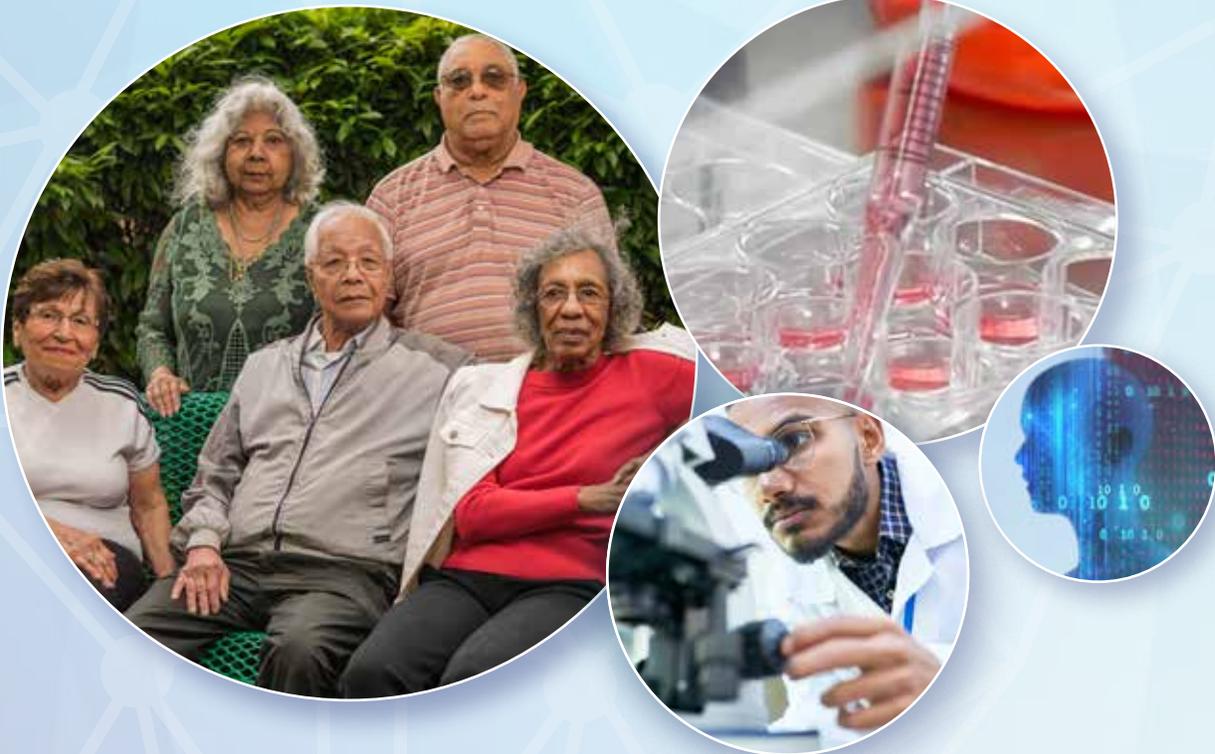


Open Science, Big Data, and You

Working Together to Treat and Prevent
Alzheimer's Disease and Related Dementias

NIH BYPASS BUDGET PROPOSAL FOR FISCAL YEAR 2020



National Institutes of Health

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OPEN SCIENCE, BIG DATA, AND YOU: WORKING TOGETHER TO TREAT AND PREVENT ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

July 30, 2018

On behalf of the National Institutes of Health (NIH), I am pleased to present our Professional Judgment Budget for Alzheimer's Disease and Related Dementias (AD/ADRD) for Fiscal Year (FY) 2020. Commonly called a Bypass Budget, this document is much more than a set of numbers. It reflects a careful and thorough analysis of completed and ongoing research, our efforts and accomplishments, and the continuing needs of everyone involved—people with Alzheimer's disease and related dementias, their caregivers, clinicians, government, academia, industry, and nonprofit organizations—to achieve the national goal of effectively treating or preventing Alzheimer's disease and related dementias by 2025.

Reflecting from the halfway mark to that 2025 goal, we recognize more clearly than ever that Alzheimer's disease and related dementias are complex and intractable foes. Yet our scientific capabilities and momentum are growing rapidly. We are closing in on the research advances that may ultimately contribute to an end to a public health crisis that has penetrated the nation and the world in a way that few other conditions have. We are seeing a remarkable assembly of—and collaboration among—many of the brightest minds in Alzheimer's research. These innovators are working on ways to rethink and reconstruct the AD/ADRD research enterprise into one that can enable the discovery and delivery of desperately needed interventions for people at all stages of the disease.

Our efforts are broad and far-reaching. We are:

- Enabling precision medicine research through advances in genomic sciences, deep molecular phenotyping of existing cohorts, and the launch of new, diverse cohorts
- Using the open-science research model of the Accelerating Medicines Partnership for Alzheimer's Disease to hasten the discovery of the next generation of therapeutic targets and biomarkers
- Creating new translational infrastructure programs to enable rapid sharing of data and research models and enhance research rigor and reproducibility
- Developing emerging therapeutics in academic centers and in the small-business community
- Making advances in disease monitoring, assessment, and care, powered by the

revolution in mobile technology, which are helping us bring in people living with AD/ADRD and their caregivers as direct partners in research

In the 3 years since our first Bypass Budget, the 6 years since our first NIH Alzheimer's Disease Research Summit, and the 6 years since the initial National Plan to Address Alzheimer's Disease, we have made unprecedented progress. The first NIH Alzheimer's Disease Research Summit set forth a blueprint for a new, transformative research agenda, which was further bolstered by the proceedings of additional summits on Alzheimer's disease research in 2015 and 2018, on Alzheimer's disease-related dementias in 2013 and 2016, and on dementia care and services research in 2017. The two most recent of these summits have provided us with nearly 100 additional recommendations to chart our course forward.

That course comes with a cost. We have built the Professional Judgment Budget estimate for FY 2020 starting with the estimated (enacted) funding level for Alzheimer's and related dementias research from FY 2018—\$1,915 million. The FY 2019 estimate for AD/ADRD spending, based on the President's budget, is \$399 million below the FY 2018 estimated (enacted) level. The FY 2020 Professional Judgment Budget includes funding to compensate for this reduction, as well as an additional increase of \$477.7 million for new research—yielding a total needed for FY 2020 of \$2,393 million. This total would represent an increase of \$876.7 million in additional funds relative to the FY 2019 President's budget proposal to keep us moving in AD/ADRD research. This Bypass Budget will be updated annually through FY 2025.

It continues to be a critical time in Alzheimer's and related dementias research. The stakes are high and growing higher. With the world desperately waiting for answers, we are uniquely positioned to keep the momentum in discovery going and to push forward not only an agenda, but concrete, specific guidance and efforts to change the times for the better for millions of affected people—and their families, friends, and communities—who need solutions.



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

INTRODUCTION

For some time, scientists have understood that Alzheimer’s disease develops by way of a complex cascade of events taking place over time inside the brain. These events, influenced by both genetic and nongenetic factors, contribute to changes in the brain that disrupt functioning and are at the center of the notorious devastation caused by Alzheimer’s disease. Our persistence in expanding research on Alzheimer’s—as well as the related dementias of Lewy body dementia, frontotemporal dementia, and vascular cognitive impairment/dementia—has helped us learn more about the sequence of detrimental events and pinpoint some of the various risk factors that play a role in disease development and progression. The pace of study has picked up considerable steam in the past several years.

The [National Institutes of Health](#) (NIH), which leads the Nation’s biomedical research on Alzheimer’s and related dementias, has led an ambitious research agenda to better understand, diagnose, prevent, and treat these diseases. Thanks to an extraordinary boost in Federal funding for research in recent years, we can now progress more quickly, connect the scientific dots more precisely, increase the opportunities for additional talent, and build new research resources. Indeed, today we can pursue the answers to fundamental questions that we couldn’t address in the not-too-distant past, such as: Why do some people show outward signs of disease, such as memory loss and cognitive decline, and others never do, despite being at higher genetic risk or despite displaying abnormal brain changes characteristic of Alzheimer’s disease?

Answering such questions is central to the ultimate success of tackling Alzheimer’s disease. Our approach reflects a “recalibration” that squarely focuses attention on the heterogeneity of disease—how Alzheimer’s and related dementias manifest differently among individuals and across groups ([Khachaturian et al., 2018](#)). Indeed, we are now better able to approach these dementias in all their complexity, which permits us to set our sights on a precision medicine approach, targeting relevant processes and delivering the right treatments at the right stage of the disease. While ultimately we want to prevent or slow Alzheimer’s disease and related dementias, we are working toward serving the needs of all patients at all stages of disease.

Much of this Fiscal Year (FY) 2020 Professional Judgment Budget discusses progress in building a national research ecosystem capable of ultimately delivering treatments to individuals at risk. It describes new tools, technologies, and approaches, from supporting the ideas of individual investigators to the collection and analyses of vast amounts of data from populations worldwide. In many cases, these advances are powered by unprecedented partnerships among

government, advocacy groups, foundations, thought leaders, and pharma, biotech, and technology companies.

Several efforts focus on fostering “open science,” an inclusive, participatory approach to research in which learning is accelerated by making data, research methods, and research tools available to all qualified researchers. Rapid and broad sharing of data and tools is particularly important in the new era of biomedical research, marked by the rise of big data and novel analytical approaches to better understand human wellness and disease in a person-specific manner.

At its core, the success of these approaches depends on broad public engagement in research, as the path to a cure—or, more accurately, cures—for Alzheimer’s and related dementias is tied directly to participation by individuals from all walks of life.

With commitment by all of us, including teams of dedicated scientists, research participants, and advocates, we have our best chance yet of success for each of us. NIH is well positioned to lead this mission. Meaningful increases in funding support have brought bold new thinking to build the transformative research agenda needed.

This report describes progress to date, new initiatives underway, and the type and cost of additional research in FY 2020 that would move us toward the national goal of effectively treating or preventing Alzheimer’s and related dementias by 2025. We have the momentum, but there is much left to do.

A Sense of Urgency

The population at risk for these mind-robbing diseases is growing. As many as 5.5 million Americans age 65 and older are estimated to be living with Alzheimer’s disease, the most common form of dementia ([Hebert et al., 2013](#)). Many more under age 65 are also affected. In addition, many thousands more have Alzheimer’s disease-related dementias. The phenomenon is worldwide. One report indicated that about 46.8 million people age 60 and older lived with dementia worldwide in 2015, a number expected to grow to 74.7 million people in 2030 and to 131.5 million in 2050 ([Prince et al., 2013](#)).

Several studies, including the long-running Framingham Heart Study, have identified declines in the incidence and prevalence of dementia since the 1970s, which scientists have associated with increases in educational attainment and better control of cardiovascular risk factors ([Wolf, 2012](#); [Knopman et al., 2015](#); [Langa et al., 2017](#)). However, if current population trends

continue, the number of people with the disease is expected to grow significantly, as age is the greatest risk factor for Alzheimer's disease.

The financial costs of dementia are staggering, for society and for individuals. Caring for people with Alzheimer's disease cost the U.S. health care and long-term care systems between \$159 billion and \$215 billion in 2010, depending on how caregiver costs were assessed. NIH-supported researchers tallied direct costs of dementia care—including costs for nursing homes, Medicare, and out-of-pocket medical expenses—at \$109 billion in 2010, which they compared with direct health care costs for heart disease and cancer of \$102 billion and \$77 billion, respectively ([Hurd et al., 2013](#)). A different study found that in the last 5 years of life, total health care spending for people with dementia was more than \$250,000 per person, about 57 percent greater than similar costs associated with other diseases, including cancer and heart disease ([Kelley et al., 2015](#)).

The Nation's Commitment Becomes Law

Alarmed by these trends, public concern about Alzheimer's and related dementias was articulated with the passage of the [National Alzheimer's Project Act](#) (NAPA). Signed into law in January 2011 to step up and intensify efforts in research and care, NAPA called for the Secretary of the Department of Health and Human Services to appoint a Federal Advisory Council on Alzheimer's Research, Care, and Services to help establish and track implementation of a [National Plan to Address Alzheimer's Disease](#). The plan, first issued in 2012 and updated every year since, plainly states an ambitious research goal—to prevent and effectively treat Alzheimer's disease and related dementias by 2025.

Since the 1970s, NIH had conducted and supported research on Alzheimer's and related dementias with an established community of scientists and advocates. When the new law required that we up the ante, NIH went to work, gathering a broad range of stakeholders to help plan and move forward with an expanded scientific effort. Now, NIH gathers input through annual national research summits, smaller workshops and scientific gatherings, and requests for information. These sources all factor into NIH's research plan for the 2025 goal, which is laid out in a series of [research implementation milestones](#). This systematic planning process has informed the research community about NIH's interests and priorities in funding projects in Alzheimer's and related dementias.

Increasing and Targeting the Investment in Research

Although NIH leadership has been committed to the study of Alzheimer’s disease—as well as the development and testing of therapies—for many decades, Congress recognized several years ago that the magnitude of this public health crisis warranted a deeper level of investment. From FY 2012 through FY 2018, the aggressive research goals outlined in NAPA were supported with major infusions of funding:

- NIH redirected funds from other programs by \$50 million in 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 appropriations—approximately \$100 million in FY 2014 and \$25 million in FY 2015—primarily directed toward Alzheimer’s and related dementias research.
- The biggest increases in funding directed at Alzheimer’s and related dementias came from Congress in the last three fiscal years. Additional appropriations in FY 2016 reached \$350 million; in FY 2017, \$400 million; and in FY 2018, \$414 million.

Overall, NIH spending on Alzheimer’s disease and related dementias research has increased by nearly \$1.4 billion since FY 2014, bringing the total FY 2018 NIH investment in these disorders to an estimated \$1.9 billion.

The funding has been applied to a broad, multidisciplinary program in which research moves through a pipeline from studies of basic mechanisms to application in clinical trials and studies. Recent boosts in funding have been directed to:

- Basic studies of the biology of these diseases, including genetics, to more deeply understand what causes pathology and what protects against it
- Translational studies that are yielding an increasing number of promising new therapeutic targets, for both pharmacologic and nondrug interventions, that address treatment and prevention. As just one example, investigators with the [Accelerated Medicines Partnership–Alzheimer’s Disease](#) (AMP-AD) have identified more than 100 potential new drug targets for Alzheimer’s and related dementias.
- Research to develop novel therapeutics. NIA’s Alzheimer’s Disease Translational Research Program supports 30 projects aimed at a variety of targets.
- Discovery and development of biomarkers to track the course of disease and test the

effectiveness of new therapies

- Data development and sharing through new infrastructure and public-private partnerships that can address key challenges in therapy development
- Clinical trials to test a range of potential therapies, featuring stepped-up efforts to involve people from underrepresented communities. NIH currently sponsors in whole or in part approximately [140 active trials](#) of interventions to enhance cognitive health in older adults and to prevent, treat, or manage Alzheimer’s and related dementias.
- Projects to spur innovation in developing better approaches to disease detection, monitoring, and assessment
- Research to support improved quality of life for people living with dementia and caregivers

Budgeting in FY 2020 to Fight Dementia

In summer 2015, NIH prepared its first-ever Professional Judgment Budget for Alzheimer’s and related dementias, as required by 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.

