



LEADING THE CHARGE

Expanding Collaborative, Cross-Disciplinary
Research for the Prevention, Treatment,
and Care of Dementia





“Because of NIH’s strategic research investments in Alzheimer’s disease and related dementias, we have made significant scientific progress toward understanding what causes these diseases, as well as developing interventions that may prevent and treat them.”

Francis S. Collins, M.D., Ph.D., NIH Director

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Message from the Director

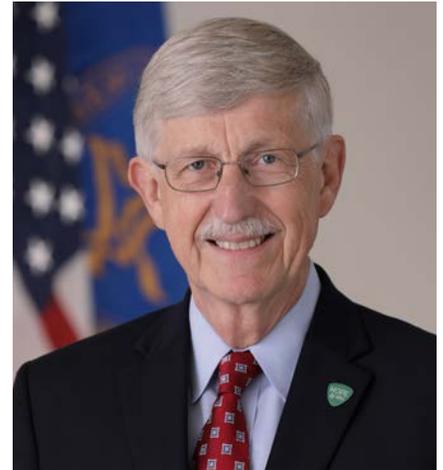
July 20, 2020

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 for fiscal year (FY) 2022. This bypass budget proposal outlines the additional funding needed in FY 2022 to advance NIH-supported research on Alzheimer's and related dementias toward the 2025 research goal for treatment or prevention.

During the five years since our first bypass budget, the increased investment in federal funding for Alzheimer's and related dementias has enabled NIH to embark on an ambitious research agenda. We have made much progress toward better understanding these complex diseases, and we continue to make significant advances in discovering approaches that may prevent, diagnose, and treat them. Some of the key areas of recent successes are described in this report. With continued investments in Alzheimer's and related dementias, NIH is poised to build upon these achievements.

Earlier in 2020, when we were in the midst of analyzing our progress and formulating this FY 2022 budget proposal, the global coronavirus disease 2019 (COVID-19) pandemic forced most of us to vacate our NIH offices to run our agency from our homes. While we have been able to keep many aspects of the NIH mission going forward, we temporarily had to close many laboratories and also delayed a substantial number of clinical trials to minimize the spread of the virus. We remain mindful that research progress was delayed substantially during this time and cannot yet predict the magnitude of the impact this unprecedented situation will have on scientific progress today and in future years. Still, our collective dedication and commitment to research to improve health and well-being, including studies on Alzheimer's and related dementias, remains unwavering.

As we persevere, critical discussion among a diverse group of stakeholders continues to be essential for ongoing enhancements to our Alzheimer's and related dementias research strategies. This collaborative approach provides the best opportunities for achieving our collective goals and has better enabled:



*Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health*

- **Multidisciplinary expertise and approaches.** We enlist experts in genetics, epidemiology, gerontology, behavioral science, disease biology, and structural biology, as well as in data science, assay development, biomarker development, medicinal chemistry, computational biology, pharmacology, clinical science, and drug discovery, to name a few.
- **Recruitment of new investigators.** We encourage young scientists representing a variety of disciplines and with many different skillsets to devote their careers to finding new methods of prevention, diagnosis, and treatment. By including fresh perspectives from both early and seasoned investigators, we may be better able to formulate and research novel hypotheses about solutions to the challenges of dementia.
- **Partnerships with other government agencies, advocacy groups and foundations, thought leaders, the pharmaceutical and biotechnology industry, and technology companies.** Through these collaborations, we have expanded openly available research resources to the broader research community.
- **Research summits, workshops, and conferences.** Although most of our interactions have by necessity been virtual since March 2020, NIH obtains input from a vast range of stakeholders to ensure we are maximizing opportunities. It is important to emphasize that our stakeholders at summits and other gatherings are not only scientists and administrators but also the men and women with Alzheimer's and related dementias and their family members and caregivers. They help shape the research program not only by providing their perspectives but also by participating as research volunteers, which is essential for the development of treatments and other interventions.

The FY 2022 Professional Judgment Budget Estimate for Alzheimer's Disease and Related Dementias includes \$289 million in additional resources for new research, with the overall resources needed totaling \$3.1 billion. To arrive at this budget estimate, NIH accounted for many factors. First, the FY 2021 estimate for Alzheimer's and related dementias spending, based on the President's budget, is \$254 million below the FY 2020 estimated (enacted) funding level. The FY 2022 estimate includes funding to compensate for this reduction and adds the \$289 million in additional resources needed for new research, which is noted above. As a result, the total FY 2022 budget estimate is \$543 million above the FY 2021 President's budget. NIH also considered funding that is projected to become available after completion of previously funded research initiatives, and that is reflected in the \$289 million estimate.

Diagnosing, treating, and caring for people with Alzheimer's and related dementias is a global challenge that requires a far-reaching, multifaceted strategy. As the economic costs of care continue to climb — along with costs associated with loss of independence and quality of life — we are more driven than ever to discover, develop, disseminate, and implement solutions that will improve the lives of those with dementia, their caregivers, and their communities.

/Francis S. Collins/
 Francis S. Collins, M.D., Ph.D.
 Director, National Institutes of Health

Introduction



Experts have estimated that as many as 5.8 million Americans 65 and older in 2020 have **Alzheimer’s disease** dementia, and the prevalence in the United States is projected to increase to 13.8 million by 2050. Alzheimer’s is the most common dementia diagnosis and the sixth leading cause of death for Americans. In addition, many people have other forms of dementia, such as **Lewy body disease**, **frontotemporal disorder**, and **vascular cognitive impairment**, either alone or more commonly mixed with Alzheimer’s changes.

But these statistics do not begin to capture the enormous impact dementia has on family caregivers, long-term care facilities, health care providers, health care systems and infrastructure, and the communities in which we all live. An analysis conducted by NIH-supported researchers found that total health care spending for a person with probable dementia in the last five years of life was an estimated \$287,000, compared with \$175,000 for an individual with heart disease and \$173,000 for someone with cancer. One of the key research goals of the **National Plan to Address Alzheimer’s Disease**, issued in 2012, is to prevent and effectively treat Alzheimer’s and related dementias by 2025.

CDC’s 10 leading causes of death	
1.	Heart disease
2.	Cancer
3.	Accidents (unintentional injuries)
4.	Chronic lower respiratory diseases
5.	Cerebrovascular diseases (stroke)
6.	Alzheimer’s disease <i>120,000 deaths, 4.3% of all deaths, a 2.3% increase between 2016 and 2017</i>
7.	Diabetes
8.	Influenza and pneumonia
9.	Kidney disease
10.	Suicide

Source: Kochanek KD, et al. *Mortality in the United States, 2016*. National Vital Statistics Reports. 2019;68(9).

Alzheimer’s Disease-Related Dementias

More often than not, people with a diagnosis of Alzheimer’s disease have a mixture of brain pathologies, which complicates both diagnosis and treatment. NIH’s research initiative to decrease the burden of dementia includes the Alzheimer’s disease-related dementias, such as Lewy body dementia, frontotemporal dementia, vascular dementia, and others.

These diseases share many features with Alzheimer’s and can be difficult to distinguish from it. Also, because most cases of dementia are a mixture of brain pathologies, it is critical to understand how and why several distinct dementia-related brain changes can develop at the same time. NIH is investing in research to better understand these various disorders and develop personalized prevention and treatment strategies.

For more information about related dementias, see the following NIH fact sheets and descriptions of NIH research programs:

- [What Is Dementia? Symptoms, Types, and Diagnosis](#)
- [The Dementias: Hope Through Research](#)
- [What Are Frontotemporal Disorders?](#)
- [What Is Lewy Body Dementia?](#)
- [Vascular Contributions to Cognitive Impairment and Dementia](#)
- [Focus on Alzheimer’s Disease and Related Dementias Research](#)
- [Focus on Lewy Body Dementia \(LBD\) Research](#)
- [Focus on Frontotemporal Dementia \(FTD\) Research](#)
- [Focus on Vascular Contributions to Cognitive Impairment & Dementia \(VCID\) Research](#)
- [Focus on Mixed-Etiology Dementias \(MED\) Research](#)
- [Alzheimer’s Disease-Related Dementias Summit 2019 Research](#)

We present this budget estimate in accordance with Public Law No. 113-235, the Consolidated and Further Appropriations Act, 2015, Sec. 230, which states the following:

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.

Because this budget estimate is provided directly to the President and to Congress outside of the traditional annual federal budget process for NIH, it is considered a “bypass budget.” This professional judgment budget estimates the additional effort needed each fiscal year to meet the 2025 goals of finding effective methods of treatment and prevention for Alzheimer’s and related dementias.

The research component of the national plan outlines the basic, translational, and clinical research needed to better understand Alzheimer’s and related dementias and to develop approaches to prevent, diagnose, treat, and care for people with dementia.

Each year, to update the strategy, NIH engages a broad range of stakeholders through national research summits as well as smaller focused scientific workshops and other events. These have involved hundreds of scientific experts across diverse fields of dementia and other research, as well as people with dementia and those who care for them, advocates, and policymakers. The purposes are to:

- Review scientific progress
- Identify gaps and opportunities for dementia research
- Prioritize the important scientific questions that must be answered to advance understanding of these complex disorders
- Identify how federal agencies, academic researchers, nonprofit organizations, and private industry can most effectively collaborate to address research priorities

Held in March 2019, the most recent [Alzheimer’s Disease-Related Dementia Summit](#) resulted in the identification of 47 research gaps and opportunities to help guide future studies of Lewy body, frontotemporal, vascular, and mixed dementias. Two emerging areas of importance were also included: understanding the role of traumatic brain injury in dementia as well as the role in common dementias of a protein called TDP-43, which like other Alzheimer’s-related proteins is prone to form toxic aggregates. Many central themes characterized the summit, including the pressing need for biomarkers, especially because of how common mixed pathologies are in dementia, and continued efforts to ramp up laboratory, clinical, and translational research. Participants also discussed ideas for enhancing health disparities research, strengthening research infrastructure and training, and developing a common nomenclature across the dementia research and practice communities.



NIH charts the course through a series of milestones, which are captured in the [AD+ADRD \(Alzheimer's Disease and Alzheimer's Disease-Related Dementias\) Research Implementation Milestones database](#). This systematic planning process informs the research community about NIH's interests in and priorities for funding projects in Alzheimer's and related dementias. The milestones are meant to be used by all stakeholders, not solely NIH, as a basis for independent but relevant research pursuits or for collaborations. The National Institute on Aging (NIA), which oversees NIH research on Alzheimer's and related dementias, leads the development and implementation of research milestones in close collaboration with the National Institute of Neurological Disorders and Stroke (NINDS), as well as with multiple other NIH Institutes, Centers, and Offices (ICOs).

In collaboration with the Alzheimer's Association, in 2010 NIA launched the [International Alzheimer's and Related Dementias Research Portfolio \(IADRP\)](#). This database, which is updated on a regular basis, provides a comprehensive assessment of research projects supported by more than 40 public and private organizations in more than 10 countries. The purpose of the IADRP is to help organizations understand where research gaps are, avoid duplication of effort, and leverage resources by coordinating funding strategies.

