

Transforming Research

To Prevent, Detect, Treat, and
Provide Better Care for Dementia



Table of Contents

July 19, 2021, NIH Director's Message	1
Introduction	4
Fiscal Year 2023 Professional Judgment Budget	12
Scientific Progress Report	14
Biomarker Research	17
Science Spotlight: First blood test of amyloid for Alzheimer's now available	19
Science Spotlight: FDA approves first diagnostic agent for tau tangles	20
Program Spotlight: What is the role of white matter lesions in dementia?	22
Program Spotlight: Alzheimer's Biomarkers Consortium — Down Syndrome	23
Research on Tools to Detect Cognitive Changes	29
Clinical Study Recruitment Initiatives to Enhance Diversity	32
Drug Candidates	35
Program Spotlight: New uses for FDA-approved drugs	39
Lifestyle, Behavior, and Cognitive Training Intervention Research	42
Science Spotlight: Choosing healthy lifestyle behaviors to reduce risk	45
Care and Caregiver Support Studies	47
Program Spotlight: 2020 Dementia Care, Caregiving, and Services Research Summit	48
Population Studies and Health Disparities	53
Science Spotlight: High blood pressure and health disparities	56
Program Spotlight: NIH expands capacity for health disparity research	57
Disease Mechanisms	62
Science Spotlight: <i>HTT</i> gene a rare cause of FTD and ALS	64
Science Spotlight: Genetic study of Lewy body dementia supports ties to Alzheimer's and Parkinson's	65
Research Enterprise	71
Program Spotlight: Compressing the timeline for treatment development	72
Moving Forward	77

NIH Director's Message

July 19, 2021

Thanks to advances over the past several years, including the [U.S. Food and Drug Administration's \(FDA\) recent accelerated approval of aducanumab](#), research on Alzheimer's disease and related dementias has never been more promising. I am pleased to present the National Institutes of Health (NIH) Professional Judgment Budget for Alzheimer's and related dementias for fiscal year (FY) 2023.

New challenges and opportunities

Since early 2020, the world has grappled with the unimaginable consequences of the coronavirus disease 2019 (COVID-19) pandemic. Both the infection with SARS-CoV-2, the virus that causes COVID-19, and initial lack of access to the vaccine illuminated health disparities in the United States. Concurrently, heartbreaking violence and other social inequities led to a new level of awareness about institutionalized racism and racial injustice. Despite these and related challenges, our research community and study participants bravely soldiered on as health and safety precautions allowed.

While the pandemic caused setbacks for some research projects, it also presented new opportunities for investigators to innovate and adapt under the circumstances. For example, some scientists used telemedicine video technology to continue to engage with research participants who could not safely leave their homes. Others pivoted their projects to directly address the challenges of the pandemic, including studying its effects on people with dementia and their caregivers.

Harnessing open science

With the record-breaking rapid development and deployment of effective coronavirus vaccines, the entire world has witnessed the power of open science. Instead of competing, scientists representing multiple disciplines collaborated and shared their data, while pharmaceutical partners quickly developed their contributions into vaccine candidates.



**“The NIH does
not just discover
opportunities for
research progress;
we create them.”**

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

The ability to quickly harness the power of open science to address the pandemic's many challenges stands on the shoulders of existing research initiatives. Through these, scientists have identified and implemented extraordinary approaches for collaborative efforts across a range of diseases and conditions, including Alzheimer's and related dementias. For several years, NIH has fostered open science partnerships through initiatives such as the [Accelerating Medicines Partnership \(AMP\)](#), which NIH launched in 2014. Our [AMP Alzheimer's Disease](#) and [AMP Parkinson's Disease](#) programs have transformed the way that [data and biological samples are shared freely](#), biological targets are discovered, and drug candidates are chosen and developed. Along with the [Alzheimer's Disease Sequencing Project](#), NIH's [other target discovery consortia](#) for Alzheimer's (M²OVE-AD, Resilience-AD, and Psych-AD) and the [MODEL-AD](#) and [TREAT-AD](#) centers also operate under open science principles.

Enhancing diversity and reducing health disparities

Observed through the lens of the pandemic, the pervasive and insidious challenge of health disparities came into sharper focus. NIH has a long history of investments to better understand and reduce or eliminate health disparities for many conditions and diseases, including Alzheimer's. These include:

- Providing researchers with [resources](#) and opportunities to ensure their studies represent the diverse racial and ethnic composition of the U.S. population, including those most at risk for developing Alzheimer's and related dementias



- Enhancing the diversity of the [dementia research workforce](#) through NIH-funded training programs
- Identifying and addressing structural racism within the NIH-supported scientific community to establish an [equitable and civil culture within the biomedical research enterprise](#)
- Advancing health disparities research through new funding opportunities to explore why there are differences in dementia incidence and care among diverse populations

Annual budget estimate

NIH does not just discover opportunities for research progress; we create them. Through our substantial investments in science, nationwide and beyond, NIH shapes the direction of the Alzheimer's and related dementias field of study.