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. These estimated projections are unusual in that they are directly transmitted to the President and to Congress without modification, outside the traditional annual Federal budget process. Hence, this approach is often referred to as a “bypass budget.”

In this report, the Professional Judgment Budget estimates the additional funding required in FY 2020 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 several years of Alzheimer's disease and related dementias research funding, as follows: The FY 2018 estimated (enacted) funding level for this research is \$1,915 million, based on the Consolidated Appropriations Act, 2018 (P.L.115-141). The FY 2019 estimate, based on the President's budget, is \$1,516 million, or \$399 million below the FY 2018 estimated (enacted) level. The FY 2020 Professional Judgment Budget is \$2,393 million, which includes funding to compensate for the estimated FY 2019 reduction, as well as an additional increase of \$477.7 million for new research. This total would represent an increase of \$876.7 million in additional funds relative to FY 2019 to sustain momentum in Alzheimer's and related dementias research.

This estimate will enable NIH to move toward enabling precision medicine research for Alzheimer's disease and related dementias by amplifying existing efforts and building new approaches, tools, infrastructure, and partnerships necessary to deliver the desperately needed cures for people at all stages of disease. These funds will enable NIH to better understand the complex causes of Alzheimer's disease and related dementias, pursue interventions to prevent or delay disease progression, characterize early disease markers and better track responsiveness to possible treatments, and improve care and support of those living with dementia.

Inclusive Planning for and Implementation of the Expanded Research Support

Since the advent of the National Plan, NIH's planning process for research on Alzheimer's and related dementias has expanded in inclusion and scope among NIH Institutes and stakeholders across the scientific and care communities. Hearing a diversity of expertise and opinion is critical to updating research recommendations based on an open review of scientific progress. It also ensures prioritization based on important scientific questions that must be answered to advance our understanding of these complex disorders and helps identify how Federal and other public and private organizations can most effectively collaborate to address research priorities.

Ultimately, these consultations and recommendations resulted in the formation and/or update of implementation research milestones that set forth activities through FY 2025 to address the ultimate goal of the National Plan, as well as selected milestones for which additional funding is envisioned specifically in FY 2020. It is important to note that the recommendations and milestones are meant to be used by all stakeholders, not solely NIH, as a basis for individual actions or for collaborations and partnerships.

Across NIH, the Institutes confer on scientific opportunities and goals. For FY 2020 bypass budget planning, NIA, which led the overall planning effort, worked in close collaboration with OPEN SCIENCE, BIG DATA, AND YOU

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the [National Institute of Neurological Disorders and Stroke](#), joined by additional institutes, including:

- [National Heart, Lung, and Blood Institute](#)
- [National Institute on Alcohol Abuse and Alcoholism](#)
- [National Institute of Child Health and Human Development](#)
- [National Institute of Dental and Craniofacial Research](#)
- [National Institute of Diabetes and Digestive and Kidney Diseases](#)
- [National Institute of Environmental Health Sciences](#)
- [National Institute of General Medical Sciences](#)
- [National Institute of Mental Health](#)
- [National Institute of Nursing Research](#)
- [Fogarty International Center](#)
- [National Center for Advancing Translational Sciences](#)

This report covers highlights of research funded and conducted across NIH.

The NIH summit series also provides important venues for the research community and stakeholders to convene and discuss research progress and priorities. The summits began in 2012 with initial planning under NAPA and have included:

- [Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention](#)
- [Alzheimer's Disease-Related Dementias \(ADRD\): Research Challenges and Opportunities 2013 Summit](#)
- [Advancing Treatment for Alzheimer Disease in Individuals with Down Syndrome](#) in 2013
- [Alzheimer's Disease Research Summit 2015: Path to Treatment and Prevention](#)
- [Alzheimer's Disease-Related Dementias 2016 Summit](#)
- [NIH Alzheimer's Disease Research Summit 2018: Path to Treatment and Prevention](#)

New to this series was the first research summit focusing on care and services for people with dementia and their caregivers. The October 2017 [National Research Summit on Care, Services, and Supports for Persons with Dementia and their Caregivers](#) was led by the U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, in

collaboration with NIA. It was the culmination of months of outreach and discussion regionally and among varied stakeholders, including experts, caregivers, and people living with dementia, to ascertain what is known to be effective in providing care and what needs further study. The final [research recommendations](#) from the meeting and the series of accompanying reports and white papers became available in April 2018.

Beyond the summits, NIH gathers community input through formal Requests for Information, through sponsors, and through staff member attendance at workshops and conferences in the United States and globally. Program updates also are presented to the Secretary's Advisory Council for Research, Care, and Services, primarily to its Research Subcommittee, which regularly provides feedback on NIH's NAPA-related activities.

Funding Opportunities, Expanding the Pool

The majority of NIH support goes to scientists who propose research projects that are reviewed and scored for a variety of factors, including relevance to the NIH mission, strength of the project, and chances of success in answering the research question posed. NIH supports both established scientists and new investigators to encourage the best combination of expertise, experience, and new thinking needed to solve complex problems like Alzheimer's disease and related dementias.

What has become particularly important with the recent expansion in Alzheimer's funding are opportunities to guide the direction of research, based on recommendations from the summits and other input. Targeting specific research gaps or promising areas of study, more than [60 Funding Opportunity Announcements](#) are active, soliciting innovative proposals in areas that NIH is seeking to support. Research areas include health disparities, cognitive resilience, training, clinical trials, caregiving, and clinical care, as well as basic and translational research. With the steep increase in funding in a relatively short period of time, NIH has been carefully monitoring the capacity of the scientific community to offer even more high-quality research proposals to match. NIA's analysis demonstrated an overall increase in the number of applications received in response to Alzheimer's disease and related dementias funding opportunities, with a high proportion of these applications scored as highly meritorious by peer review. Importantly, many of these applications are from new and early-stage investigators as well as experienced researchers who are new to the field of Alzheimer's and related dementias research.

Much of the research proposed depends on engagement by broad segments of the public. In 2017 NIA, with facilitation by the Alzheimer's Association, convened stakeholders to develop a national strategy to engage and maintain public participation in clinical research, with a focus

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on inclusion of people underrepresented in research and healthy individuals who may be at risk. The Institute convened teams of experts to draft ideas and has reached out through crowdsourcing and other venues to hear from study volunteers, caregivers, clinicians and other providers, public agencies, funders, and the scientific community. The strategy, to be implemented by both the public and private sectors, will be finalized in summer 2018.

Navigating This Bypass Budget

This bypass budget proposal outlines the additional funding needed in FY 2020 to advance NIH-supported research on Alzheimer’s and related dementias toward the 2025 research goal for treatment or prevention. 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 reflects a subset of Alzheimer’s disease and related dementias research milestones that could be started or accelerated in FY 2019, upon which the current bypass budget estimates are based.

Together, We Make the Difference

Alzheimer’s disease and related dementias affect millions of people and their families. While a handful of drugs currently help treat some symptoms for a limited time, we have not yet found a cure. But we are closer than ever. Advances in science and technology, along with increased financial support, have helped researchers better understand these diseases and identify potential ways to prevent and delay them. Thanks to 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—have identified promising pathways to effective therapies. Together, we make the difference.

FISCAL YEAR 2020 PROFESSIONAL JUDGMENT BUDGET: ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Baseline Estimate, President's Budget, Fiscal Year 2019

Alzheimer's Disease, Including Alzheimer's Disease-Related Dementias

(AD/ADRD)*

\$1,516,000,000

Professional Judgment Budget FY 2020 *Additional* Resources Needed

Molecular Pathogenesis and Pathophysiology of Alzheimer's Disease	\$82,000,000
Diagnosis, Assessment, and Disease Monitoring	\$24,000,000
Translational Research and Clinical Interventions	\$138,000,000
Epidemiology	\$51,000,000
Care and Caregiver Support	\$26,215,000
Research Resources	\$107,100,000
Alzheimer's Disease-Related Dementias	\$45,687,500
Staffing Needs and Administrative Support	\$3,710,000
ADDITIONAL FY 2020 Resources Needed for New AD/ADRD Research	\$477,712,500

Professional Judgment Budget FY 2020 *Total* Resources Needed

FY 2019 President's Budget Request for AD/ADRD Research (baseline estimate)	\$1,516,000,000
Difference Between FY 2019 President's Budget Request and FY 2018 Omnibus Appropriation for AD/ADRD Research**	\$399,000,000
ADDITIONAL FY 2020 Resources Needed for New AD/ADRD Research	\$477,712,500
TOTAL FY 2020 Resources Needed for AD/ADRD Research	\$2,392,712,500

*Baseline estimate includes Alzheimer's disease, frontotemporal dementia, Lewy body dementia, and vascular cognitive impairment/dementia. Individual disease baseline estimates are available on the NIH Categorical Spending website at https://report.nih.gov/categorical_spending.aspx.

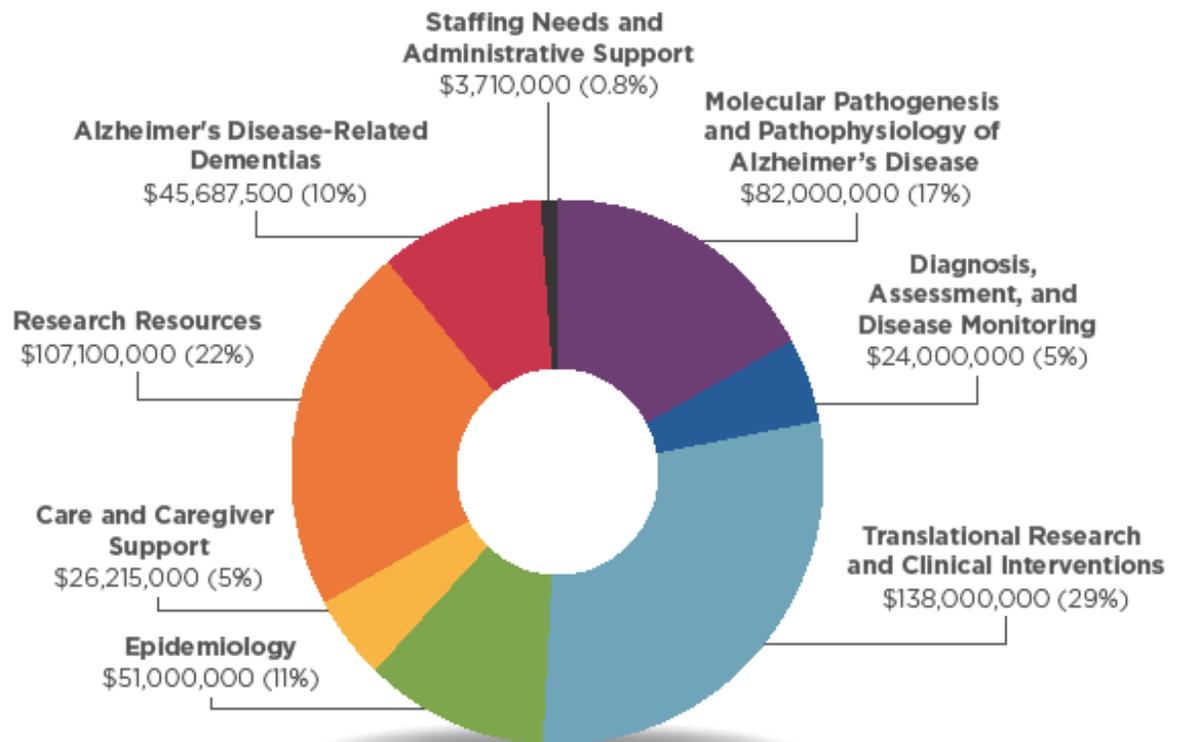
**Estimated (enacted) \$1.915 billion (AD/ADRD research funding from the Consolidated Appropriations Act, 2018) – estimated \$1.516 billion (AD/ADRD research funding from the FY 2019 President's budget) = \$399 million.

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Distribution of Additional Budget Funding Across Research Areas, FY 2020

TOTAL: \$477,712,500



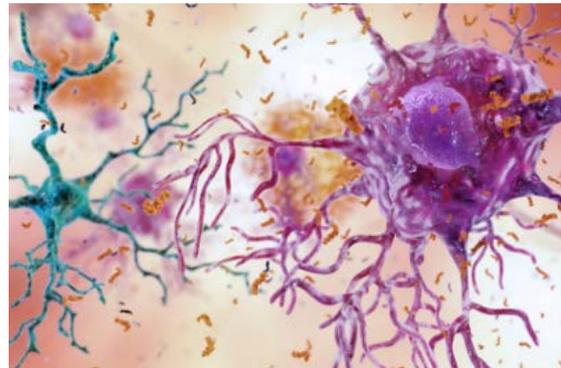
THE ROAD TO TREATMENT AND PREVENTION OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

In this narrative for the Fiscal Year (FY) 2020 Professional Judgment Budget for Alzheimer's Disease and Related Dementias, we highlight several key areas, 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 disease, as well as to improve care and services.

The programs featured below span the spectrum of research, from basic discovery science to emerging therapeutics and predictive drug development and improvements in the care and quality of life for people with dementia and their caregivers. They bring forward cutting-edge technologies, innovations in open-data and team-science approaches, development of research tools, and new infrastructure for translational and clinical research.

New Insights into the Complex Biology of Alzheimer's Disease

With a better understanding of the growing list of genetic risk factors and molecular pathways that are involved in Alzheimer's disease and related dementias, National Institutes of Health (NIH)-supported researchers are developing a new generation of research tools to identify, explore, and validate a variety of targets with therapeutic potential. These sophisticated tools allow researchers to collect and integrate layers of biological data in novel ways—opening the door to new insights into the origins and progression of Alzheimer's disease and related dementias.



These new tools are helping researchers gain a clearer picture of the complex underlying mechanisms of these devastating neurological disorders. They are leading to an understanding of the interplay among relevant molecules and systems, the relationship between amyloid and tau proteins, the role of immunity and inflammation, and the involvement of metabolic and cardiovascular pathways. This broad view of the basic biology of Alzheimer's and related dementias could lead to potential breakthrough therapies.

Clearer Pictures, Better Models of Amyloid and Tau

Imaging the details of beta-amyloid and tau

Beta-amyloid and tau are proteins that, when they abnormally accumulate in and between nerve cells, become toxic and damage brain connections. The aggregates of beta-amyloid form plaques, while aggregates of tau form tangles; together, these aggregates represent the main pathological hallmarks of Alzheimer's disease. Researchers can now image these two biomarkers in the brains of living humans using positron emission tomography years before memory loss and other symptoms appear, opening an opportunity for early intervention. NIH-supported scientists are making big strides to better understand their structure and interplay, which could lead to the development of better imaging agents and therapies.