Broad NIH Support for Alzheimer's and Related Dementias Research

Researchers with grants from any of the NIH components can apply for supplemental funding for research relevant both to Alzheimer's and related dementias and to the topic of their existing grant. Each year, representatives from NIA, NINDS, and other NIH ICOs discuss opportunities for research and collaborations in Alzheimer's and related dementias. The other ICOs are:

- [Eunice Kennedy Shriver National Institute of Child Health and Human Development](#)
- [Fogarty International Center](#)
- [National Center for Complementary and Integrative Health](#)
- [National Heart, Lung, and Blood Institute](#)
- [National Institute of Allergy and Infectious Diseases](#)
- [National Institute of Arthritis and Musculoskeletal and Skin Diseases](#)
- [National Institute of Biomedical Imaging and Bioengineering](#)
- [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 Mental Health](#)
- [National Institute of Nursing Research](#)
- [National Institute on Alcohol Abuse and Alcoholism](#)
- [National Institute on Deafness and Other Communication Disorders](#)
- [National Institute on Minority Health and Health Disparities](#)
- [Office of AIDS Research](#)
- [Office of Science Policy](#)

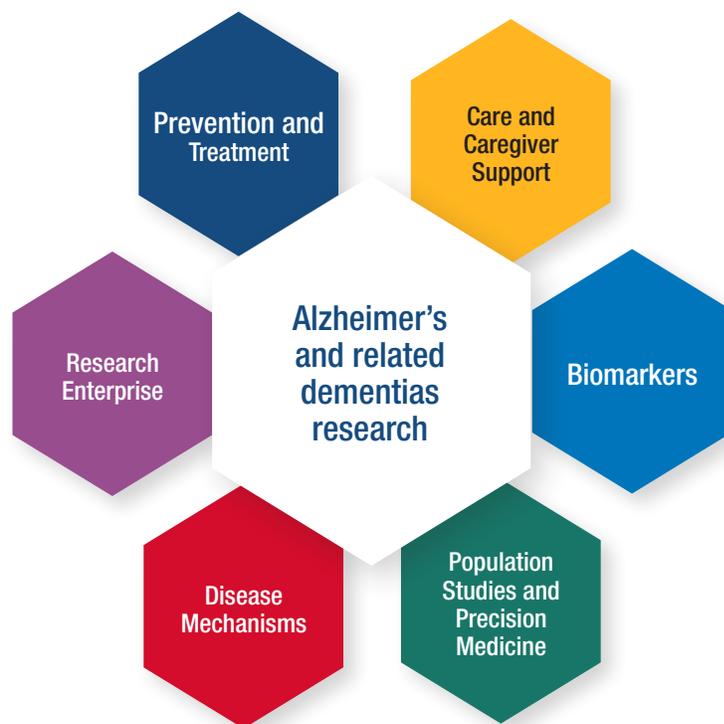
Budgeting in FY 2022 to Fight Dementia

The FY 2022 Professional Judgment Budget for Alzheimer’s Disease and Related Dementias shows \$289 million in additional resources needed for new research, with the total resources needed for Alzheimer’s and related dementias research totaling \$3.107 billion. In FY 2022, the projected costs of resources needed for new research to enhance investigator-initiated research grants and initiatives to meet the 2025 treatment and prevention goal is \$434 million. This estimate will be reduced by \$145 million in funding that is projected to become available after completion of previously funded Alzheimer’s and related dementias research initiatives. As a result, the additional resources needed for new research in the FY 2022 budget is \$289 million.

In FY 2022, the total resources needed for Alzheimer’s and related dementias research is \$3.107 billion. The total budget takes the FY 2021 President’s budget funding level of \$2.564 billion for Alzheimer’s and related dementias research as the baseline estimate, restores \$254 million to account for the difference between the FY 2021 President’s budget funding level and the FY 2020 estimated (enacted) funding level for Alzheimer’s and related dementias research of \$2.818 billion (Consolidated Appropriations Act, 2020, P.L. 116-94) and concludes that \$289 million in additional resources is needed for new research. As a result, the total FY 2022 Professional Judgment Budget is \$543 million greater than the FY 2021 President’s budget.

Overall, the \$3.107 billion Professional Judgment Budget is needed to sustain momentum in Alzheimer’s and related dementias research in FY 2022. These funds would enable NIH to advance research to improve the diagnosis, treatment, and care of those living with dementia by identifying and testing new drug candidates, advancing comprehensive models of care, developing novel biomarkers for use as screening tests and to monitor treatment response, exploring disease risk and protective factors, and improving the understanding of the role of genetics and other disease mechanisms.

Breadth of NIH-Supported Research on Alzheimer’s and Related Dementias



As NIH was in the process of analyzing progress thus far and formulating our FY 2022 budget recommendation, the COVID-19 pandemic began and rapidly evolved. As a result, NIH and the broader research community began to consider new areas of research with relevance to Alzheimer’s and related dementias, such as studies on the susceptibility of people living with these conditions to COVID-19. In particular, people living with dementia in nursing homes and long-term care facilities are especially vulnerable, but little is known about how to reduce their risk of infection or improve their care, or how COVID-19 infection may interact with structural and functional changes that occur in AD. Research has now begun in these areas.

The immediate and future impact of COVID-19 on the conduct of Alzheimer’s and related dementias research, as for all biomedical research, is uncertain. We anticipate that we will be better able to project the impact of the pandemic on research progress and costs in future years.

Still, in times of economic downturns, investments in biomedical research by funding new grants and initiatives do more than advance scientific progress; they also provide opportunities for new jobs to sustain and grow the American workforce and economy. With sustained public support of these research initiatives, NIH is poised to continue making great strides in progress despite any setbacks due to COVID-19. Thanks to previous investments, we have the infrastructure in place to achieve our research milestones for the prevention, treatment, and care of dementia through comprehensive, collaborative research.

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Reporting Scientific Advances

This FY 2022 bypass budget proposal narrative provides a snapshot of our scientific progress toward the [AD+ADRD Research Implementation Milestones](#) in several areas by highlighting a few select programs and research findings. More detail is provided through embedded hyperlinks to additional resources and information, including recent [NIH news releases](#) and [NIH Director’s Blog posts](#).

This narrative also links to many of NIA’s [featured research articles](#) about Alzheimer’s and related dementias research. In addition to providing links to related journal articles, featured articles also link to relevant research milestones.



Fiscal Year 2022 Professional Judgment Budget: Alzheimer's Disease and Related Dementias

Baseline Estimate, President's Budget, Fiscal Year 2021 Alzheimer's Disease, Including Alzheimer's Disease-Related Dementias (AD/ADRD)¹ **\$2,564,000,000**

Professional Judgment Budget FY 2022, Projected Costs, and Additional Resources Needed

Areas of Research	Amount
Molecular Pathogenesis and Pathophysiology of Alzheimer's Disease	\$51,500,000
Diagnosis, Assessment, and Disease Monitoring	\$26,000,000
Translational Research and Clinical Interventions	\$131,100,000
Epidemiology	\$56,000,000
Care and Caregiver Support	\$39,500,000
Research Resources	\$82,700,000
Alzheimer's Disease-Related Dementias	\$43,305,222
Staffing Needs and Administrative Support	\$3,993,000
Total Costs for New AD/ADRD Research	\$434,214,444
Less: Funding from Prior Appropriations that is available for New AD/ADRD Research	(\$145,000,000)
ADDITIONAL FY 2022 Resources Needed for New AD/ADRD Research²	\$289,214,444

Professional Judgment Budget FY 2022 Total Resources Needed

Factor	Amount
FY 2021 President's Budget Request for AD/ADRD Research (Baseline estimate)	\$2,564,000,000
Difference between the FY 2021 President's Budget Request and FY 2020 Appropriation for AD/ADRD Research ³	\$254,000,000
ADDITIONAL FY 2022 Resources Needed for New AD/ADRD Research	\$289,214,444
TOTAL FY 2022 Resources Needed for AD/ADRD Research	\$3,107,214,444

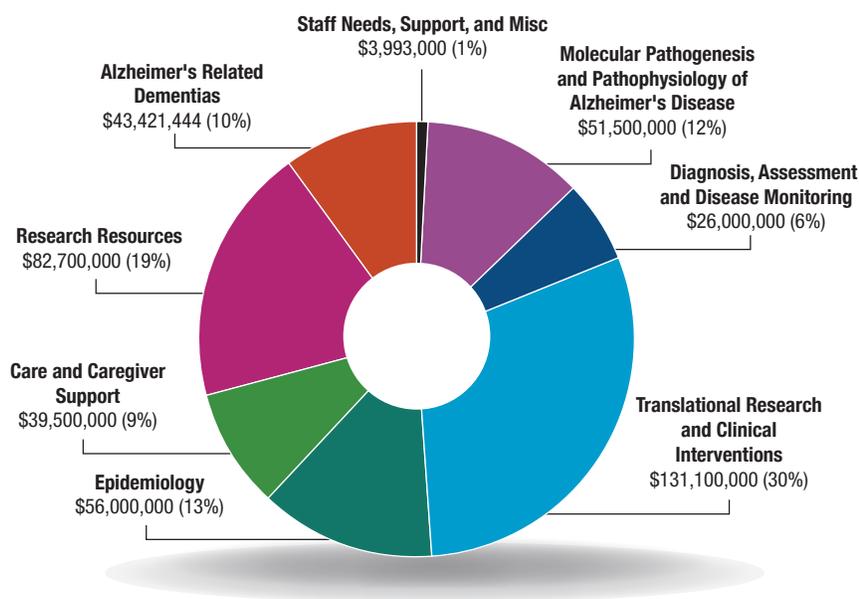
¹ Baseline estimate includes Alzheimer's disease, frontotemporal dementia, Lewy body dementia, and vascular cognitive impairment/dementia. Individual disease baseline estimates are available on the NIH Categorical Spending website at https://report.nih.gov/categorical_spending.aspx.

² In FY 2022, the projected costs of resources needed for new research to enhance investigator-initiated research grants and initiatives to meet the 2025 treatment/prevention goal is \$434 million. This estimate will be reduced by \$145 million in funding that is projected to become available after completion of previously funded AD/ADRD research initiatives. As a result, the additional resources needed for new research in the FY 2022 budget is \$289 million.

³ Estimated (enacted) \$2.818 billion (AD/ADRD research funding from the Consolidated Appropriations Act, 2020) – estimated \$2.564 billion (AD/ADRD research funding from the FY 2021 President's budget) = \$254 million.



Distribution of FY 2022 Projected Costs Across Research Areas



Total Projected Costs:

\$434,214,444*

Additional Resources Needed for New Research:

\$289,214,444

**In FY 2022, the projected costs of resources needed for new research to enhance investigator-initiated research grants and initiatives to meet the 2025 treatment/prevention goal is \$434 million. This estimate will be reduced by \$145 million in funding that is projected to become available after completion of previously funded AD/ADRD research initiatives. As a result, the additional resources needed for new research in the FY 2022 budget is \$289 million.*

Prevention and Treatment Research



“Alzheimer’s and related dementias are among the greatest public health challenges of this century. NIH is investing in innovative research to identify treatments as well as lifestyle interventions that can delay the onset or slow the progression of these devastating diseases.”

Richard J. Hodes, M.D.,
NIA Director



Alzheimer's and related dementias are highly complex conditions. They usually develop gradually: Changes in the brain take place over years and decades, long before the first symptoms appear. These complexities can be exceptionally challenging for researchers committed to discovering, developing, and disseminating new drugs and other approaches to treat and prevent these devastating diseases.

Currently, physicians can prescribe medicines that help abate some of the symptoms of Alzheimer's and related dementias. These therapies may help people temporarily maintain mental function, reduce symptoms of agitation or aggression, and slow the worsening of memory loss. Although treatments may help some people remain independent for a longer time, the dementias invariably worsen.

While researchers worldwide continue to work tirelessly to find ways to prevent and more effectively treat Alzheimer's and related dementias, it is unlikely that any single intervention will successfully halt or reverse the effects of these diseases for everyone. Much like what has been achieved for cancer treatments, which can be directed specifically against subtypes of that disease for targeted interventions, the hope for improved dementia treatment is to be able to tailor a therapy or combination of interventions to an individual's unique disease characteristics.

With this precision medicine approach in mind, NIH is advancing research through its support of large-scale genetic mapping of people with dementias, molecular studies of existing groups of research participants, identification of biomarkers that can distinguish between different subtypes of dementia, and novel behavioral, social, and environmental factors associated with risk in long-term population studies. As precision medicine researchers uncover how the variety of genetic, biological, environmental, social, and lifestyle factors interact to elevate or reduce the risk of Alzheimer's and related dementias, there will be more scientific avenues for developing precise treatments and preventions for the different types and subtypes of Alzheimer's and related dementias.

The tremendous public investment in NIH-funded research over the past five years has enabled scientists to pursue many of these avenues simultaneously as they study promising drug treatments that act upon many different elements of the disease pathway. Concurrently, researchers are using data from population studies to find additional risk and protective factors that will help them develop and test specific treatment and prevention strategies. Some approaches do not rely on drugs; rather, they focus on behavior changes and lifestyle choices such as the careful control of high blood pressure, which is an established risk factor for dementia.

NIH-supported, collective advances in genomic and population research, as well as in data science, have contributed significantly to enhanced understanding of the underlying biology of Alzheimer's and related dementias. Simultaneously, technological innovations, such as the use of machine learning to create better disease models from vast amounts of data, as well as investments in research infrastructure, have enabled more scientific discovery and greatly propelled us further along in finding more effective treatments and ways to delay symptoms and disease progression.



