to be fortified and expanded to enable true precision medicine for Alzheimer’s, which will make it possible to treat the right patient with the right drug at the right time of the disease process. Moreover, for both individuals and society, reducing risk or delaying disease onset will have tremendous impact on the

socioeconomic burden of Alzheimer's disease and related dementias.

Central to achieving our goal is our ability to gain a deeper understanding of the mechanisms of brain and cognitive resilience despite the presence of multiple pathologies, very old age, or various types of genetic risk for Alzheimer's and related dementias. The development of successful prevention strategies also will require new research programs focused on identifying critical windows of vulnerability to dementia risk and quantifying predictors of long-term brain health.

The research described in this professional judgment budget must continue to move forward, with continued and new support for studies aimed at:

- Understanding the complex interaction between genes and environment as it relates to Alzheimer's risk
- Elucidating the mechanisms by which vascular, immune, and metabolic risk factors impact brain aging and how brain aging itself impacts Alzheimer's
- Understanding mechanisms of brain plasticity—resilience, repair, and rejuvenation—in counteracting brain degeneration in aging and dementia
- Developing innovative trial designs for disease prevention in community-based cohort studies
- Advancing the science of behavior change to ensure that, as effective prevention strategies are identified, they can be successfully implemented in the population

Furthermore, advances in information technology and mobile platforms offer unprecedented opportunities to improve the ability to monitor the well-being of patients across multiple dimensions in real time. Investments in this area will be critical to optimize and customize the delivery of care. It will also be critical to continue to innovate disease monitoring and disease assessment, close research gaps in integrating care, and conduct research on technologies for in-place monitoring of individuals at all stages of the disease to alleviate the burden of care.

Beyond an army of scientists, the acceleration of the process of discovery, development, and delivery of critically needed treatment and prevention for dementia in large part depends on patient/citizen awareness and engagement. To meet the grand challenge of the National Plan to Address Alzheimer's Disease, we need to sustain and expand current efforts that focus on:

- Developing effective recruitment strategies that will lead to broad and diverse participation in clinical research
- Addressing the root of health disparities

- Engaging participants as direct partners in research

With the launch of the National Plan to Address Alzheimer’s Disease, the Nation stated its commitment to accelerate building the knowledge base and robust infrastructure for the Alzheimer’s and related dementias research enterprise. With continued, increased support, we can begin to deliver the cures that are so desperately needed by patients, their families, and society as a whole.

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