In a major step forward for Alzheimer's research, scientists for the first time imaged tau fibrils at the atomic level, providing a new, high-resolution view of the tau protein structures ([Fitzpatrick et al., 2017](#)). Using a technique called cryo-electron microscopy, or cryo-EM—whose inventors won the 2017 Nobel Prize in Chemistry—researchers were able to see stacks of paired, mirror-image, C-shaped tau filaments. These high-resolution structural images of tau aid the understanding of its role in the progression of Alzheimer's and some related dementias, with potential to explore possible new therapies.

Another NIH-supported research team ([Qiang et al., 2017](#)) used one of the most powerful microscopic viewing technologies available, solid-state nuclear magnetic resonance, to study the many shapes and structures of beta-amyloid and how they might contribute to variations in clinical or pathological characteristics of neurodegenerative diseases. The team found relatively simple structural fingerprints for both typical Alzheimer's disease and a variant called posterior cortical atrophy. However, a third, rapidly progressive variant of Alzheimer's showed a much more complicated structure and patterns. This work could eventually lead to new imaging tools, with the potential to reveal progression of the disease in living humans.

Seeing tau more accurately in mice

Researchers have long sought mouse models of Alzheimer's that more realistically mimic the human version of the disease to provide greater predictive power when testing candidate therapeutics. A scientific team ([Narasimhan et al., 2017](#)) has moved closer to this goal with a model that more accurately displays different forms of the tau protein and its key interactions with beta-amyloid.

The team developed techniques that allowed them to successfully seed different types of tau from post mortem human brain tissue, including Alzheimer's brain tissue, into transgenic mice.

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The disease pathology in the seeded mouse brains mirrored the distinct patterns seen in human disease. The team was also able to reproduce and see clearly in mice the spatial location and forms of three major types of tau found in human neurodegenerative diseases.

This process of seeding and modeling Alzheimer's disease structure in mice brains requires refinement, and scientists have not yet evaluated the mice for memory and cognition. If future projects succeed, truly innovative mouse models of human disease could be on the horizon.

Microglia, Astrocytes, Oligodendrocytes, and Alzheimer's Disease

Recent innovative studies have helped researchers better comprehend the important role of specialized brain cells—microglia, astrocytes, and oligodendrocytes—in Alzheimer's disease. Malfunctions of microglia, the central nervous system's primary immune cells, have emerged as key players in the disease. Microglia act as “housekeepers” in the central nervous system by constantly scavenging for damaged neurons, plaques, and infectious agents. Astrocytes, a star-shaped form of the glial cells that support neurons and help maintain synaptic function, are among the most numerous cells in the brain, but their role in Alzheimer's is poorly understood. Oligodendrocytes are glial cells that produce myelin, an insulating layer that forms around nerves.

First gene expression library for aged human microglia

To better understand how microglia can malfunction with advancing age, NIH-funded scientists looked at gene expression patterns in microglia isolated from post mortem tissue from aged human brains ([Olah et al., 2018](#)). Researchers found that the gene expression signature of the aged microglia contained more genes linked to Alzheimer's disease and multiple sclerosis, but not to other neurodegenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), or schizophrenia. These age-related changes in microglial gene expression associated with Alzheimer's were reduced in people carrying the ApoE2 allele, which may have a protective effect against Alzheimer's disease. This library of gene expression data will be a valuable resource for scientists exploring the role of microglia in brain disease.

Discovery of Alzheimer's risk genes associated with microglia

Studies have uncovered more than two dozen genes associated with susceptibility to Alzheimer's disease, but scientists believe there are dozens more to be found due to the high heritability (up to 80 percent) of Alzheimer's disease ([Raghavan and Tosto, 2017](#)). Heritability of Alzheimer's disease is the estimated proportion of the impact that genes, compared with the environment and random chance, have on the risk of developing the disease. These high-

heritability genes are likely to be relatively rare, and tracking them down will require new approaches.

NIH-funded researchers have identified rare coding variants in the exome—the portion of the genome that directly encodes protein—that are associated with Alzheimer’s disease ([Sims et al., 2017](#)). Using samples from approximately 85,000 people, researchers found three new gene variants associated with Alzheimer’s: a protective variant in *PLCG2*, a risk variant in *ABI3*, and a novel variant in the known Alzheimer’s susceptibility gene *TREM2*. These newly discovered variants are in genes highly expressed in microglia and provide strong evidence that the microglial-mediated immune response contributes directly to the development of Alzheimer’s.

APOE-TREM2 interaction in microglia

Several important clues about the role of microglia in Alzheimer’s have been revealed. In identifying the molecular signatures of microglia from other cell types in the brain, researchers also identified a critical role of transforming growth factor-beta 1 in the microglia development and in maintaining a healthy brain ([Butovsky et al., 2014](#)). Recently, human geneticists supported by NIH identified genetic signatures of microglia in amyotrophic lateral sclerosis (ALS), multiple sclerosis, and Alzheimer’s and noted the role of APOE in the disease state ([Krasemann et al., 2017](#)). They found that in the disease state, microglia increased APOE expression and TREM2 signaling, while low APOE expression was noted in the nondisease (normal) state. A focus on the APOE-TREM2 pathway could pave the way for the development of therapies for neurodegenerative disorders.

Researchers have recently identified a role for caspase genes in the control of microglial cell activation. Using targeted sequencing, researchers were able to confirm the presence of genetic variants of caspase 8 and caspase 3 in Alzheimer’s disease ([Rehker et al., 2017](#)). Caspase 8 plays essential roles in apoptosis, inflammation, and cellular differentiation. Caspase 3 is a downstream effector of caspase 8. Investigators found that exacerbation of this caspase-signaling pathway was associated with neurotoxicity and that caspase 8 and caspase 3 were activated in microglia in the frontal cortex of individuals with Alzheimer’s, providing further mechanistic evidence for the involvement of genes related to microglia in the disease.

Another research team ([Ofengeim et al., 2017](#)) looked at the role of *RIPK1*, a gene that encodes part of the receptor-interacting protein family linked to inflammation and cell death, and its impact on microglia in Alzheimer’s disease. Using an Alzheimer’s disease mouse model that expressed high levels of APP/PS1, they showed that inhibition of *RIPK1* reduced amyloid, inflammation markers, and memory deficits. This result suggests that *RIPK1*, through its action on microglia, may potentially be a therapeutic target for Alzheimer’s.

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Advances in understanding astrocytes' role in neurodegenerative disorders

An international research team ([Liddelow et al., 2017](#)) is tracking how a subtype of reactive astrocytes they termed A1, which are numerous in neurodegenerative diseases like Alzheimer's, Huntington's and Parkinson's disease, ALS, and multiple sclerosis, is affected by neuroinflammatory microglia.

The team found that in cases of brain injury or disease, activated microglia caused A1 astrocytes to lose the ability to promote neuronal survival, outgrowth, and maintenance. The astrocytes caused the death of neurons and oligodendrocytes. Conversely, blocking the formation of A1 astrocytes prevented neuronal death. These findings help explain how A1 astrocytes contribute to neurodegenerative disorders.

In another study, scientists found a new addition to the list of astrocytes' many protective functions: helping to clear beta-amyloid from the brain ([Liu CC et al., 2017](#)). The researchers knocked out lipoprotein receptor-related protein (LRP1), a key cell-surface receptor for beta-amyloid, in mouse astrocytes in vitro and in vivo. Cultured astrocytes lacking LRP1 were impaired in their ability to take up and degrade beta-amyloid. In Alzheimer's model mice, the loss of astrocytic LRP1 impaired brain beta-amyloid clearance and accelerated amyloid plaque deposition.

Oligodendrocytes implicated in neurodegenerative disease

Studies looking at gene expression networks in the brain have implicated oligodendrocyte dysfunction in Alzheimer's disease and other neurodegenerative diseases. NIH-funded researchers looked at oligodendrocyte gene expression networks in post mortem brain samples from a large group of people with Alzheimer's disease ([McKenzie et al., 2017](#)). Among these networks, the researchers found a cluster rich in genes previously linked to Alzheimer's disease. The researchers then focused on one of the genes in this cluster, *CNP*, and showed that this gene, which produces an enzyme important in RNA metabolism and in assembly of microtubule or cytoskeletal filament, when removed in mouse models caused changes in oligodendrocyte gene expression patterns similar to those seen in human Alzheimer's disease. Understanding changes in gene expression in oligodendrocytes in Alzheimer's may lead to targeted therapeutics in these cells.

Rediscovering Myelin: From Genetics to Molecular Mechanisms

Powerful technologies are allowing new, more detailed insights to well-studied neurological mechanisms. In the case of myelin—the fatty sheath that insulates axons (structures that

transmit signals from one cell to another) and helps speed electrical signaling in the brain—researchers ([Allen et al., 2018](#)) have compared certain pathways between Alzheimer’s disease and progressive supranuclear palsy (PSP), a disease related to Parkinson’s that involves abnormalities of the tau protein, but with minimal cognitive impairment.

Researchers looked at an area of the brain that is relatively unaffected in PSP but shows damage in Alzheimer’s disease. They found that expressions of genetic networks that control myelin were lower in PSP compared with Alzheimer’s. The findings point to new ways of thinking about myelin, its involvement in the disease process, and its potential as a therapeutic target for neurodegenerative diseases.

Revealing a Common Mechanism of Neurodegeneration

Another emerging area of interest involves RNA-binding proteins (RBPs) and their unique role in the protein misfolding associated with Alzheimer’s and other neurodegenerative diseases. RBPs are important to the functioning of messenger RNA (a large family of RNA molecules that convey genetic information within a cell and is important in protein synthesis).

In stress, RBPs linked to messenger RNA form stress granules, which function to suppress production of nonessential proteins in favor of protective stress-response proteins. Mutations in the gene that encodes a class of RBP were reported in the heritable motor neuron diseases ALS and frontotemporal lobar dementia, suggesting that certain neurological diseases may have a common genetic basis ([Maziuk et al., 2017](#)).

In investigating RBP in stress granules of Alzheimer’s, a team of NIH-supported researchers reported the presence of TIA-1 (T-cell intracellular antigen 1) and found that TIA-1 and tau reciprocally affect each other, that is, tau facilitates assembly of stress granules, and TIA-1 facilitates assembly of phosphorylated tau ([Vanderweyde et al., 2016](#)). In a follow-up study, the same team ([Apicco et al., 2018](#)) showed that reducing TIA-1 expression by half in a mouse model carrying a mutant form of tau decreased stress granules and inhibited accumulation of tau oligomer (at the expense of increased tangles), with a corresponding increase in neuronal survival, reduced behavioral deficits, and increased lifespan.

Seeking Biomarkers for the Fog of Delirium

Delirium is an acute change in mental state characterized by inattention and confusion that may be accompanied by agitation and/or hallucinations. Delirium is both common and debilitating, affecting as much as 50 percent of older adults in the hospital ([Inouye et al., 2014](#)) and other settings. Delirium is also a risk factor for long-term cognitive decline and dementia, and people with dementia are at higher risk for delirium ([Fong et al., 2015](#)).

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An NIH-supported research team ([Dillon et al., 2017](#)) recently explored novel biomarkers for delirium. This study identified elevated pre- and post-surgical plasma levels of C-reactive protein, a common biomarker for inflammation and infection. The investigators suggest that preoperative C-reactive protein levels may help identify people at risk for delirium prior to surgery, and that postoperative C-reactive protein levels may provide a way to monitor the course of delirium.

Enabling Precision Medicine for Alzheimer's Disease

The goal of precision medicine is to develop interventions that address the underlying process and symptoms of a disease in a way that is tailored to a person's unique disease-risk profile. As studies uncover the variety of genetic, biological, and clinical combinations at play in Alzheimer's disease and related dementias, precision medicine for these conditions may eventually resemble the modern model of cancer treatment, which recognizes many different subtypes of disease, each with a highly person-specific, unique fingerprint.



Diversity Is Key to Broader Understanding

The most common causes of dementia and cognitive impairment are believed to involve a combination of neuropathies, with incredibly diverse variations in pathology. Underscoring this diversity, an NIH-supported research team ([Boyle et al., 2018](#)) recently found nearly 250 unique combinations of neuropathologies in the brains of more than 1,000 older people who had taken detailed cognitive tests annually for many years prior to their deaths. The study also found that the degree to which Alzheimer's neuropathologies contributed to cognitive changes varied greatly from person to person, and the impact of any given neuropathology differed dramatically depending on the other neuropathologies present. This finding presents many new opportunities but also heightens the challenges for developing interventions for complex diseases.

The success of a precision medicine approach depends not only on an understanding of the neuropathological complexity of disease, but also on many other variables, including gender, race, and ethnicity, as well as lifestyle and environmental influences such as education and exercise. For example, important differences in how Alzheimer's disease affects men and

women are gaining new attention ([Li and Singh, 2014](#)). And scientists are particularly interested in connecting with African-American and other populations underrepresented in Alzheimer's research, so everyone can benefit from the exploration of new data that can quickly reveal differences and commonalities in how these diseases affect different populations.

NIH is pursuing research to address these issues through many efforts. One multifaceted study looked at Alzheimer's impact on different racial groups through the lens of differences in educational background, life events, environmental exposures, and geography. Tapping into 14 years of electronic health records data from members of a Northern California health system, a research team ([Mayeda et al., 2017](#)) conducted one of the largest, longest studies to date of racial and ethnic differences in dementia rates and impact. Their recent findings include:

- Higher dementia risk and lower survival rates than expected among Native Americans, compared to five other ethnic groups, whose experience with Alzheimer's disease has not been well studied
- Longer postdiagnosis survival among minorities compared with whites, which persisted after adjusting for other health conditions
- A parallel between racial/ethnic mortality inequalities in people with dementia and mortality inequalities in people without dementia

In a separate effort, researchers ([Gilsanz, Mayeda, Glymour, Quesenberry, Whitmer, 2017](#)) analyzed nearly 20 years of electronic health record data for people diagnosed with dementia. Scientists cross-referenced for birthplace, education, midlife cardiovascular risk factors, and race.

They found that being born in a Stroke Belt state, a part of the South where rates of strokes and cardiovascular disease are heightened, was associated with an overall 28 percent higher risk of dementia, compared with those born outside that region.

In another study, an NIH-supported research team ([Gilsanz, Mayeda, Glymour, Quesenberry, Mungas et al., 2017](#)) tracked early- and mid-adulthood hypertension with dementia outcomes in men and women. They uncovered profound differences in the connection between hypertension and increased dementia risk among women but not men. Onset of hypertension in middle age predicted a 73 percent higher dementia risk in women, with no evidence that hypertension or changes in hypertension increased dementia risk among men.

Through ongoing and future studies, researchers will continue to look at different racial and ethnic groups to better understand differences in rates of dementia and cognitive decline.

These are just some of the differences to be considered in a precision medicine approach to treating and preventing Alzheimer's and related dementias.