The Drug Development Pipeline

A key part of NIH’s strategy for developing new treatments for Alzheimer’s and related dementias is to bolster the drug discovery and development pipeline. This section on prevention and treatment research focuses on the many NIH-supported clinical trials currently testing several different types of drugs for Alzheimer’s and related dementias. NIH’s strategy helps ensure scientists are addressing these multifaceted diseases through a wide range of approaches. The infrastructure for our drug discovery process to develop new medicines is described later in the [Research Enterprise](#) section, which highlights preclinical development.

Historically, the length of time required for researchers to discover a biological mechanism of disease, such as a gene variant that does not function normally, and then develop an effective treatment without toxic side effects has been 12 to 15 years. Additionally, very few drug candidates succeed through the pipeline to reach Food and Drug Administration (FDA) approval, because they are not found to be both safe and effective. To accelerate the discovery of effective treatments that will become broadly available to the public, NIH has developed programs to make data, knowledge, and research tools widely available to all researchers. Instead of competing with each other, stakeholders in industry, academia, and government are collaborating to reach a common goal: developing effective treatments for Alzheimer’s and related dementias.

Thanks to the substantial investment in Alzheimer’s and related dementias research over the past several years, NIH has increased drug discovery significantly. Of the many drug candidates in NIH-supported drug development programs for Alzheimer’s and related dementias, 10 have now matured through the preclinical development pipeline to reach the clinical trial stage. These 10 drug candidates target multiple aspects of the disease process, as shown in the chart below. Of these 10, three graduated to clinical testing in 2019. One (AV-1959) is a DNA vaccine against the amyloid deposits that build up in the

brains of people with Alzheimer’s, another (AAV2-BDNF) is a gene therapy to deliver a nerve-protective protein to prevent nerve cell loss, and the third (NNI-362) is a drug that may stimulate new neurons to grow.

MW-151, also featured in the chart below, is an example of a drug candidate now in clinical trials that was developed with NIH support, including a Small Business Innovation Research (SBIR) grant. MW-151 is being tested in humans for the ability to lessen inflammation in the brain. Too much inflammation can damage brain cells and is one of the mechanisms leading to dementia.



10 NIH-Funded Drug Candidates Now Being Tested in Clinical Trials for Alzheimer’s and Related Dementias

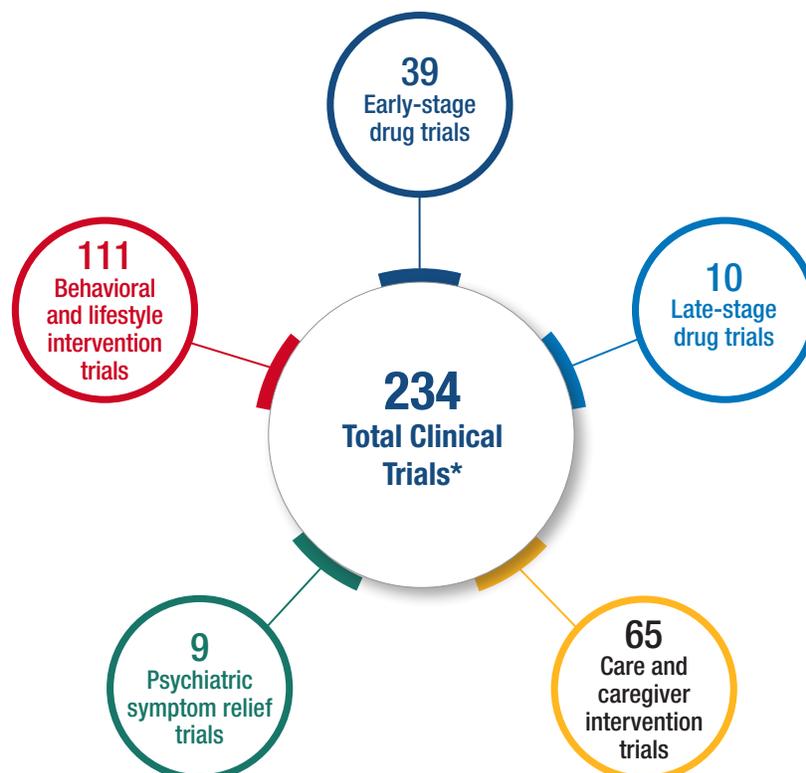
Drug candidate	How it works
LM11A-31	Promotes nerve cell survival
Elayta (CT1812)	Prevents beta-amyloid toxicity
BPN14770	Protects from losing neuron connections
Allopregnalone	Promotes nerve cell growth
MW151	Inhibits brain inflammation
MW150	Inhibits brain inflammation
PU-AD	Promotes degradation of toxic proteins
NNI-362	Promotes new neuron growth
AV-1959 DNA vaccine	Clears amyloid brain deposits
AAV2-BDNF gene therapy	Prevents nerve cell loss

NIH’s SBIR and Small Business Technology Transfer (STTR) programs are an integral source of capital for early-stage U.S. small businesses that are creating innovative technologies to improve health. These programs help small businesses break into the federal research and development arena, create life-saving technologies, and stimulate economic growth. This funding helps the private sector bring promising technologies to the consumer market. Through these programs, NIH is leveraging the economic engine of small businesses to enhance scientific innovation. Before the increased funding for Alzheimer’s and related dementias (2010-2013), NIA awarded 69 SBIR/STTR grants to 62 small companies. After the increased appropriations (2016-2019), NIA more than tripled that achievement by awarding 231 SBIR/STTR grants to 221 companies for discovery and development of new treatments, as well as biomarker research and technologies for improving care and caregiving.

As potential drug candidates make it through the development pipeline to be tested in clinical trials, the **NIA-Funded Active Alzheimer’s and Related Dementias Clinical Trials and Studies** list is continuously updated on NIA’s public website. The sections are divided into categories of how the drug candidates target the disease process:

- **Section 1: Early-Stage Clinical Drug Development**
- **Section 2: Late-Stage Clinical Drug Development**
- **Section 4: Clinical Therapy Development for the Neuropsychiatric Symptoms of Dementia**

Active NIH-Supported Trials for Alzheimer’s and Related Dementias



*As of April 2020. For the latest information, visit <https://www.nia.nih.gov/research/ongoing-AD-trials>

Phase 1 to Phase 4 Drug Trials

Most of the NIH-supported trials for Alzheimer's and related dementias are in an early stage, which means Phase 1 or Phase 2 trials, but several Phase 3 trials are also in progress. According to FDA, [with each successive phase](#), a longer period of time and more participants are needed to conduct the study.

- Phase 1.** Phase 1 trials typically involve 20 to 100 participants for several months. These trials are designed to answer questions about safety and dosage. About 70% of all drugs tested in Phase 1 proceed to Phase 2. It is important to keep in mind that FDA regulates many kinds of drugs, not just those for Alzheimer's and related dementias, and these statistics refer to all drugs in the development pipeline.
- Phase 2.** The second phase of drug testing continues safety testing and can require up to several hundred participants for several months to two years. About 33% of all FDA-regulated drugs move from Phase 2 to Phase 3.
- Phase 3.** Hundreds to thousands of participants are needed over one to four years for Phase 3 trials. These larger, longer studies enable experts to evaluate how effective interventions are and to detect whether using the drug may cause long-term or rare side effects. Only about 25% of all FDA-regulated drugs move beyond Phase 3 in the drug development pipeline toward commercialization because the data provide evidence of treatment benefit without unacceptable side effects.

SCIENCE SPOTLIGHT: Testing a New Drug Before Symptoms of Alzheimer's Begin

Through the NIA-sponsored Phase 3 [Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease \(A4\) study](#), researchers are testing whether a drug can prevent cognitive decline if given before symptoms of Alzheimer's begin. In 2014, A4 was a first-of-its-kind study, because the investigators used PET imaging so that they could select participants who were cognitively normal but were at risk of dementia from high levels of amyloid in the brain.

[Analysis of the A4 screening data reported in early 2020](#) supports the hypothesis that higher levels of amyloid in the brain, as detected with PET scans, represent an early stage of Alzheimer's. Among participants who were not cognitively impaired, high amyloid levels were associated with lower performance on cognitive tests and subtle changes in daily cognitive function.

Before amyloid PET imaging was available, previous clinical trials enrolled participants without knowing

whether they had amyloid in the brain. Experts believe the lack of biomarkers at that time may explain in part why clinical trials that tested anti-amyloid drugs have not been successful to date.

Although the researchers are sharing data now about the screened individuals to help advance knowledge about factors influencing cognitive functioning, the main purpose of the A4 study is to test whether the drug known as solanezumab can prevent cognitive decline. The people enrolled in the A4 study are receiving the drug during 66 visits to the clinic over 240 weeks, and the study is expected to be complete in late 2022.



After a drug has been approved by FDA and is marketed, Phase 4 trials are sometimes conducted. In 2019, NIH funded a Phase 4 drug study called [**Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults \(PREVENTABLE\)**](#). Through this Phase 4 trial, researchers will examine the overall benefits and risks of a commercially available cholesterol-lowering drug known as atorvastatin in 20,000 adults age 75 or older without cardiovascular disease. The trial will help determine whether the drug can help prevent dementia and disability in this age group, as well as prevent heart attacks and other cardiovascular-related deaths, without increasing adverse health outcomes.

For a more in-depth look at the research implementation milestones in this area, including progress and accomplishments, visit [**www.nia.nih.gov/research/milestones/translational-clinical-research-pharmacological**](http://www.nia.nih.gov/research/milestones/translational-clinical-research-pharmacological).

Looking to Behavioral and Lifestyle Interventions for Prevention and Treatment

Researchers are also investigating behavioral patterns and other lifestyle choices that may prevent dementia or slow the progression from mild cognitive impairment to dementia. These studies of nondrug approaches are based on results from population studies that can identify groups of people with certain lifestyle factors, such as a higher level of physical activity, who may also have a lower risk of dementia. Scientists can then design and conduct interventional studies to investigate whether changes in these lifestyle factors really can cause changes in dementia risk. Results from carefully controlled clinical trials where interventions are randomly assigned to participants can provide strong evidence about the causal role of lifestyle factors in dementia risk.

[**Section 3 of the NIA-Funded Active Alzheimer's and Related Dementias Clinical Trials and Studies list**](#) shows more than 100 nondrug clinical trials in progress. Today, NIH supports studies of a variety of approaches, including whether increasing [**physical activity**](#), making healthy [**dietary choices**](#), or getting sufficient [**sleep**](#) may improve cognitive health. Researchers have also developed other approaches to try to help adults who are concerned about cognitive impairment or dementia, including studies to test the next generation of computerized [**cognitive training**](#) interventions.

This increase in activity followed an NIH-supported systematic review in 2011 to explore the results from already completed studies to determine whether there was sufficient scientific evidence for any prevention approaches that could be shared as public health recommendations about specific ways to prevent dementia. After analyzing the available medical literature, the reviewers concluded there was not yet enough evidence to make such recommendations and pointed to the need for additional work to increase the level of evidence.

Still, because many factors were robustly associated with improvements in cognitive outcomes in observational studies, researchers continued to explore the connection between lifestyle choices and the development of dementia. By 2015, enough new data had accumulated to justify another systematic review of the literature. Based on this rigorous analysis, a [**National Academies of Sciences, Engineering, and Medicine report**](#) identified three areas of research as being supported by “encouraging although inconclusive” evidence: blood pressure management for people with hypertension, cognitive training, and increased physical activity. In addition to these areas, the report suggested pursuing other approaches to reducing the risk of developing dementia, including making certain dietary changes, improving sleep quality, and enhancing social engagement.

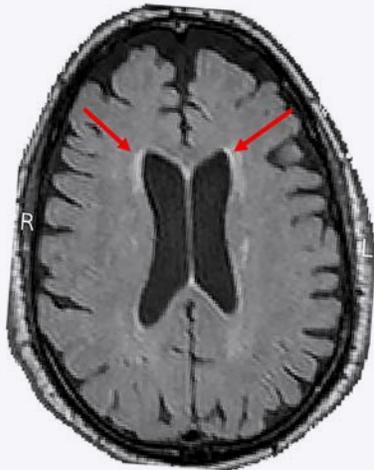


NIH continues to support investigations in all these areas to better understand the potential links between these and other lifestyle interventions and dementia. In 2019, investigators with the **NIH-funded Systolic Blood Pressure Intervention Trial (SPRINT)** published even stronger evidence for the benefits of blood pressure management:

- A study called SPRINT Memory and Cognition in Decreased Hypertension (SPRINT MIND) demonstrated that people who intensively control their blood pressure with one or more drugs can significantly reduce their risk of developing **mild cognitive impairment**, which is a well-established precursor of dementia. Intensive control was defined as reducing the systolic blood pressure below 120 millimeters of mercury (mmHg), rather than the standard goal of reducing it below 140 mmHg.
- The second report from SPRINT MIND suggested that intensively controlling blood pressure was more effective than standard treatment at slowing the accumulation of **abnormal white areas** on MRI brain scans. These abnormal areas represent an increase in water content and reflect a variety of changes deep inside the brain, including multiple strokes, leaky blood vessels, and other causes.
- Findings from a related clinical trial called **Intensive Versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline In the Elderly (INFINITY)** were consistent with the SPRINT MIND results. The INFINITY trial indicated that, after three years of treatment, intensive lowering of blood pressure slowed white matter disease in adults age 75 and older with high blood pressure.