Super-Sized Sequencing

Another piece in the growing toolkit of precision medicine for Alzheimer's disease and related dementias is the [Alzheimer's Disease Sequencing Project](#) (ADSP), an international resource of genetics data from multiple centers and studies. Launched in 2012, the ADSP is designed to promote innovative collaboration among scientists to provide genetic samples for sequencing, with the goal of identifying from multiethnic populations new genetic variants that influence risk and protection from Alzheimer's. With more than 100 investigators in the United States and Europe, the ADSP works to process, harmonize, and analyze a vast array of genomics data for Alzheimer's and related dementias and to provide it in a centralized database for the entire dementia research community to use. Several NIH-funded projects—including the Alzheimer's Disease Centers, the National Alzheimer's Coordinating Center, the National Cell Repository for Alzheimer's Disease, the Genome Center for Alzheimer's Disease, and the NIA Genetics of Alzheimer's Disease Data Storage Site—contribute data to the ADSP.

Types of Genetic Studies

Several types of genetic studies are being used to analyze the human genome.

Genome-Wide Association Studies

A genome-wide association study (GWAS) is an analysis of a genome-wide set of genetic variants in different individuals to see if a variant is associated with a particular trait or disease. GWAS compares the DNA of study participants having a disease (cases) to similar people without the disease (controls). GWAS point to regions of the genome called “loci” where single nucleotide polymorphisms are associated with a disease. GWAS does not necessarily identify the specific gene of interest, but rather indicates that this general region of the genome is associated with the disease. To identify the specific gene of interest, additional methods are needed.

Next-Generation Sequencing

DNA sequencing is the process of determining the precise order of nucleotides within a DNA molecule. Knowledge of DNA sequences is being applied in numerous fields such as medical diagnosis, personalized medicine, and analysis of biological systems. The advent of rapid DNA sequencing methods has greatly accelerated research on Alzheimer’s disease and related dementias. This information will help researchers pinpoint genetic targets that may lead to new therapeutic approaches for the disease.

Whole exome sequencing is a type of next-generation sequencing that sequences all of the protein-coding genes in a genome (known as the exome). The goal of this approach is to identify genetic variants that alter protein sequences. To do this, researchers select the subset of DNA that encodes proteins (exons). The exome constitutes about 1 percent of the human genome (about 30 million base pairs). This 1 percent of the DNA is then sequenced using a high-throughput DNA sequencing technology. Whole exome sequencing has been applied to studies of polygenic diseases such as Alzheimer’s disease. To date the ADSP has generated 11,000 whole exomes; data analysis is well underway.

Whole genome sequencing (WGS) is the process of determining the entire DNA sequence of a person’s genome at a single time. Markedly reduced costs and increased speed of sequencing have been instrumental in identifying complete DNA sequences of subjects affected by Alzheimer’s disease and related dementias. WGS is a powerful research tool. In the future, WGS will be an important tool to guide physicians to therapeutic intervention. It is projected that by 2020 the ADSP will have generated more than 20,000 whole genomes from Alzheimer’s cases and controls from several ethnic populations.

Some recent advances include:

- The ADSP team recently began a study of the genetic variations that influence late-onset Alzheimer’s disease (LOAD), in which symptoms occur in a person’s mid-60s, 70s, and 80s. Seeking a better understanding of the heritability of LOAD, the team is initiating a whole-genome sequencing (WGS) family-based study and a whole-exome sequencing case-control study that should yield new insights into genetic variants associated with LOAD risk ([Beecham et al., 2017](#)).
- A team of ADSP researchers ([Vardarajan et al., 2018](#)) using WGS data from Caribbean Hispanic families with many affected family members recently identified rare genetic variants and mutations associated with LOAD. These were: *AKAP 9* (A kinase anchor proteins), *MYRF* (myelin gene regulatory factor), and *ASRGL1* (asparaginase-like protein 1). The protein products of genes have been shown to be involved in cell signaling, and nerve synapse and memory function (*AKAP9*), in myelination (*MYRF*), and in protein misfolding (*ASPGL1*).
- The team also identified rare variants in a number of genes associated with LOAD that were previously reported in genome-wide association studies (GWAS). These include *CR1*, *BIN1*, and *SLC24A4*. The protein products of *CR1* are involved in immune response; *BIN1*, in endocytosis and trafficking in neurons, and immune response in glia cells; and *SLC24A4*, in regulating blood pressure. Further studies of these genes and their function may provide leads to new targets for therapy or prevention in Alzheimer’s.
- An allele is a variant form of a given [gene](#). In a recent genome-wide survival analysis, a protective allele in the gene *SPI1* was recently found to be associated with decreased expression of certain Alzheimer’s risk genes (*CD33*, *MS4A4A*, *TYROP*, and *PILRB*) ([Huang et al., 2017](#)). *SPI1* encodes a factor, PU.1, that is critical for microglial function. The PU.1 region of the genome turns the *SPI1* gene on and off. Lower *SPI1* expression reduces Alzheimer’s disease risk by regulating microglial gene expression and cell function. This implicates PU.1 as an important genetic factor that may lead us to a therapeutic target for the disease.

Genetic Hubs: More Than Gene Discovery

Using a combination of GWAS and advanced genome sequencing approaches, a number of Alzheimer’s disease genetic “hubs” have begun to emerge ([Naj and Schellenberg, 2017](#)). Hubs include the well-known amyloid precursor processing pathway and the less understood genetic and genomic events associated with cholesterol metabolism ([Dong et al., 2017](#)), neuroinflammation and cellular immunity ([Huang et al., 2017](#)), and endocytosis (cellular

transportation of molecules) pathways ([Small et al., 2017](#)). Some genes are observed in more than one pathway, leaving open the possibility that individuals with multiple affected pathways may be more vulnerable to the pathophysiology associated with Alzheimer's. This knowledge may provide an avenue to identify highly targeted therapeutic approaches for Alzheimer's and related dementias.

ADSP Follow-Up Study

In 2017, NIH launched the ADSP Follow-Up Study, which aims to pursue rare variants in a range of different populations, including those that have been underrepresented in sequencing studies. Leveraging the existing infrastructure of the ADSP, the Follow-Up Study aims to generate whole genome sequence data in African-American, Hispanic, Native American, and Asian populations.

It is anticipated that by 2020 the ADSP will have at least 20,000 whole genomes and 11,000 whole exomes for analysis. These data, when analyzed with existing datasets, will enhance the ability to uncover the genetic underpinnings of Alzheimer's and related dementias, furthering our understanding of rare risk and protective variants.

Accelerating Precision Medicine Research Through Open Science

[Accelerating Medicines Partnership–Alzheimer's Disease \(AMP-AD\)](#) is leading the way toward precision medicine for Alzheimer's disease through open science. AMP-AD is an NIH-supported, precompetitive partnership among government, industry, and nonprofit organizations that focuses on discovering novel, clinically relevant therapeutic targets and on developing biomarkers to help validate existing therapeutic targets. The program brings together geneticists, epidemiologists, biologists, data scientists, and drug discovery experts across many academic institutions and four pharmaceutical industry organizations. To date the members of the AMP-AD target discovery consortium have:

- Established a centralized data resource, the [AMP-AD Knowledge Portal](#), that allows researchers at large to tap into the vast data resources generated by the AMP-AD teams
- Delivered an array of human omic datasets using samples from many NIH-supported brain banks and clinical cohorts
- Developed network models of disease pathways
- Discovered more than 100 novel candidate targets that are currently being prioritized in collaboration with industry partners

The [Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease, or M²OVE-AD Consortium](#), launched in 2016, 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. The M²OVE-AD Consortium brings together scientists from diverse fields to work as teams to dissect the complex molecular mechanisms by which vascular risk factors influence Alzheimer's disease and identify new targets for treatment and prevention.

M²OVE-AD currently has nine projects in which scientists are generating several layers of molecular data from brain tissue donated by deceased Alzheimer's research participants and from blood cells and plasma donated by living study participants with various types of vascular risk. They will then develop mathematical models of the molecular processes that link vascular risk factors to Alzheimer's onset and progression by combining molecular data with data on cognition, brain imaging, and several measures of vascular health. In parallel, the teams will use animal models that show different vascular disease traits to tease out the molecular mechanisms linking vascular risk factors and Alzheimer's and to test the predictions made from the analyses of the human data.

One of the key questions being addressed by the M²OVE-AD Consortium is the role that ApoE and sex differences play at the molecular level in the disease process. Researchers hope that understanding these differences can be used to identify biomarkers specific to different subtypes of the disease, which would allow participants in future clinical trials to be treated with targeted therapies tailored to their specific risk factors.

All of Us Research Program

[All of Us](#) is a historic effort to gather data from 1 million or more people living in the United States to accelerate research and improve health. By taking into account individual differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine. To enable precision medicine research that delivers targeted therapies for Alzheimer's, NIH is fostering a new ecosystem of research that is open and participatory and that takes advantage of cutting-edge advances in technology. At both the recent [Research Summit on Dementia Care](#) and the [Alzheimer's Disease Research Summit](#), attendees emphasized the importance of an open research ecosystem that allows a wider range of researchers to ride a wave of technological advances to improve the health and wellness of all.

Understanding Resilience and Resistance to Disease

To date, the pursuit of disease-modifying therapy development for Alzheimer's disease has been primarily informed by the study of people with the disease, often by comparing genomic and other molecular, cellular, and physiologic features in people with and without Alzheimer's disease. This has proven extremely challenging given the disease's complexity. There is a growing appreciation that the development of effective treatment and prevention for complex diseases such as Alzheimer's disease can benefit from a much deeper understanding of what it means to be well and which genomic, epigenomic, environmental, social, and behavioral factors promote wellness and protection against disease. However, it is becoming clear that we need to go beyond genetics in identifying the dynamic interaction of a host of factors that offer protection from and resilience to disease. Scientists are working to understand why some people, despite having underlying Alzheimer's pathology in their brains, show remarkable physical or cognitive resilience. A better understanding of these outliers could provide a potential treasure trove of information that may lead to better prevention strategies.

The Resilience-Alzheimer's Disease Consortium is a new program, launched in 2017, bringing together six multidisciplinary and multi-institutional teams aiming to address the question: Why and how do some individuals remain dementia-free despite being at high genetic or biomarker risk of Alzheimer's? The program aims to generate deeper understanding of the mechanisms by which gene-environment interactions lead to cognitively resilient phenotypes in the presence of high risk for disease and identify new therapeutic targets amenable to pharmacologic and nonpharmacologic prevention strategies.

Consortium members are generating dense molecular profiling data (genomic, proteomic, metabolomic) using existing or newly collected biosamples from the rare individuals who resist/escape Alzheimer's despite having high genetic risk (including $\epsilon 4$ homozygous carriers, centenarians, and individuals with Alzheimer's pathology). They will apply network biology modeling and harness data from resilient mouse strains, as well as data collected in individual brain cells from resilient individuals, to understand resilience mechanisms from population levels to the cellular level.

- One of the teams in the Resilience Consortium is studying the genetics of some of the most resilient outliers: centenarians. In 670 Ashkenazi Jewish centenarians (chosen for their genetic homogeneity, not longevity) and their families, the researchers found that these older adults have a surprising number of genetic mutations, many of which, such as certain APOE genotypes, should have increased their risk for dementia and/or death at a much younger age. The researchers are also looking at mutations in specific

biological pathways that seem to protect against aging and cognitive impairment. A second, longitudinal study is recruiting about 1,400 people, half of them the children of centenarians, to examine the effects of genetics and genetic expression as participants age.

- Another team supported by this program is using innovative imaging techniques to explore phenotypic molecular or pathological features associated with resilience and cognitive impairment. The team studied 400 patients, including some with and some without Alzheimer's neuropathology. They focused on individuals who had minimal cognitive defects at death but showed neuropathology in post mortem examination of brain tissue. Using a molecular imaging technology called multiplex ion beam imaging, they examined both anatomical and cellular features, even to the synaptic level of resolution. This new frontier in imaging technology also brings new complexities in layers of data. With advanced computational analyses, including machine learning, the team will be able to generate unique insights in the mechanisms of cellular resilience.

Understanding the Impact of Sex Differences in Alzheimer's

Almost two-thirds of Americans diagnosed with Alzheimer's disease are women. The usual explanation for this disparate impact—that age is the biggest risk factor for Alzheimer's, and women live longer than men—is being enriched by new research showing biological differences between men and women that may affect Alzheimer's risk and progression.

Sex differences in the risk of Alzheimer's, vulnerability to ApoE genetic load, and severity of Alzheimer's pathology burden have been well established. It is also well known that sex differences exist for many of the physiologic states and comorbid conditions known to be risk factors for Alzheimer's disease, including inflammation, obesity, and cardiovascular disease. In addition, multiple genes in the molecular pathways involved in Alzheimer's disease, such as brain bioenergetics, are located on the X chromosome. Animal studies have pointed to some protective effects of estrogen and other sex steroids; however, evidence from clinical trials is lacking. In addition, fundamental understanding of the mechanisms by which sex differences impact how Alzheimer's disease presents among individuals and specific populations, and how sex differences affect responsiveness to pharmacologic and nonpharmacologic interventions, is lacking.

To fill this critical knowledge gap, NIH launched a new funding initiative to support cross-disciplinary research programs that will employ integrative, experimental, and analytical approaches and engage basic and translational/clinical research to elucidate:

- The molecular mechanisms underlying sex differences in brain bioenergetics, blood-brain barrier and neurovascular unit function, myelin integrity, synaptic plasticity, and neural circuits integrity as they relate to the transition from healthy to pathological brain aging and neurodegeneration
- Molecular mechanisms by which sex differences influence the vulnerability to metabolic, vascular, and inflammatory risk factors
- The impact of sex differences on the trajectories of brain aging and on the molecular determinants of Alzheimer's risk and progression across diverse ethnic groups
- Molecular mechanisms by which hormonal transition states, such as perimenopause, menopause, and andropause, influence the heterogeneity of Alzheimer's risk and progression
- Molecular determinants of sex differences in responsiveness to pharmacologic and nonpharmacologic treatment

The central goal of this 3-year initiative is to develop a robust research program by supporting cross-disciplinary teams that will explore how genes, the environment, and sex-hormonal status interact at various levels of biological complexity (cell, tissue, organs/organ systems, and populations) to produce heterogeneous phenotypes of disease risk and responsiveness to therapy in Alzheimer's and related dementias. This knowledge is critically needed to enable precision medicine research.

Lessons from Special Populations: Down Syndrome and Early-Onset Alzheimer's

Many, but not all, people with Down syndrome develop brain changes associated with Alzheimer's disease by age 40, and a high percentage of them go on to develop dementia. To better understand the link between Down syndrome and Alzheimer's disease, NIH has launched the Alzheimer's Biomarkers Consortium of Down Syndrome. The consortium focuses on better understanding the risk factors for Alzheimer's in adults with Down syndrome using brain imaging, genetic analyses, and biochemical biomarkers. Using this mosaic of data, the consortium will compare data for control and high-risk populations to find common threads of risk and resilience for further study.

Learning from Early-Onset Alzheimer's and Genetics

Researchers are also working to better understand early-onset Alzheimer's disease, which often begins when people are in the prime of life, between age 40 and 50. Early-onset Alzheimer's is very aggressive, with a faster rate of progression compared to the more common late-onset

type. Overall, early-onset Alzheimer's disease provides a model for genetics and genetic expression, and several NIH-funded whole genome sequencing studies are underway. These studies have already revealed that early-onset Alzheimer's is associated with gene variants known to disrupt intracellular transport functioning. This disruption may alter the way amyloid precursor protein is handled by the cell ([Kunkle et al., 2017](#)). Data from these studies supports a role for cell trafficking in the etiology of the disease.

NIH-supported scientists have recently embarked on the Longitudinal Early-Onset Alzheimer's Disease Study, or LEADS, a 15-site study in the United States. LEADS aims to collect detailed cognitive, clinical, and biomarker data, including imaging, biomarkers, and whole genome sequencing data. Run by a public-private partnership with industry and advocacy groups, LEADS aims to improve understanding of a population that often sees incorrect or delayed diagnoses.

Late-Onset Alzheimer's Disease Family-Based Study

NIA's Family-Based Study of Late-onset Alzheimer's Disease began in 2003 with awards to a few investigators who studied large families with many members affected by Alzheimer's. It has since grown to include phenotypic, biomarker, and genetic data on thousands of families.

The Family-Based Study is now following up with participating families to confirm current and past diagnoses and recruit new family members, as well as new families from diverse groups, including Mexican American, Central and South American, and Asian populations. Researchers are collecting data that includes genetic samples available for use by the broader scientific community.

Translational Tools and Infrastructure for Drug Development

The development of new drugs is a costly, time-consuming endeavor, and the failure rate is high. The field of Alzheimer's clinical trials has been especially difficult. Given that Alzheimer's and related dementias are likely caused by a highly complicated set of overlapping pathologies, researchers will need to analyze massive quantities of data from numerous people in many clinical studies. To hasten the complex process while maintaining scientific rigor, researchers are trying to fine-tune the way they identify target therapeutics.



That's one of the reasons NIH is focusing on building and enhancing multidisciplinary teams to gather and analyze data in new ways. Current and new partnerships and consortiums are actively working to produce solid data, perform robust analysis, and share their results for others to test. Those tasks require robust tools and infrastructure.

Genetics Infrastructure and Data Resources

One of the most significant scientific contributions that additional appropriations have supported is an expansion of open science to accelerate the development of Alzheimer's therapies. The only way to learn fast as a community is to collect and share vast amounts of data throughout the research ecosystem as quickly and efficiently as possible. But in the era of big data, scientific rigor and reproducibility become increasingly unwieldy. That is one of the reasons NIH supports and incentivizes open systems to democratize modern tools for research. As a result, even small labs can be enabled to do cutting-edge research on a par with larger labs.

NIH-supported clinical research studies have produced vast amounts of data that may yield valuable insights, setting the foundation for development of the right dementia treatment for the right person at the right time. The next challenge is to relay that data to the research community via big-data infrastructure. Speed is essential, with an urgent need for faster generation of high-quality molecular measurements (genetic, proteomic, metabolomic) across existing diverse cohorts. Data scientists and their collaborators hope to bring a lifespan approach to the study of Alzheimer's disease, harnessing and analyzing clinical data captured in various ways, for example, via secure mobile technologies and wearable devices.

NIH's investments to advance a precision medicine approach to Alzheimer's and related dementias research include several projects. Some of them are described below.

The [Genome Center for Alzheimer's Disease](#) (GCAD), funded by NIA in spring 2016, serves as a national resource for integrating and analyzing Alzheimer's disease genetic data, with the goal of identifying genetic and genomic factors for potential therapeutic approaches and prevention. GCAD supports a multidisciplinary attack on Alzheimer's and related dementias. GCAD harmonizes and analyzes all sequence data generated by the ADSP and works with the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) to share data with the research community at large.

GCAD has broad interaction with researchers and coordinates data collection and sharing with the:

- [National Centralized Repository for Alzheimer's Disease and Related Dementias](#) (NCRAD)
- [Alzheimer's Disease Genetics Consortium](#) (ADGC)
- [Cohorts for Heart and Aging Research in Genomic Epidemiology](#) (CHARGE)
- International Genomics of Alzheimer's Project (IGAP)
- [Alzheimer's Disease Neuroimaging Initiative](#) (ADNI)
- [National Alzheimer's Coordinating Center](#) (NACC)
- [Database of Genotypes and Phenotypes](#) (dbGaP)
- [Alzheimer's Disease Centers](#) (ADCs)
- National Human Genome Research Institute-funded [Centers for Common Disease Genomics](#) (CCDG)
- National Heart, Lung, and Blood Institute-funded [Trans-Omics for Precision Medicine](#) (TOPMed) Program
- [Multi-Ethnic Study of Atherosclerosis](#) (MESA)

The NCRAD is a state-of-the-art repository for DNA samples, cell lines, plasma, serum, RNA, brain tissue, cerebrospinal fluid, and peripheral blood mononuclear cells or fibroblasts. NCRAD manages these biosamples—receiving, storing, and distributing them for ADSP and other researchers across the United States. It coordinates with a range of stakeholders in government, academia, and industry, including NACC and NIAGADS. It also coordinates with the ADCs to provide any sample replacements at the sequencing centers.

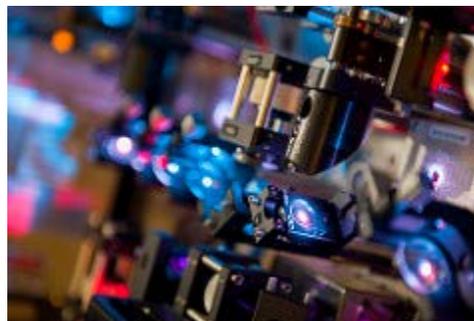
NIAGADS

[NIAGADS](#) plays an important role in understanding the genetic and cellular underpinnings of Alzheimer's by archiving, processing, and distributing data related to the disease's genetics and genomics. Established in 2006, NIAGADS currently stores a petabyte (quadrillion bytes) of data, including genotypes and DNA samples, and offers tools for their analysis. The NIAGADS repository was created to give qualified researchers free access to data for the study of late-onset Alzheimer's, fulfilling a key goal of the National Plan to Address Alzheimer's Disease to "establish a searchable, open access database for the purpose of identifying regions of the genome that contain novel targets."

Recently, NIAGADS augmented its ability to share genetic data with the research community by moving all ADSP data to a secure cloud-based environment with a capacity for investigator analysis, as well as undertaking a major effort to harmonize phenotypic data across multiple types of studies, including imaging and biomarker studies. In addition, NIAGADS released Genomics Database v. 3.1, which allows any investigator to compare their own data with that of the ADSP and analyze it based on gene function and cellular pathways.

AMP-AD Target Discovery and Preclinical Validation

The [AMP-AD Target Discovery and Preclinical Validation Project](#) is a discovery engine for Alzheimer’s research, fueled by the AMP-AD public-private partnership to support a consortium of six multi-institutional, multidisciplinary academic teams. Its main 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.



Building on successful collaborations, these teams are now able to apply 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 studies that evaluate therapeutic targets in a variety of cell-based and animal models.

A key feature of the program is the broad and rapid sharing of biological data and analytical results, made possible by the [AMP-AD Knowledge Portal](#).

What Are “Omics”?

The suffix “omics” serves to collectively characterize and quantify pools of biological molecules that translate into the structure, function, and dynamics of living organisms.

- **Genomics:** study of the genomes of organisms
- **Proteomics:** study of proteins, particularly their structures and functions.
- **Metabolomics:** study of chemical processes involving metabolites

Launched in 2015, the AMP-AD Knowledge Portal [is](#) a big-data hub that allows researchers to access and analyze human as well as cell-based and animal-model datasets on a scale that would not be possible by individual research teams, academic institutions, or pharmaceutical companies. Initially developed to enable data sharing for the AMP-AD Target Discovery Consortium, today the portal is an NIH-designated repository hosting data from multiple NIH-supported Alzheimer's systems biology consortia and is open to data contributions from researchers at large. To date, the knowledge portal has more than 1,300 users and contains contributions from 42 investigators across 22 institutions, representing samples from 36 research studies.

Using the data from the Knowledge Portal, consortium members and researchers at large are making methodological advances and building knowledge about commonalities and differences in the molecular networks associated with the neuropathology and clinical features of Alzheimer's and related dementias ([Seyfried et al., 2017](#); [Ping et al., 2018](#)), the selective vulnerability of brain regions in Alzheimer's ([Wang M et al., 2016](#)), the molecular networks of the aging human frontal cortex ([Mostafavi et al., 2018](#)), and the potential role of herpes virus genes in Alzheimer's pathogenesis ([Readhead et al., 2018](#)), among other new insights.

Rush University Research Resource Sharing Hub

A prime example of the open science ecosystem is the Rush University Alzheimer's Disease Center's [Research Resource Sharing Hub](#), which has distributed data across the United States and around the world. The Rush Center (RADC) is an NIH-funded and -designated Alzheimer's Disease Center dedicated to research on the cause, treatment, and prevention of Alzheimer's and related dementias. RADC studies have generated an enormous variety of unique data and biospecimens to support this effort.

For example, one study has shown that common brain diseases often overlap but impact cognitive impairment differently for different people ([Boyle et al., 2018](#)). The findings point to the importance of developing therapies that treat the broader complexity of cognitive decline. In this case, the RADC team looked at cases of more than 1,000 older people who took detailed cognitive tests annually for many years and whose brains were donated and examined after death.

Critically, these resources from the RADC Research Resource Sharing Hub are available for the wider aging and Alzheimer's research community, with the goal of accelerating the pace at which new knowledge is created for the treatment and prevention of dementia and other age-related neurological conditions. The RADC Research Resource Sharing Hub was specifically

designed to help non-RADC researchers navigate and identify the complex data and biospecimens that support a variety of projects.

MODEL-AD

One reason for the high failure rate of Alzheimer's drugs in humans is the poor predictive power of studies in Alzheimer's transgenic mouse models. To remove this roadblock, NIH is building better mouse models to help research the disease. Capitalizing on recent advances in gene sequencing and genome-editing technologies, NIH in 2017 launched [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. These more precise models will be based on newly identified late-onset Alzheimer's risk genes and will undergo extensive staging to align the pathological features in mice with the 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. To date, seven new mouse models have been created, and two additional models are in the works. All data and models generated are freely available to researchers in academia, industry, and other institutions.

As an example, researchers are working to synergize mouse models with human data to enable the discovery and validation of Alzheimer's therapeutic targets. The scientists produced a more genetically diverse strain of lab mouse that better models the genetic complexity and variation in age at onset of cognitive symptoms seen in humans. These new mouse lines can be easily generated and reproduced across multiple labs at multiple ages. This approach aims to find potential therapeutic targets at early stages of disease that could promote resilience to Alzheimer's disease.

Alzheimer's Preclinical Efficacy Database (AlzPED)

Data sharing is just as important for animal-model data as it is for human data. To this end, [AlzPED](#) serves as a platform for the dissemination of animal-model data and analysis to scientists. The goal is to promote efficiency, transparency, reproducibility, and accuracy of research aimed at preclinical therapy development for Alzheimer's disease.

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 standardized best practices for the rigorous preclinical testing of promising Alzheimer's therapeutics.

To address the issue of publication bias against negative data, AlzPED now has the capacity to accept and curate unpublished, negative data from the scientific community. Data are reviewed by AlzPED curators and, if found acceptable, deposited into the AMP-AD Knowledge Portal.

Stem Cells as Research Tools

Animal models are one of many critical research tools that NIH supports with its additional funds. The use of stem cells has opened a variety of research opportunities. This technique of reprogramming human skin cells into induced pluripotent stem cells (iPSCs) expands the set of research tools available to study molecular and cellular mechanisms underlying brain disorders ([Cheng et al., 2017](#)). Last year, NIA supported several grants characterizing the function of Alzheimer's disease genetic variants using iPSCs and genomic editing approaches.

iPSC technology can be used to create a variety of brain-cell types, which can in turn be studied and tested. Many groups have succeeded in generating various kinds of neurons from iPSCs and, more recently, in producing glial cells.

For example, scientists have succeeded in generating human microglia-like cells from iPSCs ([Abud et al., 2017](#)). The research team developed a defined, efficient way to make human iPSC-derived microglia-like cells (iMGLs), which could be used to study the role of microglia in diseases like Alzheimer's. The iMGLs were developed in the lab similar to the way microglia develop in an organism, and genetic analyses showed strong similarities to adult and fetal microglia. These new iMGL lines were used to study beta-amyloid and tau in Alzheimer's as well as mechanisms for pruning synapses. The new cell lines also were transplantable into transgenic mice and human brain cells, giving the scientific community important new capabilities for studying the role of microglia in human neurological disease.

Another research team developed an improved method for generating astrocytes from human iPSCs, reducing the time needed to generate them from 6 months to 30 days ([Tcw et al., 2017](#)). Again, the iPSC-derived astrocytes mimicked their normal counterparts in several functional assays, including their ability to stimulate microglial digestion of myelin.

Researchers also have used high-throughput screening in neurons derived from human iPSC to identify potential therapeutics, specifically tau-lowering compounds ([Wang C et al., 2017](#)). Lowering total tau levels is an important part of therapeutic strategies for Alzheimer's disease. Researchers have successfully engineered an iPSC line and developed a way to identify gene

targets or small-molecule compounds. The hope is that this cheaper, quicker, and more reliable screening technology will facilitate drug discovery.

An NIH-supported research team ([Zhang et al., 2017](#)) has pinpointed the hypothalamic cells closely associated with the aging process. Surprisingly, a tiny population of neural stem cells involved in the formation of new brain neurons controls this major physiological event. This population of cells normally starts dwindling during middle age in mice and mostly disappears by old age. The team found that destruction of the cells in middle-aged mice accelerated aging and caused early death. Conversely, injecting extra neural stem cells into the hypothalamic regions of middle-aged mice slowed or reversed various measures of aging.

The researchers also showed that the hypothalamic stem cells exert their anti-aging effects, at least in part, by releasing tiny particles called exosomes in the cerebrospinal fluid. Exosomes contain molecules called microRNAs that help regulate gene expression. Identifying exactly which microRNAs are involved in staving off aging may lead to the development of new therapeutics for Alzheimer's and other age-related diseases.

Human Brain Connectivity

Mapping all the connections within the human brain—the connectome—is emerging as a valuable way to understand many neurological and psychiatric disorders. Both the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative and the NIH Human Connectome Project are open-science efforts to identify and create tools for discovery.

Launched in 2013, the [BRAIN Initiative](#) is a large-scale effort to push the boundaries of neuroscience research and equip scientists with the insights and technologies necessary for treating a wide variety of brain disorders, including Alzheimer's disease. NIH continues to [build on advances](#) funded by the BRAIN Initiative. Maps of whole brains in action, the ability to identify thousands of brain cells at a time, and innovative brain scanners are just a few of the programs, advances, and tools needed to better understand the brain.