Behavioral and Lifestyle Intervention Research for Alzheimer’s and Related Dementias





NIH-funded Systolic Blood Pressure Intervention Trial found link between uncontrolled high blood pressure and abnormally bright white areas (at red arrows) on MRI scans of the brain. Credit: SPRINT MIND Investigators.

Several previous observational studies also suggested that people who have uncontrolled high blood pressure have a greater chance of accumulating white matter lesions and also of experiencing cognitive disorders and dementia later in life, as described in detail with references on [NIH’s Mind Your Risks website](#).

For a more in-depth look at the research implementation milestones in this area, including progress and accomplishments, visit www.nia.nih.gov/research/milestones/translational-clinical-research-non-pharmacological.

The Urgent Need for Increased and Diverse Participation in Studies

The increased investment in Alzheimer’s and related dementias research has enabled the scientific community to ask and pursue broad clinical questions. With the increased number of treatment, prevention, and care studies comes the urgent need to recruit and enroll dozens to thousands of participants. Alzheimer’s and related dementias research studies especially need participants

who better represent the diversity of the U.S. population. To address the imperative for diverse participation in clinical studies, NIH is investing in a range of methods, resources, and research to help investigators with recruitment and retention:

- NIA, in collaboration with the Alzheimer’s Association, sought expertise and insights from stakeholders representing government, nonprofit organizations, private industry, and academic institutions, as well as individuals with dementia, their caregivers, and active study participants. Released in late 2018, [Together We Make the Difference: National Strategy for Recruitment and Participation in Alzheimer’s and Related Dementias Clinical Research](#) is a compilation of the information and guidance obtained, and outlines steps needed, to address the challenges and opportunities for recruitment. NIA plans to convene a meeting of key stakeholders, both those who participated in the strategy’s development and those engaged in implementation efforts, to address several key topics, including:
 - » Reporting on progress made thus far for each goal, both from NIA and its grantee researchers across the nation
 - » Identifying remaining challenges to the strategy’s implementation
 - » Setting priority areas and goals for the next three years to build on progress, address the gaps identified, and disseminate lessons learned to date
 - » Ensuring that recruitment strategies support ethical and inclusive approaches that address the broad spectrum of people with dementia.
- To provide researchers with practical and proactive approaches for engaging a wider, more diverse range of research participants, NIH is investing in a vast range of supportive resources, including the [Why I Participate in Alzheimer’s Research](#) video series, developed and released in 2019. This series is designed to motivate individuals to volunteer for research by enabling

them to hear members of underrepresented communities describe their personal stories of why they chose to enroll in an Alzheimer's study.

- NIA continues to develop outreach and education materials that take into consideration a range of cultural and language-specific communication needs and preferences:
 - » In 2019, NIA conducted formative research to develop a set of materials tailored to African American audiences, including videos, print ads, posters, social media, and other multimedia messages.
 - » In 2020, NIA is using a similar approach to develop a set of materials, tailored to Latinos, in both English and Spanish. Formative research and communication activities to enhance outreach to other underrepresented populations will be conducted in subsequent years.
 - » NIA is currently developing a web-based communication tool that will enable health care professionals in the community to easily produce a package of tailored materials and strategies that can be branded locally to increase participant recruitment for clinical studies. This web-based tool will allow the research community to access, adapt, and personalize the materials that NIA has developed for underrepresented communities.
- As part of the implementation of the national strategy, [NIA's website](#) features [Alzheimer's & Dementia Outreach, Recruitment & Engagement Resources \(ADORE\)](#), an online, searchable database of materials for clinical trials recruitment and retention. The ADORE platform is designed to facilitate the sharing of materials on topics related to engagement, recruitment, and retention of participants in clinical studies. Resources in ADORE, such as the Why I Participate in Alzheimer's Research videos described above, represent some of the materials and activities developed by NIA-supported Alzheimer's disease research centers

Developing Improved Methods for Recruiting Diverse Study Participants

NIH is committed to expanding the scientific knowledge and to enhancing and accelerating research efforts regarding recruitment strategies for Alzheimer's and related dementias clinical research and population studies. In 2018, NIA released a funding opportunity called [Examining Diversity, Recruitment, and Retention in Aging Research](#) (PAR-18-749) for investigators who are focused on improving the research tools, methods, and recruitment practices used in clinical studies to produce a significant number of committed research participants in aging research. Through this funding opportunity, NIH is supporting eight projects at research institutions nationwide to help inform scientists how to overcome barriers to enrolling research participants from underserved communities. These projects include approaches to build trust in communities and engage specific ethnic and racial groups in Alzheimer's and related dementias research. This funding opportunity will remain active until January 2021.

NIH also continues to fund collaborative teams to target gaps in methods and outcomes regarding diversity in research participant recruitment and retention. In November 2018, NIH released an invitation to researchers ([NOT-AG-18-047](#)) to encourage grant applications for projects that examine health disparities related to Alzheimer's, as well as strategies for recruitment and retention into clinical studies. To date, NIH has funded more than 60 projects in response to this initiative, and the funding opportunity will remain active until November 2021. Topics range from investigating racial and geographic disparities in the risk of Alzheimer's and related dementias to exploring the effects of participation in long-term community-based trials on lifestyle and risk for Alzheimer's.

NIA, working in collaboration with the Alzheimer's Association, is planning a science of recruitment preconference meeting to take place at the 2020 Alzheimer's Association International Conference. The goal is to provide a broad perspective that will ultimately build on the scientific knowledge and ultimately accelerate and expand the research efforts on recruitment strategies for clinical trials for Alzheimer's and related dementias.

and other grantees. The database also includes relevant resources from other organizations, as well as published research articles.

Tracking the enrollment and recruitment performance of NIH-supported clinical studies for Alzheimer’s and related dementias is also a priority. To this end, NIH is investing in the expansion of its clinical trial data infrastructure to more seamlessly track enrollment in NIH-funded clinical studies. This effort will also proactively support recruitment needs across the breadth and scope of the research portfolio.

The NIH-funded Alzheimer’s Clinical Trials Consortium (ACTC), a clinical trials infrastructure to accelerate and expand studies for therapies in Alzheimer’s and related dementias, also is investing in methods and strategies to enhance recruitment of racial and ethnic minority participants. ACTC relies on community engagement using an innovative hub-and-spoke model to create a core of community-based minority and patient advocates who work closely with the recruitment units at ACTC sites. These advocates serve as liaisons between the community and the ACTC sites, and they communicate the concerns and perspectives of potential and enrolled study participants.

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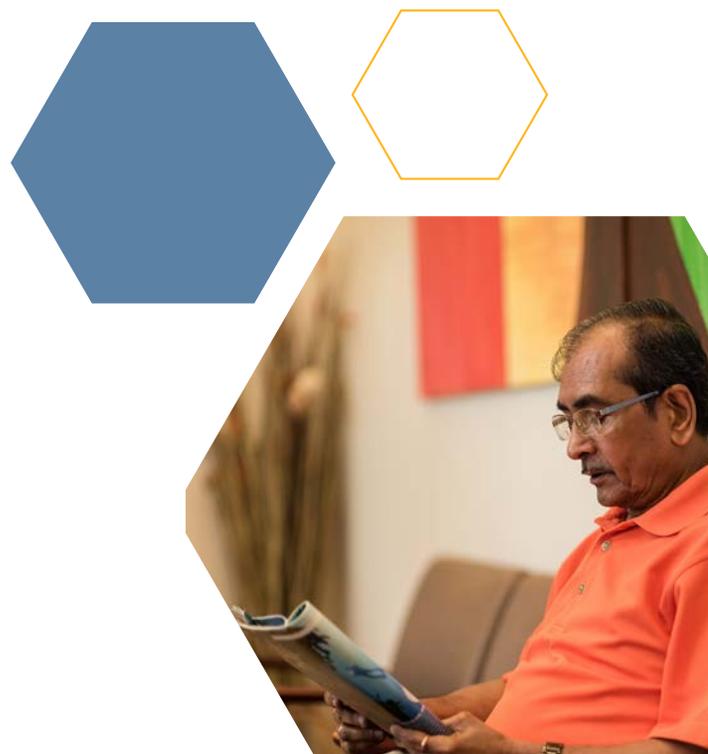
For a more in-depth look at the research implementation milestones in this area, including progress and accomplishments, visit www.nia.nih.gov/research/milestones/trial-innovation.

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Care and Caregiver Support Studies



“NIH is invested in developing new, scalable approaches to dementia care, care giver support, and dementia care coordination. The goals of this research are to improve the health and well-being of persons living with dementia and to support the individuals who provide their care.”

Lis Nielsen, Ph.D.,
Director of NIA's Division of
Behavioral and Social Research



NIH is committed to enabling better outcomes for people with Alzheimer's and related dementias, as well as for their caregivers. NIH-supported efforts have led to improved quality of care and quality of life for those living with these conditions and the development of resources designed to help ease burdens on care providers. Our efforts to encourage broad sharing of data and resources include raising awareness about evidence-based social and behavioral interventions.

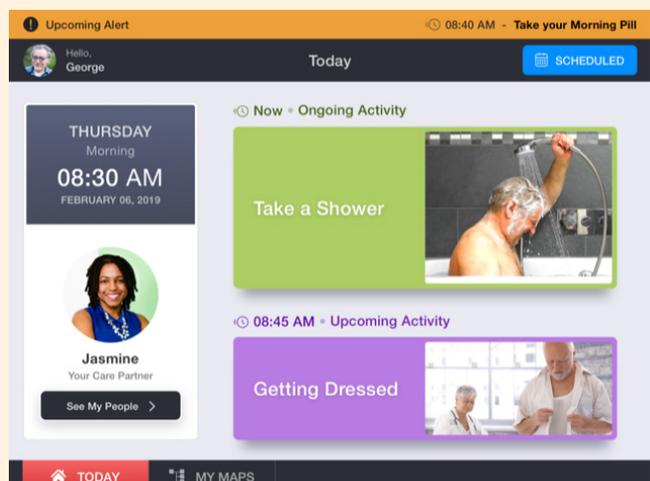
In 2019, NIA expanded its network of [Roybal Centers for Translational Research in the Behavioral and Social Sciences of Aging](#) to focus on the development of behavioral interventions for dementia care providers, both at the individual and health care system levels. The Roybal network, which was established in 1993, is designed to translate findings from basic behavioral and social research into evidence-based interventions and programs that can be shared and implemented in the community. The four new centers, called collectively the [Roybal Centers for Translational Research on Dementia Care Provider Support](#), will develop and pilot test dementia-related interventions and their related materials for feasibility, acceptability, and efficacy. For example, at the new Roybal Center for Palliative

Care in Dementia, the first planned pilot studies will focus on better end-of-life planning, including testing an online advance care planning tool tailored for use with people with dementia in long-term care facilities. The ultimate goal is to deliver evidence-based behavioral interventions for use in communities nationwide.