The [NIH Human Connectome Project](#) is mapping the neural pathways that underlie human brain function. By acquiring and sharing data about the structural and functional connectivity of the human brain, the project will provide a reference dataset for understanding normal and pathological changes in brain networks and behavior across the lifespan. For example, the [Alzheimer's Disease Connectome Project](#) is collecting data from cognitively healthy people and those with dementia due to Alzheimer's disease. The goal is to develop robust technology to accurately characterize Alzheimer's disease across the full spectrum of its progression.

The importance of human brain connectivity in Alzheimer's research is borne out in two studies suggesting that at preclinical stages of cognitive decline, beta-amyloid and tau disrupt brain connections in different ways. Both studies combined amyloid and tau positron emission tomography imaging with functional-connectivity magnetic resonance imaging scans (which measure brain circuit activity based on regional blood flow) from elderly people with normal cognition. The first study focused on cortical circuits important for attention, called the default mode network and salience network ([Schultz et al., 2017](#)). The scientists saw increased connectivity in those networks in people who had only amyloid in their brains when tau levels are low (early stage of the Alzheimer's disease), but decreased connectivity in people who had both amyloid and tau (late stage of the disease).

A second study from the same team looked at the whole cortex and found increased connectivity in regions of amyloid deposition and decreased connectivity in areas of tau deposition ([Sepulcre et al., 2017](#)).

Together, these studies suggest that amyloid deposits cause hyperactivity in the brain circuits where they first accumulate, while tau deposits inhibit brain circuit activity. These results offer new insights into the biology of Alzheimer's disease and could lead to new imaging tests for detecting the first signs of the disease before clinical symptoms appear.

A Smarter Way Forward for Clinical Trials

Launched in 2017, a new clinical trials consortium funded by NIA is expected to accelerate and expand studies for therapies in Alzheimer's disease and related dementias. The [Alzheimer's Clinical Trial Consortium \(ACTC\)](#) is a next-generation infrastructure designed to harness best practices and latest methods for Alzheimer's trials. The ACTC includes 35 sites across the United States and will address the complexity, time, and expense of participant recruitment and site activation to find new and effective ways to treat or prevent these devastating disorders.

The ACTC's design allows rapid startup of clinical trials and provides infrastructure and support in areas such as imaging, biostatistics, data management, and recruitment. It also requires and supports sharing of data and biosamples. With the [current funding announcement](#), NIH anticipates applications to develop and implement Phase I to III clinical trials that would use ACTC coordination and management for promising pharmacological and nonpharmacological interventions.

Creating Principles for Clinical Trials Data Sharing

Public-private partnerships are a key component of the open science ecosystem. One example is the Collaboration for Alzheimer's Prevention (CAP). CAP is a public-private partnership that brings together research groups to harmonize biomarker, clinical, and cognitive measures and align data- and sample-sharing approaches used in certain trials so that findings can inform the entire research community. CAP includes researchers from three trials co-funded by NIH, industry, and foundations: the Alzheimer's Prevention Initiative, the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study, and the Dominantly Inherited Alzheimer Network Trials Unit ([Aisen et al., 2017](#)). Collaborative efforts like CAP provide an effective platform for implementation of Alzheimer's research standards ([Neville et al., 2017](#)) and advancing Alzheimer's prevention research with rigor, care, and maximal impact ([Reiman et al., 2016](#)).

Clinical trial-ready research participants

To enhance recruitment for clinical trials and studies, NIH is traveling several avenues. For example, it has funded an innovative approach using registries to identify potential participants. The [Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease](#) is designed to accelerate Alzheimer's drug development through establishment of a trial-ready group of 2,000 people, including 1,000 without symptoms (preclinical) and 1,000 with early signs of Alzheimer's (prodromal). The initial goal is to enroll participants at approximately 35 sites in the United States. Efforts are underway to join multiple feeder registries to the [Alzheimer Prevention Trials \(APT\) Webstudy](#).

The APT Webstudy in turn will use demographic, medical, lifestyle, and genetic factors, as well as longitudinal web-based cognitive testing, to assess each participant's risk for positive Alzheimer's biomarkers so they can be matched to an appropriate trial. Researchers expect this approach with the APT Webstudy will dramatically shorten the timeline for preclinical/prodromal trials and will address a series of scientific hypotheses to guide further development in the field.

New infrastructure for flexible, streamlined, and improved study

The NIH-supported [Alzheimer's Disease Centers](#) (ADCs) have been a crucial part of Alzheimer's research. For example, ADCs have contributed to numerous large genetic studies, developed amyloid imaging, furthered our understanding of heterogeneity, and helped set standards and develop tools for clinical care. Based on recent recommendations from an expert panel, the ADC program is undergoing strategic revisions designed to achieve objectives of the National Plan to Address Alzheimer's Disease. The new ADCs will increase flexibility and collaboration by leveraging resources, capabilities, and research participants across the network of centers.

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Solving the Recruitment Problems of Alzheimer’s and Related Dementias Clinical Trials and Studies

Recruiting volunteers for Alzheimer’s and related dementias clinical trials and studies is a persistent problem that poses unique challenges for researchers. These challenges may include strict eligibility requirements for participation of study partners, invasive and time-consuming procedures, and barriers for underrepresented communities. A newer aspect is the engagement of presymptomatic or healthy volunteers as researchers try to intervene as early as possible in the disease process.

To tackle these issues, NIH and several stakeholders are developing a national strategy to address the difficulties of reaching study recruitment goals. NIA, with nonprofit and other organizations, has asked a wide range of stakeholders, particularly those underrepresented in research, to help develop a comprehensive [National Strategy for Recruitment and Participation in Alzheimer’s Disease Clinical Research](#).

As part of this National Strategy, NIA sought ideas and views from academic and industry researchers, patients and families, clinicians and other health care providers, advocates, government and community leaders, communications experts, research funders, and more—in short, everyone who can help formulate the National Strategy and join in its implementation.

This action toward a comprehensive, unified National Strategy was undertaken as part of the National Plan to Address Alzheimer’s Disease to make a difference for the growing number of aging adults with or at risk for dementia.

Clinical trials in real-world settings

Often, the positive results from typical clinical trials have been found to be less effective in practice than they were in the lab because several factors not present in the controlled trial setting can affect the eventual outcomes. Looking at how interventions may work in real-world settings is the goal of pragmatic clinical trials. Pragmatic trials are becoming increasingly popular because they’re well suited for studies of the expansion of health services into wider practice.

NIH is [currently planning](#) to use pragmatic clinical trials to address the pressing need to improve care for people with dementia and their caregivers within the context of health and long-term care systems. Lack of continuity of care is associated with higher rates of hospitalization, emergency department visits, testing, and health care spending. Late diagnoses of dementia and lack of coordination among providers and care settings can lead to inappropriate care, premature institutionalization, and burdensome transitions in late-stage dementia. Through a [new funding opportunity](#), NIH plans to generate research that brings together health systems, health insurance companies (for example, managed care plans), home health care providers, and nursing homes to improve care for people living with dementia and their families and caregivers.

Emerging Therapeutics

Growing evidence indicates that disease pathways in Alzheimer’s and related dementias likely vary from person to person. Accordingly, researchers are investigating an array of interventions that target many potential pathways, including the toxic accumulation of beta-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 therapies to treat or prevent Alzheimer’s disease, as has been done for other complex diseases, including cardiovascular disease and cancer.



Although recent scientific advances have led to better understanding of the complexity of Alzheimer’s, the development of effective therapies has been challenging. Failure to translate scientific advances into new therapies, coupled with increased research and development expenditures, has dampened some pharmaceutical companies’ enthusiasm for Alzheimer’s drug development. To fill this critical gap, NIH has invested in programs to catalyze the development of new therapies, using data-driven drug design that uses predictive models to select the most promising compounds for testing.

These programs include the Alzheimer’s Disease Drug Development Program, the NIH-wide [Blueprint Neurotherapeutics Network](#), and the NIH [Small Business Innovation Research](#) program.

These programs tap into the creativity of researchers, providing a lifeline for growing and sustaining biomedical 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.

Alzheimer's Disease Drug Development Program (ADDP)

The overarching goal of the ADDP is to create a robust pipeline of novel therapies that target Alzheimer's disease, including treating the symptoms and attacking root causes of the disease. The ADDP pipeline comprises several projects that use a broad range of therapeutic strategies, including small molecule, immune, regenerative, and gene therapies. Since 2013, NIH has funded 11 preclinical drug development projects through the ADDP. Summaries of some of these projects are listed below:

- Allopregnanolone ("Allo") is a natural neurosteroid. NIH-supported scientists conducted a 5-year preclinical development program 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 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.
- LM11A-31, developed with NIH funding, is one of the first compounds able to activate the brain's own defense mechanisms and protect neural connections from degeneration in the brain. Researchers have recently applied to begin a Phase II study to test its efficacy and side effects in people with Alzheimer's.
- AV-1959D is a novel, DNA-based vaccine developed with NIH support. In preclinical studies, it has been shown to generate a robust cellular immune response, eliminate activation of potentially harmful autoreactive T cells, and induce strong and therapeutically potent anti-beta-amyloid antibodies in animal models. The program is completing an FDA-required investigational new drug application to enable a Phase I trial.
- NIH-supported researchers are targeting key mediators of abnormal glial activation and neuroinflammation, including several enzymes known as stress-activated protein kinases. In Alzheimer's disease, there is an imbalance between the pro- and anti-inflammatory activities of glia, which leads to the abnormal overproduction of proinflammatory molecules that may damage healthy nerve cells. This damage causes the cells to lose function and eventually die, leading to cognitive impairment, memory loss, and dementia. To date, scientists have synthesized a number of potent small-molecule inhibitors of these enzymes and found that they do in fact stop production of

proinflammatory molecules in cell and animal models. The most promising of these inhibitors, MW151, is expected to complete FDA-required safety studies in 2018 and enter clinical trials in early 2019.

- NIH-supported scientists are developing a novel gene therapy that uses a friendly virus to deliver brain-derived growth factor (BDNF), a protein in the brain known to maintain nerve-cell function and survival and memory, to the brains of people with Alzheimer's. This newly introduced gene leads to the production of large amounts of BDNF. To date, scientists have completed feasibility studies in animal models showing that BDNF gene therapy prevents nerve-cell loss, enhances nerve-cell function, reverses molecular and biochemical features associated with Alzheimer's, and improves learning and memory. The BDNF program will complete FDA-required safety studies in 2018, and clinical trials may begin as early as 2019.

Advancing Drug Repurposing and Combination Therapies

Although drug repurposing has a number of advantages over the development of new drugs and has been done for other conditions, multiple attempts at repurposing drugs to treat Alzheimer's disease have been unsuccessful. As we learn about the enormous complexity of Alzheimer's pathogenesis and associated comorbid conditions, it is becoming apparent that effective treatment for an individual person must target multiple aspects of the disease and be directed toward several pathogenic processes. This kind of treatment will likely require combination therapy. However, despite tremendous interest in these therapeutic avenues, there is little data and knowledge to guide rational drug repurposing and the development of combination therapies.

Molecular profiling and sophisticated computational approaches applied to the analysis of longitudinal clinical data are refining definitions of human diseases and expanding our understanding of drug-drug target interactions, leading to unprecedented opportunities for rational drug repositioning and combination therapy development. Emerging data-driven approaches such as translational bioinformatics, systems pharmacology, and network pharmacology are successfully used in other disease areas to identify approved drugs that can be repurposed for new disease indications as well as drug combinations that have superior efficacy and toxicity profiles compared to single-drug treatments.

To capitalize on these advances, NIH in 2017 launched a [new funding initiative](#) that encourages researchers to use existing drugs and develop novel computational approaches to identify drugs or drug combinations used for other conditions that might be effective against

Alzheimer's and related dementias. This funding initiative calls for a cross-disciplinary, team-science approach and encourages academic-industry collaborations.

Projects funded through this initiative include purely computational research aimed at using existing methodology to analyze various types of molecular and clinical data, including electronic health records, to identify individual drugs or drug combinations with favorable efficacy and toxicity profiles as candidates for drug repurposing. The initiative will also support research that combines computational and experimental approaches to test therapeutic candidates in proof-of-principle animal and human studies.

Four research teams have been funded through this initiative, and several more are expected to be funded in coming months. This initiative is leveraging the open-science data resources created by AMP-AD and related programs. Recently funded projects include:

- A drug repositioning strategy that combines novel computational drug prediction, novel computational brain-blood barrier permeability prediction, retrospective large-scale clinical corroboration, and prospective experimental testing to rapidly identify repositioned anti-Alzheimer's drug candidates. The project will develop and rank a list of drug candidates with interpretable mechanisms of action, high blood-brain barrier permeability in humans, clinical efficacy evidence gathered from people with Alzheimer's disease, and efficacy in mouse models of Alzheimer's. If successful, these findings can be translated into clinical trials.
- An analysis of publicly available, large-scale transcriptomic datasets of people with Alzheimer's disease and age-matched controls to identify APOE genotype-specific gene expression signatures of Alzheimer's. The team also will pursue drug repositioning based on these gene expression signatures and validate the top drug candidates in mouse models of Alzheimer's. The outcomes of the proposed studies will shed light on the pathogenesis of Alzheimer's and potentially identify existing drugs for treating or preventing the disease.

Preventing Alzheimer's by Understanding the Impact of Environmental Stressors

Alzheimer's is likely caused by a mix of genetic, environmental, and other stressors, some of which cannot change, like the genes we inherit. Researchers are looking at factors that can be changed, such as sleep, education, having other health conditions, and exposure to environmental toxins. The interaction between genes and environment may play a role in increasing or decreasing disease risk.



Polygenic Risk Scores Predict Cognitive Impairment in Middle-Aged Men

Much of a person's genetic risk for Alzheimer's disease reflects the combined effects of common variations in hundreds of different genes, each of which increases or decreases a person's overall risk by only a tiny amount. Hence, scientists are now studying the predictive value of "polygenic risk scores." To generate a polygenic risk score, a person's DNA is screened for thousands of Alzheimer's-associated variations. The likely positive or negative effects of these variations are combined into a single value. So far, polygenic risk scores calculated for older people have been shown to predict their risk of developing Alzheimer's disease.

A new study suggests that polygenic scores can also be used to predict Alzheimer's risk in middle-aged people ([Logue et al., 2018](#)). Researchers calculated Alzheimer's disease polygenic risk scores for a group of white, non-Hispanic men and found that those with higher scores were significantly (up to 43 percent) more likely to have already developed amnesic mild cognitive impairment, the usual precursor to Alzheimer's disease.

Looking to Links Between the Brain and Microbiome

Part of our environment is our microbiome, the population of bacteria, viruses, and other microbes living on us and in us. In recent years, researchers have studied a "gut-brain axis" where communication occurs between the gut, its microbiota, and the brain. Although not fully understood, this axis appears to have a role in the onset and severity of many neurological diseases.

In 2017, NIH held a workshop to discuss the field and research opportunities for the microbiome and aging. The [NIA Symposium on Microbiome and Aging](#) identified effective

strategies to stimulate research on changes of microbiomes during aging and the effects on aging-related conditions and diseases.