Also in 2019, NIH funded a new effort called the [Imbedded Pragmatic Alzheimer's disease and related dementias \(AD/ADRD\) Clinical Trials \(IMPACT\) Collaboratory](#) to meet the urgent public health need to deliver high quality, evidence-based care to people living with dementias and their caregivers. Through this effort, researchers will develop and test care interventions in real-world settings such as hospitals, assisted living facilities, nursing homes, and adult day care centers. In general, a "pragmatic clinical trial" means participants are enrolled as part of a real-world setting, rather than selected from a broader community based on narrowly defined criteria. The IMPACT project will bolster the nation's capacity to conduct pragmatic clinical trials of interventions, embedded within health care systems, for people living with dementia and their caregivers. IMPACT supports pilot projects that have the

PROGRAM SPOTLIGHT: Improving Care for People with Alzheimer's and Related Dementias Using Technology

In 2019, a panel of judges selected MapHabit, Inc., as the first-place winner of NIA's [Improving Care for People with Alzheimer's Disease and Related Dementias Using Technology \(iCare-AD/ADRD\) Challenge](#). The Atlanta-based MapHabit team, led by Stuart Zola, Ph.D., received the \$250,000 prize for their mobile device application that helps people with dementia follow simple commands to perform daily tasks such as taking pills and brushing their teeth. It also provides feedback to caregivers, allowing them to monitor adherence to medication schedules or track other activities. The challenge was designed to spur technological innovations with the goal of improving the overall quality of dementia care.



Used with permission by Stuart Zola and Matt Golden/MapHabit.



potential to inform the design of larger scale pragmatic trials.

The costs of dementia care and the challenges families face as caregivers continue to be a priority area of research. In early 2020, researchers reported results from two notable NIH-supported analyses:

- A recent analysis of Medicare and Medicaid data shows that the [costs of health care for people with dementia](#) are much higher than for those without dementia, and the burden of those higher costs falls disproportionately on people with dementia and their families. The authors also noted that overall costs were roughly equal for people with dementia regardless of where they lived — either in a nursing home or in the community. However, community dwellers and their families paid most of the total cost, compared to less than one-half of the costs if the person with dementia lived in a nursing home.
- Researchers used data from the 2015 National Health and Aging Trends Study, an NIH-funded study of Medicare recipients age 65 and older, to show that only one-quarter of people with dementia and about one-half of those with advanced dementia living in the community received paid care. Even with [paid care](#), family caregivers provided more than one-half of reported care hours. Men, the unmarried, those with Medicaid, and those requiring more help with daily activities had the highest likelihood of receiving paid care. People in the middle-income range were less likely to receive paid care.

In 2018, NIA launched a collaboration with the Agency for Healthcare Research and Quality (AHRQ) and the National Academies of Sciences, Engineering, and Medicine (NASEM) to review the evidence on dementia care and caregiving interventions. NIA asked AHRQ to conduct a rigorous

systematic review to evaluate the evidence and to assess the potential for broad dissemination and implementation of any efficacious findings.

The draft review, released in March 2020, identified low-strength evidence for specific categories of interventions and outcomes. Specifically, the review found that intensive multicomponent interventions may improve informal caregiver depression and quality of life. The findings also suggest that collaborative care models may improve both quality of life for people living with dementia and system-level markers, such as reduction in emergency department visits. Still, there is insufficient evidence for drawing conclusions about the effects of all other interventions assessed in this study.

In parallel, NIA asked NASEM to establish an expert committee to assess the findings of the AHRQ review as well as other relevant sources, to develop recommendations on the readiness of relevant interventions for broad dissemination and implementation, and to identify research gaps. The committee report will be released in early 2021.

The findings from these efforts will inform NIA’s decisions for future research investments and guide research projects that are already underway.

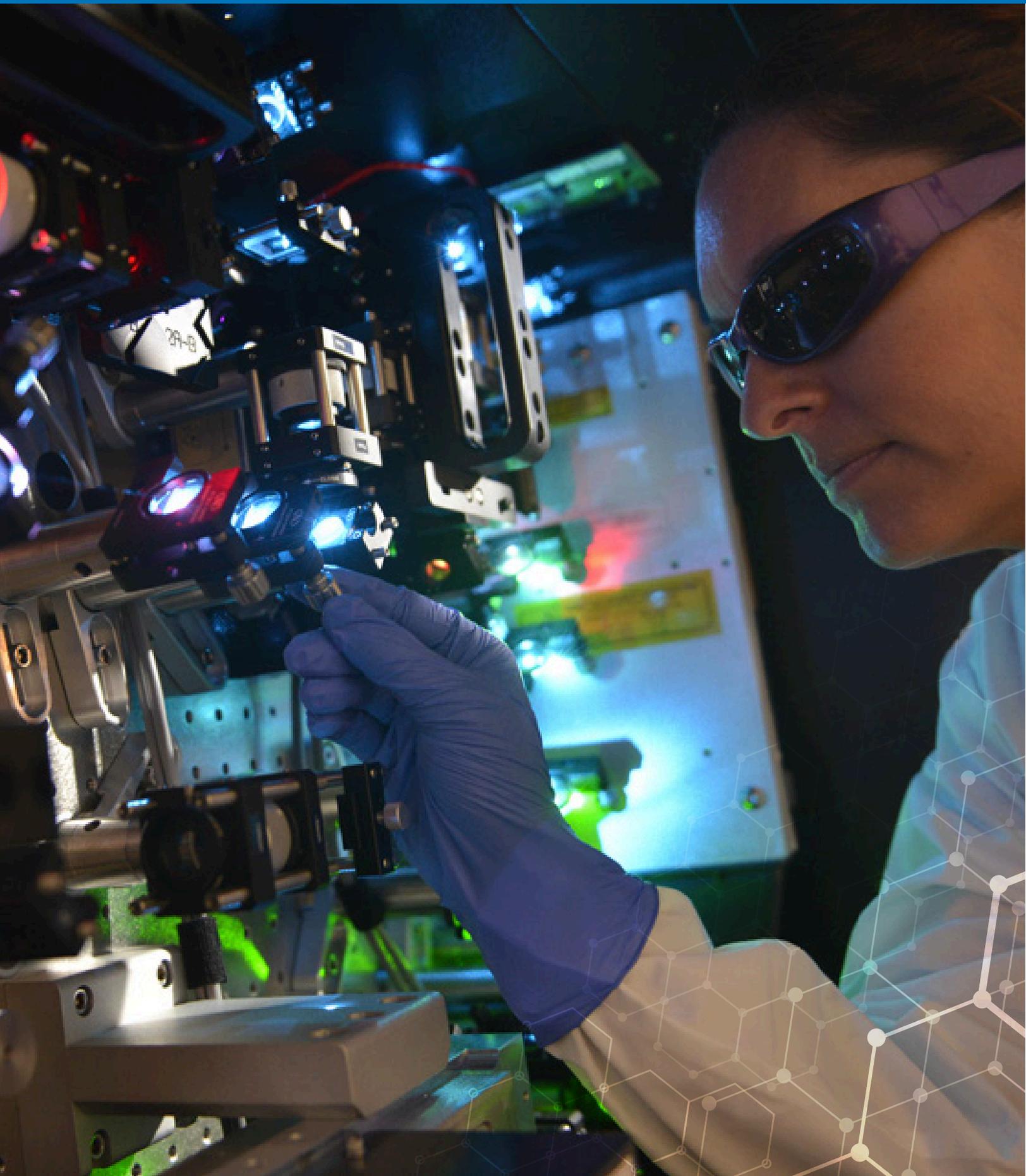
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For a more in-depth look at the research implementation milestones in this area, including progress and accomplishments, visit www.nia.nih.gov/research/milestones/care-caregiver-support.

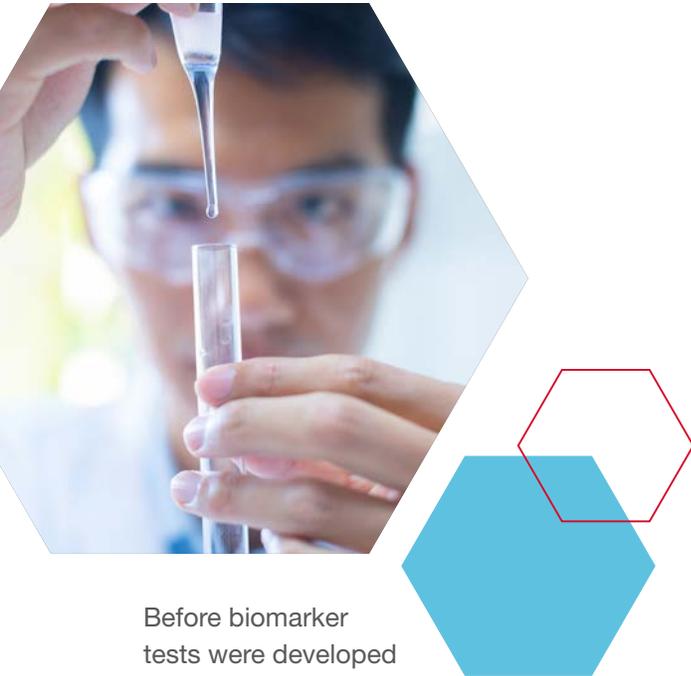
Biomarker Research



“Biomarkers are essential for identifying the early signs of the disease process before an individual has cognitive damage from dementia and for developing effective ways to prevent the disease or treat its symptoms.”

Eliezer Masliah, M.D.,
Director of NIA's Division
of Neuroscience





Before biomarker tests were developed in the early 2000s, the only sure way to know whether a person had Alzheimer's was via autopsy. Today, thanks to multiple, recent scientific advances, researchers can now use either brain imaging methods, such as PET scans with radioactive tracers, or lab tests of substances in spinal fluid to diagnose people living with the disease. Biomarkers allow for a more accurate diagnosis by helping to discern between the different diseases that cause dementia. For example, detecting [beta-amyloid plaques and tau tangles](#) with either brain scans or spinal fluid tests helps researchers differentiate between Alzheimer's and Lewy body dementias.

NIH funding has enabled significant recent progress in developing, testing, and validating biomarkers for diagnosing Alzheimer's and related dementias. These technological advances have helped scientists discover that changes in the brain that occur during Alzheimer's are evident long before a person shows outward signs of cognitive impairment or dementia. Scientists have early results that show that beta-amyloid plaques, tau proteins, and other biomarkers not only are present in the brain and spinal fluid but also circulate in the bloodstream. In 2019 and early 2020, NIH-supported scientists reported advances in the development of blood-based tests that could enable rapid screening of volunteers who wish to

enroll in studies. Using a blood test to screen instead would reduce the number of research volunteers who undergo brain PET imaging or spinal taps, which are expensive and invasive.

Some of the progress reported recently from diverse biomarker projects underway includes:

- Amprion's Protein Misfolding Cyclic Amplification system for analyzing [alpha-synuclein protein](#) in blood and spinal fluid to detect Parkinson's disease
- A blood test for the protein [neurofilament light chain](#) to detect Alzheimer's
- The ratio of [beta-amyloid 42 to beta-amyloid 40 proteins](#) in a sample of blood to detect Alzheimer's
- [Tiny particles shed by brain cells](#) that circulate in the blood, for predicting Alzheimer's
- Unhealthy levels of [liver enzymes](#) in the blood as a possible sign of Alzheimer's
- [Certain loops of ribonucleic acid – "circular RNAs"](#) – in the brain, which can also be detected in spinal fluid and blood, for detecting Alzheimer's
- A [novel protein signature in the blood](#) that may have potential as a biomarker indicating genetic resistance to Alzheimer's

For now, these blood tests can be used only by researchers in clinical studies. It is likely that eventually, FDA-approved tests will be made available to physicians, enabling them to screen their patients for Alzheimer's and related dementias before symptoms appear.

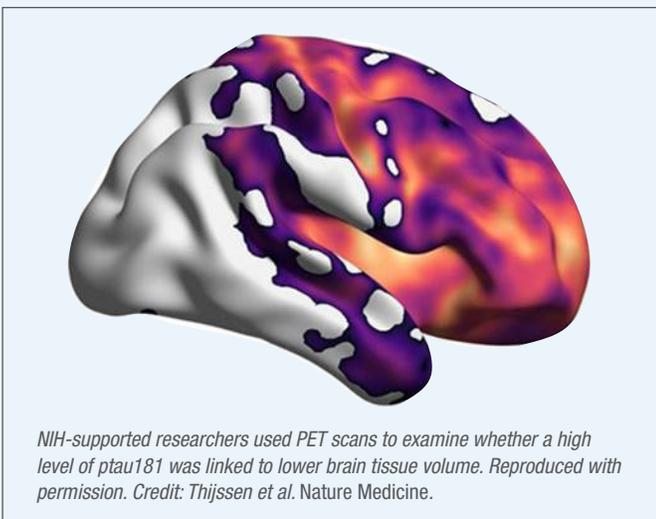
In addition to blood tests, other NIH-supported research projects are designed to look beyond current measures to detect people with dementia. These include changes in [vision and pupil responses](#) that may signal Alzheimer's, or a combined decline in [memory and walking speed](#) as a sign of dementia.