The Role of Sleep in Alzheimer's Disease

Older adults with Alzheimer's disease often exhibit sleep disturbances and circadian clock (internal timing system) disruptions. Although this may be a consequence of the disease, there is new evidence that sleep disturbances may contribute to risk for the disease as well. NIH-funded researchers found an association between preclinical Alzheimer's disease and poor sleep and sleep fragmentation, suggesting that sleep quality could be a biomarker of preclinical Alzheimer's ([Musiek et al., 2018](#)).

Further evidence for the relationship between sleep and Alzheimer's disease can be found at the molecular level. Amyloid accumulation in the brain predicts and exacerbates sleep disruption in humans and in animal models, and experimental manipulation to increase sleep results in decreased amyloid levels in the brain ([Roh et al., 2012](#)).

In addition, researchers looking at different stages of sleep have shown a coupling between sleeping brain waves, called slow waves, and memory retention ([Helfrich et al., 2018](#)). The aging brain's failure to coordinate brain waves during sleep is most likely due to degradation or atrophy of the medial frontal cortex, a key region of the brain's frontal lobe that generates deep, restorative slumber. Accumulation of beta-amyloid in the medial frontal cortex in Alzheimer's disease might thus contribute to the poor memory that is characteristic of Alzheimer's disease.

Rapid eye movement sleep (REM) is a stage in sleep cycles, distinguishable from other stages by random, rapid movement of the eyes; low muscle tone throughout the body; and the propensity to dream. A study in mice has shown that REM sleep has multiple functions in brain development, learning, and memory consolidation ([Li W et al., 2017](#)). This research shows evidence of pruning and maintenance of synapses during REM sleep, which may have implications for Alzheimer's disease in humans. This pruning helps in salient memory maintenance. REM sleep also strengthens and maintains newly formed spines on neuronal dendrites, which leads to memories becoming more permanent.

Such findings suggest that improved sleep in older adults may reduce the risk of developing Alzheimer's disease. Effective interventions exist to improve sleep, and researchers are looking at whether they may help prevent Alzheimer's disease.

Heavy Metal Exposure and Alzheimer’s Disease Risk

Heavy metals, such as lead, cadmium, and mercury, are toxic to nerve cells. Exposure to high doses of heavy metals—for example, through contaminated air, food, water, or hazardous occupations—can cause acute neurological and neuropsychological symptoms in people of all ages. Two new studies suggest that long-term exposure to low doses of heavy metals can also contribute to age-related cognitive decline:

- NIH-funded researchers found that men with higher cumulative lifetime exposures to lead (as measured by sampling lead levels in their leg bones) showed faster age-related decline in performance on cognitive tests ([Farooqui et al., 2017](#)).
- Another NIH-funded study looked at cadmium exposure in older U.S. adults and found that increased cadmium levels in both urine and blood samples were associated with increased risk of Alzheimer’s mortality 5 to 13 years after exposure ([Peng et al., 2017](#)).

These two studies add to evidence suggesting that long-term exposure to heavy metals can have negative consequences for cognitive health in late life and indicate the need for additional studies on exposure to environmental toxins.

Other Risk and Prevention Factors

Getting an education makes a difference, shows a pioneering study in a nationally representative sample that describes rural-urban differences and the socio-demographic determinants of dementia and cognitive impairment without dementia. The Cohort Studies of Memory in an International Consortium (COSMIC) seeks to find out which risk and protective factors are universal and which are specific to certain populations. Established in 2012, COSMIC now includes 26 studies from 16 countries on 5 continents, with a combined sample of more than 70,000 people.

NIH also has funded research looking at the relationship between brain pathologies and eating patterns. Researchers are using epidemiology studies to see if eating patterns, including the Dietary Approaches to Stop Hypertension (DASH) diet, the Mediterranean diet, and a hybrid of these diets called MIND (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay) are associated with maintenance of cognitive health and/or decreased risk of clinical dementia.

What about people who seem to have exceptional cognitive function for their age, sometimes referred to as “super agers”? NIH supports research looking at people 80 years and older who have memory function as good as or better than that of people 20 to 30 years younger to understand which factors may contribute to their resilience to impairment. Understanding fundamental mechanisms through which potential protective factors (such as social activity,

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physical activity, and vascular health) alter Alzheimer’s trajectories is crucial to facilitate bench-to-bedside translation. Other findings underscore the importance of including an assessment of frailty alongside cognitive performance when determining the risk factors for developing dementia ([Rogers et al., 2017](#)). Individuals who are frail or becoming frail are at risk of developing dementia. This study lays the groundwork for future research to explore different thresholds of frailty severity in relation to dementia progression.

Dementia Prevention: What Does the Evidence Tell Us?

To help better understand the quality and weight of available evidence around the prevention of dementia and cognitive impairment, NIA commissioned experts to conduct an extensive scientific review and provide recommendations for public health messaging and future research priorities. In response to that request, a National Academies of Sciences, Engineering, and Medicine committee in 2017 released a report “Preventing Cognitive Decline and Dementia: A Way Forward.” The committee found that current evidence does not support a mass public education campaign to encourage people to adopt specific interventions to prevent cognitive decline or dementia. Importantly, the committee found “encouraging although inconclusive” evidence for three specific types of interventions—cognitive training, blood pressure control for people with hypertension, and increased physical activity. As part of the report, the committee encouraged continued research in these three areas, as well as other priority areas such as new anti-dementia treatments, treatments for diabetes and depression, dietary interventions, lipid-lowering treatments, sleep quality interventions, social engagement, and vitamin B12 plus folic acid supplementation.

Research on Care and Support for People with Dementia, Their Families, and Other Caregivers

NIH increasingly supports research to improve the quality of care and quality of life for people with Alzheimer's and related dementias, as well as to alleviate the physical, emotional, and financial burdens associated with providing care. With expanded funding, NIH seeks to support research on dementia care, including research in real-world settings such as nursing homes, assisted living, private homes, and primary and acute care. NIH also plans to maintain research programs designed to improve care, including end-of-life care, for people with advanced dementia.



NIH-funded investigators have already gained a better understanding of the scope and specific challenges of dementia care and caregiving and interventions to support well-being at different stages of the care continuum. Research findings this past year demonstrate how the characteristics and health of caregivers are intertwined with the health of the people for whom they provide care. The availability of specialized care, long-term services and supports, and clinical consulting also contributes to better outcomes for people with dementia and caregivers.

First National Research Summit on Dementia Care

Driven by the National Alzheimer's Project Act (NAPA) to expand research to support people living with dementia, the first-ever [National Research Summit on Care, Services, and Supports for Persons with Dementia and their Caregivers](#) was convened in October 2017. Hosted by NIH and led by the Office of the Assistant Secretary for Planning and Evaluation of the U.S. Department of Health and Human Services (HHS) and the NAPA Advisory Council on Alzheimer's Research, Care, and Services, the summit aimed to set priorities for future care and caregiving research. The aim was to identify what we know and what we need to know to accelerate the development, evaluation, translation, implementation, and scaling up of comprehensive care, services, and supports for people with dementia, families, and other caregivers. The meeting's steering committee included experts, advocates, people with dementia, and caregivers from public- and private-sector organizations and Federal agencies. The summit was supported in large part by the private sector through donations to the Foundation for the NIH, as well as by funding from the HHS Office of Women's Health.

More than 1,000 people participated in the 2-day meeting. The result was nearly 700 recommendations, which were reviewed and organized into 12 major themes:

1. Heterogeneity of people living with dementia and their caregivers
2. Research methods to develop more effective dementia care, services, and supports
3. Caregiver relationships, roles, and networks
4. Clinical approaches and the lived experience of dementia
5. Engaging people living with dementia and caregivers in research
6. Dementia-related terminology, nomenclature, and stigma
7. Comprehensive models for dementia care, services, and supports
8. Strategies for scaling and disseminating existing evidence
9. Living places, physical and social environments, and processes of care
10. Financial burden and out-of-pocket costs
11. Ensuring an adequate and qualified workforce
12. Technology

A [final report](#), including these recommendations, was issued on April 27, 2018, and will help inform NIA investments and set the agenda for the next dementia care summit on March 24-25, 2020.

In response to the 2017 dementia care research summit, NIA has already increased its efforts in dementia care and caregiver research with funding in areas such as:

- Disparities in quality and access to care
- Improving the lives of people with dementia, families, and communities
- Alzheimer's and related dementias health care systems research collaboration
- Research on informal and formal caregiving for Alzheimer's disease
- Pragmatic trials for dementia care in long-term services and support
- Dementia care and caregiver support interventions

National Study of Caregiving (NSOC)

One key NIA-funded initiative, the [National Study of Caregiving](#) (NSOC), is a longitudinal study of caregivers of older adults, both with and without Alzheimer's disease, who participated in the [National Health and Aging Trends Study](#) (NHATS). In NSOC, caregivers are interviewed about their caregiving experience, including intensity/duration of caregiving, care activities, positive/negative aspects, services and supports, health and well-being, and caregiving effects

on employment, income, and participation in activities. Linking NSOC data with information from NHATS makes available data from both the care recipient and caregiver perspectives.

Recent investments in Alzheimer's disease and related dementias are allowing the creation and public availability of this dataset, providing new opportunities for researchers to gain a better understanding of trends in late-life functioning of both older adults and their caregivers.

Research Advances in Dementia Care

Recent research advances on caregivers and people with dementia cover a range of topics across multiple settings. They address the link between caregiver mental health and mortality of care recipients, palliative care, interventions for those living with dementia, and the need for continuity of care.

Family caregiver characteristics linked to unmet needs of disabled older adults

Unpaid family caregivers provide most care to disabled older adults. A recent NIA-funded study demonstrated the substantial unmet need for care among older adults with family caregivers ([Beach and Schulz, 2017](#)). Younger caregivers, caregiving sons, caregivers not living with care recipients, and having supplemental paid caregivers were associated with higher levels of unmet needs in older adults receiving care. Findings demonstrate the need for caregiver support and services to reduce caregiving burden, improve care quality for older adults, and mitigate the risk of neglect or abuse. Moreover, this work points out the need for research on quality of care and the use of longitudinal data to investigate caregiving over time.

Poor mental health of family caregivers linked to patient mortality

Many caregivers experience significant financial, emotional, and physical stress that can lead to anxiety, fatigue, and depression. NIA-funded researchers ([Lwi et al., 2017](#)) found that worse caregiver mental health predicted increased patient mortality. Even after controlling for risk factors such as diagnosis, sex, age, dementia severity, and patient mental health, caregiver mental health symptoms were still a significant predictor of patient mortality. These findings suggest that interventions to improve the health and well-being of caregivers may also increase the lifespan of people with dementia.

Palliative care consultations benefit nursing home residents

Half of nursing home residents in the United States have dementia ([Harris-Kojetin et al., 2016](#)), and half of people who die in nursing homes have dementia ([Miller et al., 2012](#)). However, most nursing home residents with dementia have limited access to specialty palliative care beyond Medicare's hospice benefit. In one recent study ([Miller et al., 2017](#)), NIA-supported researchers

found that specialty palliative care consultations for nursing home residents with moderate to advanced dementia substantially reduced acute-care use and stressful, potentially burdensome transitions near the end of life, compared with residents without consultations, without additional Medicare costs. Timing of consultations earlier (31 to 180 days before death) versus later (1 to 30 days before death) dramatically reduced acute care and care transitions. Given the known risks and limited benefits of hospitalization for patients with advanced dementia, specialty palliative care consultations would likely improve both the quality of life and care for nursing home residents with dementia.

Personalized music therapy program improves outcomes of nursing home residents

Research has shown that music-related interventions are associated with reductions in depression ([Ueda et al., 2013](#)), anxiety ([Chang et al., 2015](#)), and behavioral and psychological symptoms in people with dementia. A recent study by NIA-supported researchers ([Thomas et al., 2017](#)) offers the first evidence that a personalized music program, MUSIC & MEMORY, is associated with reductions in behavioral and psychological symptoms, as well as in antipsychotic and anxiolytic medication use among long-stay nursing home residents with Alzheimer's and related dementias.

Continuity of care in older adults with dementia

A recent NIA-funded study ([Amjad et al., 2016](#)) examined the association between medical-clinician continuity and health care utilization, testing, and spending in older adults with dementia. Among older fee-for-service Medicare beneficiaries with a dementia diagnosis, lower continuity of care was associated with higher rates of hospitalization, emergency department visits, testing, and health care spending. Further research into these relationships, including potentially relevant clinical, clinician, and systems factors, can indicate whether improving continuity of care in this population may benefit patients and the wider health care system.

Mechanical ventilation use by residents with advanced dementia

Another NIA-funded study ([Teno et al., 2016](#)) revealed how excess capacity in hospital intensive care units (ICUs) led clinicians to admit patients with advanced dementia to ICUs, even when these patients may not have benefited from ICU care. While mechanical ventilation can be lifesaving, for patients with advanced dementia it often prolonged suffering and added costs without lengthening survival. The findings draw attention to care appropriateness, system-based incentives for ICU-level care, and implications for informed consent and treatment preferences and care costs.

Seeking Solutions Through Disease Monitoring, Assessment, and Care

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. Researchers are studying ways to optimize and customize the delivery of care and monitor and assess the progression of dementia and cognitive decline.



Web-Based Tools for Social Engagement

A strong body of research demonstrates associations between the incidence of Alzheimer's disease and individuals' personality characteristics, level of social engagement, and educational attainment. To better understand this type of dynamic, NIH supported a workshop in 2017, [Understanding Pathways to Successful Aging: Behavioral and Social Factors Related to Alzheimer's Disease](#). It was designed to build on an earlier workshop on the importance of delineating causal relationships underlying associations between behavioral, social, and biological factors and long-term health.

The workshop identified four themes:

- Mechanisms that might explain relationships between personality, social engagement, and educational attainment and the risk of Alzheimer's disease
- Research to test the hypothesized mechanisms: interdisciplinary work could improve existing measures, harmonize data across measures, and develop new approaches to measurement, such as through the use of wearable sensors
- Development of richer, more detailed measures in the context of a theoretical construct
- Enhanced efforts to recruit a more diverse participant base for studies and to go beyond the United States for some studies

Harmonized Cognitive Assessment Protocol (HCAP)

The HCAP is a new dementia protocol using a battery of neuropsychological instruments for the assessment of cognitive impairment and dementia within a large, random subsample of the NIA-funded, nationally representative Health and Retirement Study (HRS). HCAP was designed to be in harmony with other large dementia studies in the United States (such as the Rush Memory and Aging Project) and to be readily adaptable for use in large, nationally

representative samples in other countries that follow the HRS data collection model. Currently, Mexico, China, India, and England are collecting data that will be directly comparable to U.S. HCAP data, enabling analyses of worldwide trends and differences in dementia epidemiology.

NIH plans to continue funding HCAP projects that will encourage new approaches to the study of subpopulation and cross-national research on cognitive impairment and dementia. The harmonization of data from the United States and other countries will provide a detailed, more accurate picture of cognitive impairment and dementia.

SBIR Technology Projects for Alzheimer’s Clinical Care and Management

NIA has developed several small-business (SBIR/STTR) funding opportunity announcements for using technology to assist persons with Alzheimer’s and related dementias and their caregivers. Twenty such grants were funded between 2015 and 2017.