SCIENCE SPOTLIGHT: Blood Test Method May Predict Alzheimer's Protein Deposits in Brain

In early 2020, two NIH-supported research teams independently reported advances in the development of a blood test that could help detect pathological Alzheimer's disease in people who are showing signs of dementia. This approach would be less invasive and less costly than current brain imaging and spinal fluid tests. The blood test detects the abnormal accumulation of [a form of tau protein known as phosphorylated-tau-181 \(ptau181\)](#), which is a protein that suggests brain changes from Alzheimer's.

The first research team used the new test to measure the concentration of ptau181 in plasma, which is the liquid part of blood. The samples were collected from more than 400 participants from the University of California, San Francisco, Memory and Aging Center, an NIA-funded [Alzheimer's Disease Research Center](#); the NIH-supported [Advancing Research and Treatment for Frontotemporal Lobar Degeneration \(ARTFL\) consortium](#); and a research study sponsored by Eli Lilly and Company.

Their analysis demonstrated that ptau181 in plasma could differentiate healthy participants from those with Alzheimer's pathology and differentiate those with Alzheimer's pathology from a group of rare neurodegenerative diseases that also involve the tau protein known collectively as frontotemporal lobar degeneration (FTLD). In addition, the results of the



plasma ptau181 test mirrored results of two established biomarker tests for Alzheimer's: a spinal fluid ptau181 test and a PET brain scan biomarker that detects amyloid plaques. The research team, which includes NIH's [ARTFL-LEFFTDS \(Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects\) Longitudinal Frontotemporal Lobar Degeneration \(ALLFTD\) research consortium](#) announced in 2019, is now aiming to refine and improve the ptau181 blood test method.

The second research team reported similar findings using the same plasma ptau181 test. This team was able to differentiate between Alzheimer's and other neurodegenerative diseases nearly as well as they could with a spinal fluid ptau181 test or a PET brain scan for tau protein. In addition, they followed participants for several years and observed that high levels of plasma ptau181 among those who were cognitively normal or had mild cognitive impairment predicted later development of Alzheimer's dementia.

In the future, improved biomarkers like ptau181 may help not only researchers but also physicians to detect and diagnose Alzheimer's and related neurodegenerative disorders earlier, when interventions are more likely to be effective.

These important findings were also captured in the following articles:

- [Getting closer to a blood test for Alzheimer's disease?](#) in the *NIH Director's blog*
- [New blood test method may predict Alzheimer's disease](#) in *NIH Research Matters*
- [Collaborative approach aids development of potential blood test for use in Alzheimer's, rare syndromes diagnoses](#) from NIH's National Center for Advancing Translational Sciences



Some examples of NIH-funded programs to develop biomarkers include:

- Alzheimer's Disease Neuroimaging Initiative.** The NIH-supported [Alzheimer's Disease Neuroimaging Initiative \(ADNI\)](#) is a long-standing public-private partnership to help researchers develop tools for clinical trials by tracking how brain imaging and fluid biomarkers change as the disease progresses from cognitively normal to mild dementia to Alzheimer's. Investigators developing drugs in clinical trials use ADNI-developed tools in their studies. Researchers can access ADNI brain scans, biomarker data, and DNA and fluid samples. Now in its 16th year, the three phases of ADNI (ADNI1/GO, ADNI2, and ADNI3) have developed biomarkers for use in selecting clinical trial participants and for assessing treatment outcomes. When ADNI3 was launched in 2016, ADNI data had already been downloaded for research purposes more than 11 million times, and scientists had used ADNI data to publish [more than 1,200 scientific papers](#). Because of its open-access policy of sharing data, ADNI has enabled scientists to develop a better understanding of biomarkers and the progression of Alzheimer's.
- Accelerating Medicines Partnership-Alzheimer's Disease.** The [Accelerating Medicines Partnership-Alzheimer's Disease \(AMP-AD\) Biomarkers Project](#) is a consortium of two NIA-supported Phase 2/Phase 3 secondary prevention trials, the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study, and the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU). Through these, scientists are testing several anti-amyloid therapies. The goal is to explore tau brain imaging for tracking responsiveness to treatment and disease progression. Data and biosamples from both studies will be made broadly available to the research community. In fact, the screening/prerandomization data and biosamples from the A4 study are already available via the [Laboratory of Neuroimaging \(LONI\) Image and Data Archive](#). The A4 study

Advancing Research with Biomarkers

Developing and validating a wide range of biomarkers in general will help advance Alzheimer's and related dementias research in many ways:

- Using biomarkers, researchers can examine the biological processes leading to diseases that cause dementia, studying cause and effect in the cascade of biological steps. They can also detect the onset of disease and track progression. When used in a treatment or prevention study, biomarkers can help evaluate whether that approach might help people in the earliest stage of disease, before cognitive decline from dementia.
- Researchers can use biomarkers to predict who is at risk of developing Alzheimer's and related dementias in people before cognitive symptoms appear. For example, biomarker tests can identify people who are cognitively healthy but have high levels of amyloid plaques and tau tangles in their brains.
- Investigators can screen people with biomarkers to differentiate people who have Alzheimer's from those with other dementias. Before biomarker tests, investigators relied on tests of cognitive ability and enrolled people who may not have had dementia from Alzheimer's, which reduced the likelihood the Alzheimer's treatment under study would be successful.

is the first pivotal Phase 3 study to release data prior to the completion of the trial in accordance with [Collaboration for Alzheimer's Prevention: Principles to guide data and sample sharing in preclinical Alzheimer's disease trials](#).

- The Accelerating Medicines Partnership-Parkinson's Disease.** Complementing AMP-AD, NIH has also launched [AMP-Parkinson's Disease \(AMP-PD\)](#) to develop and test treatments for Parkinson's disease and related disorders like Lewy body dementia. One of the hallmarks of Parkinson's is clusters of Lewy

bodies in the brain. In 2020, AMP-PD will be adding whole genome sequences from more than 2,000 people with Lewy body dementia to its data platform. These will be made available for analysis by the general research community and are intended to further the goal of providing a better understanding of the disease and potential treatment targets.

- **ALLFTD Research Consortium.** In 2019, a [new NIH-supported consortium](#) integrated two ongoing studies of frontotemporal lobar degeneration. The goal is to advance the development of treatments by helping researchers better understand the disease process by finding improved brain imaging and other methods for accurately identifying participants and for measuring disease progression.
- **The Lewy Body Disease Center Without Walls.** A key finding in the brain tissue of people with Lewy body disease (LBD) is an accumulation of abnormal alpha-synuclein protein, similar to what is observed in Parkinson's disease. However, abnormal deposits of the Alzheimer's-related beta-amyloid protein are also commonly observed. The Lewy Body Disease Center Without Walls (LBD CWOW) is a collaboration between six research institutions to determine why both proteins accumulate in LBD brain tissue, whether the protein structures are unique to LBD (versus Alzheimer's or Parkinson's disease), and how these proteins lead to tissue damage and dementia. Using samples from hundreds of brains from donors, the investigators will identify the exact protein structures, genes, and proteins that are unique to LBD brain cells and circuits. They will then use cell models to learn how these components interact with each other to impair brain function.
- **MarkVCID.** Although researchers have conducted many clinical studies to find ways to prevent cognitive impairment and dementia from certain blood vessel diseases, they have been hampered by the limited availability of biomarkers. [MarkVCID](#) involves seven research

sites and a coordinating center to develop biomarkers for the small vessel diseases of the brain. The consortium has developed and is currently testing 11 different biomarker kits — which include several types of vascular imaging and fluid-based biomarkers — across several clinical research sites, including within the [SPRINT MIND](#) research consortium.

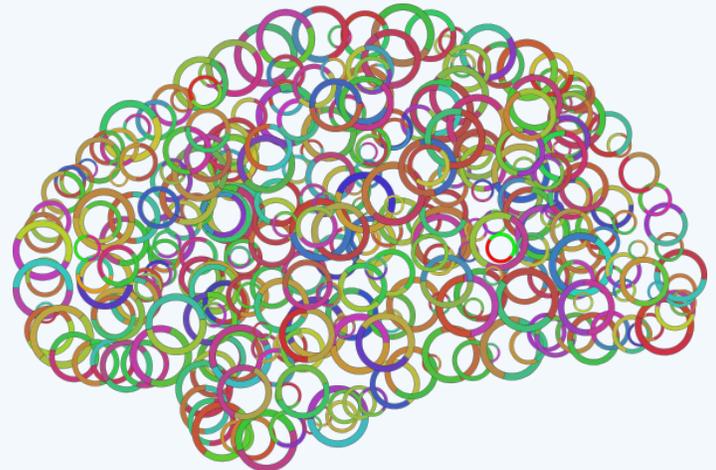
New tools and technologies will be critical for advancing biomarker research or extending its use beyond the measurement of blood or spinal fluid. Some recent examples of tools and technologies under development include:

- **EHR Risk of Alzheimer's and Dementia Assessment Rule.** By analyzing Kaiser Permanente electronic health records (EHRs) of more than 16,000 visits by more than 4,000 older adults over two decades, a research team developed [the first dementia risk prediction model](#), which they called EHR Risk of Alzheimer's and Dementia Assessment Rule (eRADAR). Some predictors of dementia included missing appointments, having diabetes, and exhibiting symptoms such as psychosis. Their findings suggest that a tool like this could be used with EHRs to accurately detect people who may have undiagnosed dementia. When they tested the tool, they found that 498 of the 1,015 researcher-confirmed dementia cases had not been recognized by clinicians before study investigators independently identified these cases from predictors recorded in the EHR.



- Advances in cognitive testing.** The very earliest signs of cognitive decline can be very subtle and may require data collected over days, weeks, or months to detect. As it happens, current digital devices are quite good at capturing large amounts of behavioral and physiological data without requiring people to make multiple, in-person visits to research sites. NIH has made significant investments in improving the sensitivity of cognitive measures for use on [mobile devices](#). These measures may help with detection of the very earliest signs of cognitive decline in an individual and also enable the collection of data from many users to ultimately correlate cognitive change with other health, behavioral, and social variables. The NIH-supported [Mobile Toolbox](#) is developing smartphone-based cognitive tests, which would move testing from the lab to people's daily lives, and also a testing infrastructure for widespread use by researchers in population studies of cognitive change.

Biomarkers enable researchers to more accurately identify participants for studies that are testing approaches for specific forms of dementia.



Loops of RNAs in the brain. Credit: Umber Dube, Washington University School of Medicine.

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For a more in-depth look at the research implementation milestones in this area, including progress and accomplishments, visit www.nia.nih.gov/research/milestones/biomarkers-diagnosis.



Population Studies and Precision Medicine Research



“By supporting large population studies and precision medicine research, NIH is making significant progress toward a time when clinicians can detect Alzheimer’s and related dementias earlier and tailor treatment plans to an individual’s unique symptoms and risk profile.”

Marie A. Bernard, M.D.,
NIA Deputy Director



Because of the accelerated pace of research in recent years, we now know that Alzheimer's and related dementias are complex conditions that stem from the interplay of genetic, lifestyle, and environmental factors. NIH-supported researchers continue to explore the reasons why some people develop these conditions while others do not, and which genes, lifestyle choices, and other factors seem to be associated with the disease. By studying large, diverse groups of people, investigators can identify which behaviors and lifestyle choices are associated with the development of certain diseases.

NIH's investments in population studies have already revealed that factors such as sedentary behavior, low socioeconomic status, low level of education, and poor neighborhood may increase the risk of developing dementia. These discoveries, paired with knowledge of genetic and other factors, can be used to design clinical trials to test whether these factors truly confer risk or offer protection. Results from carefully controlled trials could then advance the development of methods for precision diagnosis, prevention, and individualized treatment for Alzheimer's and related dementias, as has been achieved already for certain cancers. In the future, it is hoped that results from population studies may be used to help researchers develop precise interventions that can address the underlying disease process by tailoring treatment to an individual's unique disease profile and symptoms.

Some of the recent findings from population studies include:

- In 2019, an international team of NIH-supported researchers pooled data from more than 3,400 people from multiple observational studies in the U.S., Europe, Canada, and Australia to explore how genetics and family history relate to the age when **frontotemporal dementia** symptoms develop. In the pooled data, the researchers noted that symptoms developed in people as early as their teen years or as late as their 90s, but the average age varied between 50 and 61, depending on the presence of one of three genetic mutations. Understanding the causes of variation in age of onset could provide important clues about the causes of frontotemporal dementia.
- A population study of 10,000 British civil servants showed that **regularly seeing friends and family during midlife** was associated with a lower likelihood of dementia diagnosis in later life. Analysis of the same data source showed that people with better **heart health at age 50** may be less likely than those with poor heart health to develop dementia later in life. A third analysis, however, did not find an association between a **healthier diet in midlife** and a lower risk of dementia 25 years later. A separate analysis of multiple genetic and lifestyle risk factors conducted with UK Biobank Database records from nearly 200,000 participants suggested that **choosing healthy lifestyle habits** is associated with a lower risk of dementia in cognitively healthy older adults at varying levels of genetic risk.
- After examining Medicare records for more than 82,000 people who had participated decades earlier in a nationwide high school test that measured personality traits, scholastic aptitude, and interests, researchers discovered that **certain personality traits as a teenager may predict dementia risk** more than 50 years later.



- A team of international scientists analyzed data from six comprehensive, community-based observational health studies conducted in the U.S., France, Iceland, and the Netherlands to show that [treating high blood pressure](#) is associated with a reduced risk of Alzheimer's and related dementias.
- Researchers analyzed 101 older adults, enrolled in the Berkeley Aging Cohort Study, for Alzheimer's disease-related beta-amyloid and tau protein levels in the brain. They noticed that cognitively healthy adults whose [sleep quality](#) declined in middle age were more likely in late life to accumulate amyloid and tau proteins in the brain than those whose sleep quality improved or did not change.
- A long-term study of 270,000 individuals in Utah suggested that [having extended family members](#) with Alzheimer's, such as having only several third-degree relatives with the disease, increased a person's risk of developing the disease.
- The Healthy Cognitive Aging Project, the widest ranging and most representative cohort study on a random subsample of U.S. adults at greatest risk for dementia, [released detailed cognitive data](#) for other researchers to use in their work.
- The risk of dementia is highest among African Americans and American Indian or Alaska Natives; intermediate for Latinos, Pacific Islanders, and non-Latino whites; and lowest for Asian Americans.
- Women are at higher risk of dementia than men.

NIH is committed to supporting studies on risk factors related to health disparities and, through [NOT-AG-18-047](#), is funding more than 60 research projects at universities across the country. Collectively, projects will compare differences in risks for these conditions for men versus women, different racial and ethnic groups, rural communities, socioeconomically disadvantaged neighborhoods, and other societal and individual factors.

Another example of health disparities research is the recent launch of the [Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on Recovery \(DISCOVERY\)](#) study. The goal of this six-year NIH-supported prospective clinical research study is to determine the specific subsets of stroke-related events that cause cognitive impairment and dementia in people who have had a stroke, especially within racial and ethnic minorities who are at higher risk of stroke, cognitive impairment, and dementia.

Recruiting research participants who are representative of the diverse American population is crucial to addressing health disparities, and NIH is investing in a wide range of activities to help investigators reach underrepresented communities. Many of the challenges and opportunities for enhancing recruitment efforts, including the national recruitment strategy and the use of [Together We Make the Difference: National Strategy for Recruitment and Participation in Alzheimer's and Related Dementias Clinical Research](#), are described in the [Prevention and Treatment Research](#) section.

Tackling Challenging Health Disparities Through Research

Developing a better understanding of how and why many diseases affect diverse communities in different ways is paramount in our search for treatments and prevention for Alzheimer's and related dementias. NIH-supported studies in health disparities already have found that the development of Alzheimer's and related dementias may be influenced by many factors, including race, ethnicity, sex, level of education, geography, and socioeconomic status. For example, research has suggested that:

- Those who do not graduate from high school are at higher risk.

For a more in-depth look at the research implementation milestones in this area, including progress and accomplishments, visit www.nia.nih.gov/research/milestones/population-studies-precision-medicine-health-disparities.

PROGRAM SPOTLIGHT: 1 Million Diverse Research Participants by 2024

NIH is committed to enrolling participants from diverse backgrounds to help identify the genetic variants and other risk and protective factors involved in health and disease. As a prime example of NIH's investments, the nationwide NIH-led initiative known as the [All of Us Research Program](#) is seeking to enroll 1 million participants by 2024 who will reflect the diversity of the U.S. The diagnosis of dementia is captured through electronic health records and survey responses, and many of the participants who have already enrolled have Alzheimer's and related dementias (data collected thus far may be viewed through the [public-access database](#)). The broader scientific community, including dementia researchers, will soon have access to a cloud-based, researcher-restricted

data repository to conduct analyses by factors such as lifestyle differences, socioeconomic factors, environment, and genes and other biologic characteristics. Participants are providing data through surveys, electronic health records, physical measurements, biological samples, and even wearable sensor devices. Although data regarding cognitive performance are not captured yet, NIH is working to include such measures to make the data more robust.



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Disease Mechanism Studies



“Recent scientific breakthroughs have demonstrated that many different disease pathways can lead to Alzheimer’s and related dementias. In addition, individuals with Alzheimer’s dementia frequently have more than one disease pathway active at the same time. Because of this, researchers are now pursuing novel, traditional, and simultaneous disease pathways as potential targets to prevent, diagnose, and treat these diseases.”

**Roderick Corriveau, Ph.D.,
NINDS Program Director for
Neurodegeneration**



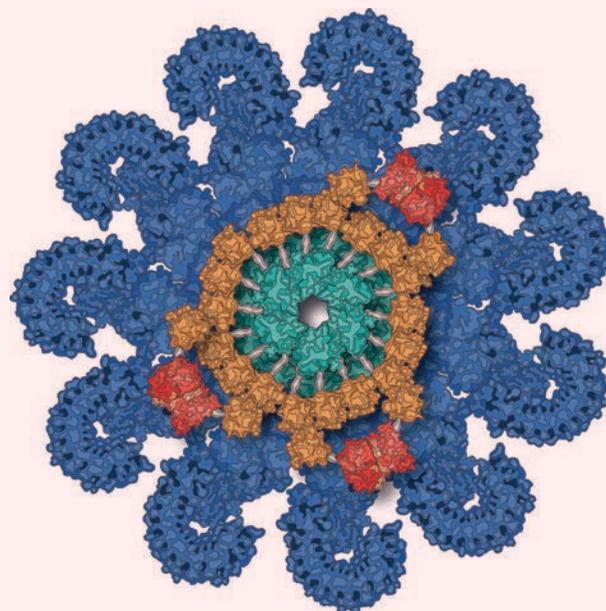
NIH investments in research to identify underlying biological mechanisms that cause Alzheimer's and other dementias are fundamental for the discovery of potential drugs targeting those processes. After a molecule, such as a protein, is identified in a disease-promoting **biological pathway**, researchers then study the molecule's structure and function. The next scientific challenge is to identify a compound that will bind to that molecule and change its activity. Because Alzheimer's is a complex pathology that is believed to involve regulation of the immune system, brain inflammation, lipid metabolism, and pathways for beta-amyloid and tau proteins, among others, there are many biological pathways that scientists can target with investigational drugs.

Here is a sample of the wide array of recent findings from NIH-supported studies of biological mechanisms:

- Several studies have further illuminated how components of the immune system, brain inflammation, and possibly viruses and bacteria contribute to the development of Alzheimer's and related dementias:
 - » Scientists continued to gather evidence that certain cells of the **immune system** can play a role in the brain deterioration that causes disorders like Alzheimer's.
 - » A recent mouse study demonstrated that circumventing the activation of **an immune system complex that drives inflammation** could prevent the collection of abnormal tau tangles in the brain. The researchers showed that this immune system complex is a key step in the pathway between abnormal beta-amyloid plaques and tau tangles, two of the hallmarks of Alzheimer's disease.
 - » One factor that may influence the immune response in the brain is **viruses**, bacteria, or other microbes — or the inflammatory molecules they produce, which can travel from infections in the body through the bloodstream to the brain. Studies have suggested that this is one mechanism of influencing the cascade of events leading to beta-amyloid deposits and tau tangles.

To test whether viruses may play a role in Alzheimer's, NIH is supporting a **Phase 2 clinical trial** of an FDA-approved antiviral drug to determine whether it may slow or prevent Alzheimer's in people with mild Alzheimer's who also test positive for the herpes simplex virus.

- » Using data made available by the NIH-funded **Alzheimer's Disease Neuroimaging Initiative (ADNI)**, researchers analyzed levels of **a protein that helps immune cells clear harmful beta-amyloid plaques** from the brain. Their results suggest that a treatment that could boost that protein might slow the progression of Alzheimer's.
- A mouse study showed that an extremely **high-salt diet** leads to cognitive problems through the abnormal tangling of tau protein in the brain.
- An analysis of more than 3,000 proteins in brain and spinal fluid samples revealed that certain sets of proteins that control **sugar metabolism** were strongly associated with the brain changes in Alzheimer's.



This immune system complex drives inflammation and may play a role in Alzheimer's. ©2020 Dr. Kate Schroder, The University of Queensland, www.inflammasomelab.com.

- **Drugs that selectively removed certain cells** slowed down the progression of brain changes related to dementia and enabled mice to complete maze tests in half the time.
- In mice, researchers reversed **faulty protein networks** that caused abnormal brain function with a **drug called PU-AD**. Biotech company Samus Therapeutics is now sponsoring a Phase 2A clinical trial (**NCT04311515**) of people with mild Alzheimer's dementia with PU-AD, which was developed with support through NIA's Alzheimer's Translational Research Program.
- Recent NIH-funded research has identified a gene mutation associated with frontotemporal dementia and another neurodegenerative condition that seems to hinder the normal way that **RNA hitchhikes through nerve cells in the brain** to help with protein synthesis.

Brain Studies of Toxic Proteins

Three recent NIH-supported studies explored how the unique ways that abnormal proteins fold may account for their toxicity and accumulation in brain diseases that cause dementia. A comparison of brain tissue from people with Lewy body dementia (LBD) and Alzheimer's suggests that, for people with LBD, the amygdala region of the brain is key to the accumulation of toxic proteins known as alpha-synuclein. The study also suggests that the **alpha-synuclein** form in LBD is distinct from the form in Alzheimer's.



Two cryoelectron microscopy studies explored the intricate folding of the tau filament structure and how structures differed across several diseases that cause dementia. The research team demonstrated differences in the structure of the abnormal tau protein filaments that collect in the brains of people with Alzheimer's versus two neurodegenerative conditions, chronic traumatic encephalopathy that boxers and football players experience from **repeated head trauma** and a rare brain disease called **corticobasal degeneration**. Understanding the specific differences between brain diseases for the folding of the tau filament structure can aid researchers in exploring the role of structural differences in disease development. The discoveries may also lead to diagnostic tests for these diseases to help differentiate between types of dementia.

Genetic Advances

Brain cells send signals and receive them through biological pathways. This is how genes are turned on and off, for example. When something goes wrong in a biological pathway, disease can result. Researchers can study all the genes, proteins, cells, and other elements in a biological pathway to better understand the processes leading to health and disease.

Scientists search for mutations or variations in genes because they might play a role in the development of disease. Twenty years ago, scientists found variants of four genes that were linked to Alzheimer's. Because of advances in genetic sequencing technology and the ability to analyze the genes of thousands of people, many more discoveries have been made in the past decade. Today, thanks in part to the increased investment in Alzheimer's research, scientists have identified variants in more than 50 regions of the genome that may increase risk for the disease. Of these, variants in more than 23 individual genes have been linked to increased risk of late-onset Alzheimer's. These genetic regions appear in clusters that point toward what may be highly relevant molecular pathways. By understanding key pathways, researchers may be able to develop prevention strategies and treatments for Alzheimer's.



In 2019, NIH-supported researchers who are part of a large data-sharing collaboration reported **findings from the largest-ever genomic study of Alzheimer's**. Their analysis of the genomes of more than 35,000 people with late-onset Alzheimer's **revealed previously unknown variants in five genomic regions of interest** that convey greater risk of the disease. The study also confirmed other regions that had been implicated previously in Alzheimer's. A single genetic variant may convey only a small amount of increased risk for an individual, but groups of genes may work in combination to increase risk.