NIA recently issued several new SBIR/STTR funding opportunity announcements:

- [Assistive Technology for Persons with Alzheimer’s Disease and Related Dementias and Their Caregivers](#) (R41/R42 - Clinical Trials Optional)
- [Assistive Technology for Persons with Alzheimer’s Disease and Related Dementias and Their Caregivers](#) (R43/R44 - Clinical Trials Optional)
- [Development of Socially Assistive Robots to Engage Persons with Alzheimer’s Disease and Related Dementias and their Caregivers](#) (R43/R44 - Clinical Trial Optional)
- [Development of Socially Assistive Robots to Engage Persons with Alzheimer’s Disease and Related Dementias and their Caregivers](#) (R41/R42 - Clinical Trial Optional)

Leveraging Mobile Technology to Better Understand Changes in Cognition

NIH-supported efforts to develop sensitive cognitive tests for mobile devices that are suitable for long-term use could revolutionize the understanding of aging-related changes in cognition, including when the earliest changes related to Alzheimer’s and related dementias neuropathology could be occurring.

For example, one project is developing new measures of cognitive function that could detect the very earliest signs of impairment and recognize patterns of normal and abnormal cognitive aging using a mobile device platform. To expand research on the use of mobile technology, NIH has released the [Mobile Monitoring of Cognitive Change](#) funding announcement. The goal is to fund research to develop and validate cognitive tests on mobile devices that would help identify possible participants for clinical trials or observational studies. Such measures could

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provide a wealth of publicly available data on cognitive performance in midlife, now recognized to be a key juncture in possible changes related to Alzheimer's and related dementias.

Progress in Understanding Alzheimer's Disease-Related Dementias

As noted above, while Alzheimer's disease is the most common dementia diagnosis, other neurodegenerative conditions, called Alzheimer's disease-related dementias (ADRD), are included in NIH's substantive research initiative to decrease the burden of dementia in our aging population. About 20 to 40 percent of people with dementia have vascular cognitive impairment/dementia, Lewy body dementia, frontotemporal dementias (FTD), or other types. Brain autopsy studies show that many people over age 80 diagnosed with Alzheimer's have more than one type of dementia—mixed dementia—revealed by multiple pathologies in the brain and overlapping clinical symptoms.



Knowledge, funding, and resources across NIH have enabled progress through individual research studies and ongoing collaborations. In 2018, NIH launched [DetectCID](#) to address the problem of high rates of undiagnosed cognitive impairment and dementia in the United States. This 5-year program is developing clinical standards for brief (less than 10 minutes) and simple assessments, with primary care-friendly recommendations for follow-up, to use in primary care and other common clinical settings.

As with Alzheimer's disease, NIH-supported scientists are following many paths to better understand the complex biological and genetic risk factors and causes of ADRD, as well as the natural history of these disorders. This research lays the groundwork for the development and testing of drugs to allay, and maybe one day prevent, the debilitating cognitive, movement, and behavior problems faced by people with ADRD. Some current initiatives include:

- [Pathway and Target Identification for ADRD](#). NIH is supporting projects that will study complex molecular patterns of a single cell or a group of cells through large-scale analysis of existing data and biospecimens from individuals with ADRD.
- [Structural Biology of ADRD Proteinopathies](#). This program will leverage recent advances in cryo-electron microscopy to better understand the structural biology of ADRD-associated proteins such as tau, alpha-synuclein, and TPD-43 in human brain tissue.
- [Center without Walls for PET Ligand Development for ADRD](#). The Centers will aim to

make high-quality imaging biomarkers available by improving existing ligands or testing new compounds that identify pathologies in ADRD.

As mentioned in the introduction to this report, NIH will continue this progress by convening an ADRD Summit in March 2019, building on summits in 2013 and [2016](#), that will set actionable goals in the form of [milestones for ADRD research](#). As with past summits, the 2019 event will allow NIH to assess scientific progress, set research priorities, and generate specific recommendations to achieve these priorities.

Vascular Contributions to Cognitive Impairment and Dementia (VCID)

Many older adults with dementia have both Alzheimer's disease and vascular disease, which may involve damage to the brain resulting from stroke and other conditions that impair the function of the brain's network of small blood vessels. In this wide-ranging field, one focus of NIH-funded research is to identify the preventable risk factors for VCID.

NIH supports hypothesis-testing [research](#) to investigate cellular and molecular mechanisms underlying small vessel brain diseases and diffuse white matter disease. In addition, NIH is supporting [MarkVCID](#), a national consortium to accelerate the development and validation of biomarkers that could serve as measurable targets in therapeutic trials to prevent cognitive impairment and dementia from small vessel diseases.

Midlife vascular factors raise risk of late-life dementia

A growing body of evidence links cerebrovascular health in midlife to dementia in later life. The good news is that risk factors such as high blood pressure can be treated, suggesting a possible strategy to prevent dementia in later life.

In one of the largest, longest studies of its kind (involving 15,744 black and white Americans, followed for an average of 23 years), researchers found that middle-aged people with vascular risk factors, including diabetes, elevated blood pressure, or smoking, were more likely to develop dementia in later life than people without such risk factors ([Gottesman, Albert et al., 2017](#)). Diabetes was the most dangerous: It increased dementia risk by more than 75 percent—almost as much as the APOE ε4 allele, the strongest genetic risk factor for Alzheimer's. Slightly elevated blood pressure and high blood pressure increased dementia risk by 30 percent and 40 percent, respectively.

A brain-scan study of a subset of participants from the same study shows that midlife vascular risk factors can also impact a key brain change characteristic of Alzheimer's in later life ([Gottesman, Schneider et al., 2017](#)). The researchers found that cognitively normal, middle-

aged people with two or more vascular risk factors were almost three times more likely than those with no vascular risk factors to develop high levels of beta-amyloid deposits in the brain, one of the signature pathological characteristics of Alzheimer's disease. Midlife obesity (a body mass index of 30 or higher) was on its own associated with high brain amyloid levels among people in their 70s. This study suggests that vascular and perhaps other changes due to obesity directly exacerbate amyloid accumulation, perhaps by interfering with the brain's amyloid clearance mechanisms.

A third study lends further support to the link between blood pressure abnormalities in midlife and the risk of dementia in late life ([McGrath et al., 2017](#)). People who had high blood pressure in midlife were at greater risk of developing dementia in late life, and that risk increased even more in people whose hypertension persisted into late life. This study also found a twofold higher risk of dementia for people who had normal or slightly higher-than-normal blood pressure in midlife, but whose blood pressure started dropping to lower levels as they got older.

Together, these studies offer insights that may help scientists develop dementia prevention strategies and design trials that will enable testing in at-risk individuals and the general population.

Pericytes and brain health

Pericytes are specialized vascular cells with fingerlike projections that wrap around the small blood vessels of the brain. These cells' functions remain somewhat mysterious, but a new study suggests that pericytes boost blood flow in response to increased activity of neurons ([Kisler et al., 2017](#)). When neurons are more active, they require more oxygen, which is carried in the blood. Genetically modified mice with fewer pericytes than normal showed diminished blood flow and oxygen levels in the brain. As the pericyte-depleted mice grew older, their cortical and hippocampal neurons showed impaired responses to sensory stimulation and other signs of degeneration. This study points to pericytes as an important link between cerebrovascular health and neuronal health.

Lewy Body Dementia (LBD)

(LBD is a brain disorder associated with Lewy bodies, abnormal deposits of the alpha-synuclein protein in the brain, which are also the signature pathological feature of Parkinson's disease. In addition, people with LBD often have amyloid plaques and tau tangles, typical features of Alzheimer's, in their brains. A common cause of dementia, LBD leads to serious problems with

thinking, behavior, and mood that compound issues with movement. LBD is used to describe two closely related conditions: dementia with Lewy bodies and Parkinson's disease dementia.

An NIH initiative in this area seeks to develop [biomarkers to help diagnose LBD or track disease progression](#). In 2018, NIH announced two funding opportunities in LBD research. One will provide researchers with support they need in [designing Phase III clinical trials for LBD](#), and the other will establish the [LBD Center Without Walls](#), a collaborative, multidisciplinary group that will focus on understanding interactions between alpha-synuclein and beta-amyloid and their contributions to LBD.

Predicting cognitive decline in Parkinson's and dementia with Lewy bodies

Many but not all people with Parkinson's disease develop some degree of dementia, but it is difficult to predict who will. Researchers used clinical and genetic data from 3,200 people with Parkinson's to develop a scoring system that can predict risk of future cognitive decline ([Liu G et al., 2017](#)). The scoring system calculates risk based on seven health, genetic, and demographic factors. This new scoring system has multiple benefits; it is noninvasive and inexpensive because it uses existing clinical records, and it may improve the accuracy of patient selection for and the subsequent outcome of large clinical trials.

In another study, a team of NIH-funded researchers analyzed post mortem brain tissue to identify pathological markers that predict progression to dementia in people with Parkinson's disease and dementia with Lewy bodies ([Irwin et al., 2017](#)). Many of these people also had typical Alzheimer's pathology, such as amyloid beta plaques and tau tangles, in addition to Lewy bodies in the brain. Among these pathological markers, tau tangles were the most strongly associated with faster progression to both dementia and death after the onset of movement symptoms.

Frontotemporal Dementias (FTD)

FTD are forms of dementia that are part of a family of neurodegenerative brain diseases called frontotemporal lobar degeneration, referring to the frontal and temporal lobes of the brain primarily affected. These disorders' behavior, language, and movement symptoms vary widely in individuals, who often have initial symptoms in their 40s and 50s.

NIH supports research on FTD, including their natural history, biomarkers, and genetics. Among ongoing trans-NIH collaborations, the [Advancing Research and Treatment for Frontotemporal Lobar Degeneration \(ARTFL\)](#) and the [Longitudinal Evaluation of Familial Frontotemporal Dementia \(LEFFTDS\)](#) studies are developing new clinical rating scales and supporting biomarker discovery that will hopefully lead to improved clinical trial design through better patient

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stratification, early detection, and advances in analysis of disease progression. ARTFL looks across the spectrum of neurodegenerative brain diseases, while LEFFTDS is a longitudinal study of families who carry mutations in the *C9ORF72*, *GRN*, or *MAPT* genes. Eighteen clinical sites in the United States and Canada participate in the ARTFL and LEFFTDS studies.

As noted elsewhere in this report, harmful forms of the tau protein are found in the brain of people with Alzheimer's disease, some FTD, and other "tauopathies." NIH supports research on tau in the hope of better understanding its damaging activity in the brain and how to stop it. One such effort, the NIH-funded [Tau Center Without Walls](#), is a multicenter project to identify and validate molecular mechanisms that contribute to tau toxicity in FTD.

Alzheimer's risk gene interacts with tau to worsen brain changes

The ApoE4 gene is known to promote deposits of the beta-amyloid protein in the brains of individuals with Alzheimer's disease. An NIH-funded study shows that it also affects tau, leading to harmful brain changes in Alzheimer's and FTD ([Shi et al., 2017](#)). Researchers studied mice bred to carry a mutation in the tau gene that causes FTD. Deleting the ApoE4 gene protected the mice from developing brain neurodegeneration. Conversely, introducing a copy of the human ApoE4 gene increased levels of toxic forms of tau and worsened brain degeneration and inflammation. Subsequent studies in humans indicated that the ApoE4 allele is also associated with more severe regional brain degeneration in people with tauopathies. This study suggests that drugs targeting ApoE4 could be beneficial not only for Alzheimer's but for other neurodegenerative diseases involving tau pathology, such as FTD.

A new anti-tau drug?

For the first time, researchers have used a genetically designed drug, called an "antisense oligonucleotide," to block tau production and prevent brain degeneration in mice that develop tau pathology ([DeVos et al., 2017](#)). Antisense oligonucleotides are short nucleic acid strands that bind to the RNA encoding a specific cellular protein and interrupt assembly of the protein. The researchers injected an anti-tau oligonucleotide into mice carrying a gene for a mutant, toxic form of human tau. The drug treatment not only reduced the formation of tau tangles in the mutant mice, but also prevented both the death of hippocampal neurons and the development of behavior abnormalities (problems with nest-building) normally seen in these mice. The drug-injected mutant mice also lived 25 percent longer than control mutant mice.

Potential biomarker for FTD/ALS clinical trials

"Repeat expansion" mutations in the *C9ORF72* gene are the most common genetic cause of both ALS (Lou Gehrig's disease) and FTD. These mutations consist of short DNA sequences

repeated many times in a row, and they encode abnormal, neurotoxic proteins. Using an antibody-based laboratory procedure, researchers were able to detect one of these abnormal proteins, poly(GP), in the cerebrospinal fluid and peripheral blood cells of both symptomatic and asymptomatic carriers of the C9ORF72 mutation ([Gendron et al., 2017](#)). Studies in mice carrying the C9ORF72 mutation showed reduced poly(GP) levels in mice treated with an antisense oligonucleotide targeting the mutant RNA. The poly(GP) protein could serve as a useful biomarker in clinical trials of drugs for C9ORF72-linked ALS and FTD.

Working Together Toward a Cure

With the historic and unprecedented investment in research, we have made substantial progress in understanding the complexity of Alzheimer's disease and related dementias. From basic biology and genetics to translational and preclinical targets and new approaches to clinical trials, disease monitoring, and care, the advances are many. However, there is much more to accomplish, and many questions remain unanswered.

To bring us closer to solving these questions, NIH is building and strengthening an infrastructure to enable researchers to collect, share, and analyze big data in ways never before possible. This open-science approach has fostered partnerships and collaborations among public and private sectors nationally and internationally, resulting in broad and rapid sharing of research tools and data. And the increased funding has allowed us to not only take advantage of the talent of established Alzheimer's researchers, but to recruit to the field new and creative thinkers who may not have realized that what they were doing might advance the cause.

With the infrastructure and tools being built, research outlined in this Professional Judgment Budget must continue to move forward through studies focused on multiple approaches including:

- Developing a better understanding of the complex and multifactorial causes of Alzheimer's disease and related dementias
- Enabling precision medicine research to develop interventions that can address the underlying disease process, as well as the disease symptoms, and be tailored to a person's unique disease risk profile for Alzheimer's disease
- Enhancing the research infrastructure and developing translational tools to accelerate therapy development
- Understanding the impact of the environment and its interaction with genetic and biological factors to advance effective prevention strategies for Alzheimer's disease

- Leveraging emerging digital technologies and big data approaches to improve our ability to discover early markers of disease, better track responsiveness to treatment, and provide better care
- Supporting research on the development of effective dementia care, services, and supports
- Developing comprehensive models of care for people living with dementia and their caregivers

These efforts will ideally lead to individualized treatments for people at risk for dementia, as well as improvements in care and services that make life better for people with dementia and their caregivers.

Finding a cure for Alzheimer's disease and related dementias will take teamwork and commitment from all of us. The transformative research agenda is in place. Now is the time to press on. Working together, we can find a cure for Alzheimer's disease and related dementias.

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