These new genetic discoveries enable scientists to explore the many biological pathways that provide a richer set of treatment targets. Having a clear understanding of groups of genes with common function may guide researchers to discover drugs that either block cellular events that are part of Alzheimer's or enhance the events that convey resilience against it. The report also suggested certain genetic similarities between early-onset and late-onset Alzheimer's, which raises the possibility that treatments now being developed for people with early-onset disease may also help people with late-onset disease, which is far more common.

The achievement of this largest-ever genomic study of Alzheimer's can be attributed to the collaborative resources made possible by NIH investments. This advance in our understanding of genetics illustrates how scientific advances are multiplying the effect of infrastructure investments. The study would not have been possible without data sharing and coordination among the following consortia, research centers, and studies:

- **International Genomic Alzheimer's Project**, which is made up of four consortia, including the NIA-supported **Alzheimer's Disease Genetics Consortium**
- **Alzheimer's Disease Research Centers**, which are funded under a variety of NIH awards
- **National Alzheimer's Coordinating Center**
- **NIA Genetics of Alzheimer's Disease Data Storage Site**
- **National Centralized Repository for Alzheimer's Disease and Related Dementias**
- **Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium**
- The Collaborative for Alzheimer's Disease Research
- Late-Onset Alzheimer's Disease Family Study

Recently, researchers provided a map for further research into the multiple gene-related molecular processes that are altered in Alzheimer's. After analyzing protein-coding genes from more than 80,000 brain cells, the researchers identified **unique clusters of genes** that are turned on during Alzheimer's in certain types of brain cells, including specific types of neurons and supporting cells in the brain region involved in high-level thinking, decision-making, and attention. Molecular processes in these brain cell types were consistently disturbed in people with Alzheimer's. This kind of cell-specific molecular analysis is a new approach for examining the molecular and cellular basis of Alzheimer's.

SCIENCE SPOTLIGHT: Unique Case of Disease Resistance Reveals Possible Alzheimer's Treatment

In 2019, a team of geneticists reported that a certain variant of the **apolipoprotein E (APOE) gene**, which is the gene most commonly associated with Alzheimer's, may play a role in protection against the disease. Their discovery of an individual in Colombia who was seemingly **protected against developing Alzheimer's** despite a strong family history may provide a new direction toward developing a treatment.

The individual at the center of the investigation is a member of a Colombian family with more than 6,000 living members at high risk for early-onset Alzheimer's disease. She was remarkable because she did not develop dementia for decades beyond what was anticipated, despite having a rare inherited gene mutation called *PSEN1 E280A*, which usually causes early-onset Alzheimer's. Brain imaging tests showed that she had only minor neurodegeneration. Although she had amyloid protein plaques, a hallmark of Alzheimer's disease, in her brain, the level of tau tangles was relatively low.

By analyzing the rest of her genome, researchers determined that she also had two copies of an exceptionally rare *APOE ε3* gene variant. The role of the $\epsilon 3$ form of *APOE* is not well understood. The investigators surmised that two copies of this gene variant may somehow have protected her from developing Alzheimer's 30 years earlier.

After additional experiments, the research team found that the *APOE ε3* variant may reduce the ability of *APOE* to bind to certain proteins in cells. If *APOE* cannot bind to these proteins, then it may thwart the cascade that leads to the amyloid and tau deposits that ultimately destroy the brain. Scientists are now planning studies of this gene variant to learn whether it may be an avenue to a treatment or prevention approach.



Lewy body dementia

Until recently, LBD was not thought to have a strong genetic component but results from large-scale genetic studies now suggest otherwise. In 2019, a study showed that, in addition to environmental risk factors, genetic risk factors contribute to many cases of LBD. Some of the LBD-related genes also appear to play a role in Alzheimer's and Parkinson's, which suggests that LBD shares biological pathways in common with these diseases. In addition, the researchers found genetic changes that appear to be

unique to LBD. A better understanding of how these genetic changes impair biological function will yield a deeper understanding of what happens in the brains of people with LBD and offer researchers potential targets for therapies that could treat the disease.

For a more in-depth look at the research implementation milestones in this area, including progress and accomplishments, visit www.nia.nih.gov/research/milestones/disease-mechanisms.

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Research Enterprise



“The development of effective treatments for complex diseases like Alzheimer’s requires a research infrastructure that can deliver high-quality data, biosamples, and research tools. This ‘translational brick and mortar’ enables researchers to turn their innovative ideas into products.”

Suzana Petanceska, Ph.D.,
Director for Strategic Development
and Partnerships in NIA’s Division
of Neuroscience



The steady increase in funding for Alzheimer's and related dementias research has enabled NIH to redouble investments in key research areas necessary for laying the groundwork for a precision medicine approach to treatment and prevention, from cutting-edge disease mechanisms and genetics research to population studies and innovative drug and biomarker development programs. In addition to these efforts, NIH has launched a number of programs over the past six years to provide researchers with an infrastructure for developing their ideas for medicines and other products, including:

- [Accelerating Medicines Partnership for Alzheimer's Disease \(AMP-AD\)](#)
- [Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease \(MODEL-AD\)](#)
- [TaRget Enablement to Accelerate Therapy Development for Alzheimer's Disease \(TREAT-AD\)](#)

A hallmark of these programs is that they bring together scientists from academia and the pharmaceutical industry who are working in many different disciplines, from epidemiology and genetics to data science and computational biology, molecular and cell biology, and medicinal chemistry and pharmacology. Working in collaboration, the researchers take an open-science/open-source approach to the key steps of the translational process. They are discovering new and better targets for treatment; producing and analyzing extremely large sets of molecular data; and developing high-quality translational research tools, such as animal models, chemical tools, and cellular assays.

Translational research — a term often used interchangeably with translational medicine, translational science, or bench to bedside — is an effort to build on basic scientific research to create new therapies, medical procedures, or diagnostics.



Accelerating Medicines Partnership for Alzheimer's Disease Target Discovery Program

The **AMP-AD Target Discovery Program** was established in 2014 as a partnership among government, nonprofit organizations, and the pharmaceutical industry. This NIA-led program, which is managed by the Foundation for the NIH, is leveraging decades-old public investment in epidemiology research and **brain tissue** banking by generating high-quality multi-omic data (such as genome, proteome, metabolome, and microbiome data) and deploying cutting-edge computational and experimental methods to deliver deeper understanding of the complex biology of the disease, identify the next generation of therapeutic targets, and make all data, methods, and insights rapidly available to researchers in the U.S. and around the world.

During the first five years of the program, this open science discovery engine delivered an unparalleled amount of high-quality molecular and biological data and enabled many new mechanistic disease insights on the role of the genome, proteome, metabolome, and microbiome. As a result of the open-science research model and team-science approach, seven academic research teams discovered and made publicly available more than

500 unique candidate drug targets along with a wealth of supporting evidence and data. To date, more than 3,000 researchers have accessed the AMP-AD data resources through the NIA-supported big data infrastructure: the [AD Knowledge Portal](#) and the portal-linked [open source platform known as Agora](#). About 60% of users are from academia, and nearly 40% are from the biotechnology-pharmaceutical industry.

To ensure a seamless transition to the second phase of the partnership, NIH reinvested its support of the program. For this next phase, the NIA-supported data coordinating center and six research teams will collaborate with a new set of pharmaceutical industry and nonprofit sector partners. This expanded partnership will enable a precision medicine approach to the discovery of therapeutic targets and biomarkers. The team will analyze brain tissue, spinal fluid, and blood plasma samples from diverse groups of people, and the team will use new computational methods including machine learning to build predictive models of Alzheimer's and its subtypes.

Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD)

Launched in 2016, the MODEL-AD consortium is tasked with building better genetically modified mouse models for Alzheimer's research based on the newly discovered genetic risk factors for late-onset disease and making them available along with all the

data and methods used in characterizing the models. In four short years, the MODEL-AD teams have created 28 new genetically modified mouse models and made them available to all researchers for use in basic research or Alzheimer's therapy development without intellectual property barriers.

A key component of MODEL-AD is the Preclinical Efficacy Testing Core (PTC) responsible for establishing a pipeline for rigorous preclinical testing of promising candidate treatments. In 2020, the PTC launched the [Screening the Optimal Pharmaceutical for Alzheimer's Disease \(STOP-AD\) portal](#), which enables drug developers from academia and industry to nominate candidate compounds. Compounds that are selected for preclinical efficacy testing will be paired with a genetically modified mouse model appropriate for the molecular process that is being targeted.

TaRget Enablement to Accelerate Therapy Development for Alzheimer's Disease (TREAT-AD)

The [TREAT-AD consortium](#) is the latest addition to NIH's translational infrastructure established through the [Alzheimer's Centers for Discovery of New Medicines](#). This \$73 million enterprise has two translational centers with a common mission: to diversify and accelerate therapy development for Alzheimer's through the development of open source tools, reagents, and methods for robust validation of candidate targets delivered by AMP-AD and other target discovery programs and by integrating a set of novel targets into drug discovery campaigns. Each TREAT-AD center brings together world-class expertise in data science, computational biology, disease biology, structural biology, assay development, medicinal chemistry, pharmacology, and clinical research.

- **TREAT-AD Center at Emory University, Sage Bionetworks, and Structural Genomic Consortium** will leverage the data and results from the AMP-AD program and develop a series of new therapeutic hypotheses centered around a prioritized set of novel targets. The center will develop a suite of target-enabling tools, including



PROGRAM SPOTLIGHT: Training the Next Generation of Scientists for Translational Research

Complementing the new translational infrastructure is support for new cross-disciplinary training programs funded through NIH's [Institutional Training Programs to Advance Translational Research on Alzheimer's Disease and AD Related Dementias](#). Through several programs across the U.S., NIH is supporting a new generation of translational scientists with expertise in biology, data science, engineering, and drug development who are able to participate and lead team-science programs from target discovery to clinical trials.

For example, the University of Arizona's [Translational Research in Alzheimer's Disease and AD-Related Dementias \(AZ-TRADD\)](#) training

program is cultivating a cadre of graduate students representing many scientific disciplines to have the skills needed to become translational scientists and who have the expertise to develop drugs along the pipeline from discovery to clinical trials. The training includes an internship with pharmaceutical industry and nonprofit organization collaborators and clinical experience with people with Alzheimer's and their caregivers.



high-quality antibodies and chemical probes, and openly disseminate all data, methods, and reagents to any interested academic or commercial investigator to accelerate validation of novel drug targets and to seed new drug discovery efforts.

- **TREAT-AD Center at Indiana University School of Medicine and Purdue University** will bridge target discovery work done by the AMP-AD program with newly discovered molecules that will be studied for disease-modifying potential in Alzheimer's animal models developed by the MODEL-AD centers. The research team will create a diverse portfolio of Alzheimer's disease drug targets representing new therapeutic hypotheses with a particular focus on immune pathways and make all data and research tools available to the scientific community.

Over the next five years, these centers will join forces to deliver high-quality target-enabling tools, including crystal structures, antibodies, chemical probes, and cell-based assays, for an array of novel targets; initiate drug discovery for a diverse portfolio of novel targets; and make all data, tools, and methods available to researchers in academia and the biotechnology and pharmaceutical industry for laboratory research and drug discovery.

For a more in-depth look at the research implementation milestones in this area, including progress and accomplishments, visit www.nia.nih.gov/research/milestones/enabling-infrastructure.

Looking Ahead



The recent, unprecedented increases in research funding targeting Alzheimer's and related dementias have enabled enormous advances in our understanding of the complexities of these devastating diseases, but much work remains. Continued and sustained investments are critical to ensure that the broad range of research projects enable:

- Discovery, development, and testing of promising therapies and approaches to prevent or delay disease
- Clinical trials that are more inclusive, efficient, and practical
- Development of comprehensive models of care for people living with these diseases
- Better biomarkers to detect disease and monitor treatment response
- Greater knowledge of risk and protective factors in individuals and across populations
- Basic science studies in genetics and disease mechanisms
- Leverage of emerging digital technologies and "big data" to hasten discoveries

Although we cannot yet predict the long-term effect that the novel coronavirus pandemic will have on current and future research efforts and rate of progress in these areas, our commitment to developing diagnostic, prevention, treatment, and care interventions for Alzheimer's and related dementias is steadfast. Now more than ever, further investment in the research enterprise will not only accelerate the discovery of treatments and prevention strategies for Alzheimer's and related dementia, it will serve as an economic engine for new jobs and workforce opportunities. Millions of Americans and their loved ones are counting on us. Together, we will meet our ultimate goal of preventing and effectively treating Alzheimer's and related dementias.