This budget proposal outlines the additional funding needed in fiscal year 2023 to advance NIH-supported research closer to the [National Plan to Address Alzheimer's Disease](#) goal to prevent and effectively treat these devastating diseases by 2025. The professional budget estimate includes \$226 million in additional resources for new research, with the overall resources needed totaling \$3.4 billion.

The projected cost of resources needed in FY 2023 for new research to meet the 2025 goal is \$376 million. This estimate will be reduced by \$150 million in funding from completed projects that is now available for new research initiatives. As a result, the additional resources needed for new research in the FY 2023 budget is \$226 million.

2025 goal of effective treatment and prevention

NIH continues to work toward the realization of our shared vision: a world in which dementia can be prevented, people at risk can be tested before dementia symptoms develop, and people can

be treated so that symptoms can be averted or much delayed. We diligently strive for the release of successful interventions, tools, and support for people living with severe dementia and for their families and other caregivers.

Recent increased investments in building and evolving the research enterprise were crucial in preparing NIH to pivot efforts to address the unforeseen challenge of the global coronavirus pandemic. The scientific infrastructure that has enabled new and innovative discoveries for Alzheimer's and related dementias also enabled some researchers to address the immediate needs of people living with dementia during the pandemic quickly and efficiently.

While the recent FDA accelerated approval of aducanumab marks a milestone in Alzheimer's disease research, the work to identify effective therapeutic and preventive measures continues. We know now that different types of dementia will likely require specific types of treatments, including some that may eventually target an individual's unique disease characteristics — much like the cancer treatments that are available today. This [precision medicine](#) approach could eventually be based on a person's specific type of dementia, determined using precise diagnostics and biomarkers from lab and imaging tests.

Continued and sustained investment will equip NIH with the ability to persist in advancing research to effectively prevent, detect, and treat Alzheimer's and related dementias. We are much closer now to living in a world in which these conditions do not take the enormous toll they do today.

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

Director, National Institutes of Health

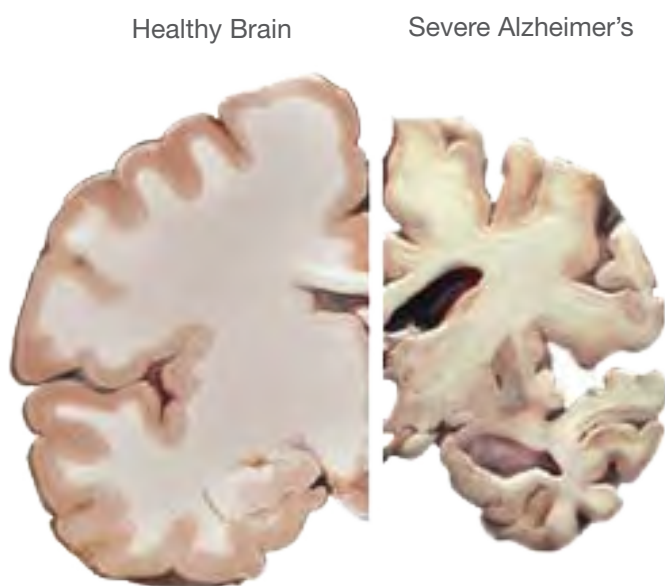


The background is a complex abstract composition. It features several overlapping hexagonal shapes in various shades of blue, teal, and orange. A large, semi-transparent white hexagon is positioned in the center, serving as a backdrop for the title. In the background, there is a blurred image of a person, possibly a woman, looking down. The overall aesthetic is modern and geometric.

Introduction

Types of brain changes in dementia

Alzheimer's and related dementias are complex brain disorders caused by a cascade of molecular events in the brain. The resulting damage to the brain eventually leads to symptoms such as memory loss and problems with thinking, as well as changes in behavior. As brain changes worsen, people with these devastating diseases eventually may lose independence and become reliant on others for care. NIA's video "[How Alzheimer's Changes the Brain](#)" shows how Alzheimer's affects the brain.



Studies of brain tissue have found that people with dementia usually have a mixture of brain changes. They may have the hallmark signs of Alzheimer's mixed with variations typically linked to another form of dementia, such as [vascular dementias](#), [frontotemporal dementia](#), or [dementia with Lewy bodies](#).

Alzheimer's disease-related dementias share many features with Alzheimer's, making precise diagnosis difficult. With the goal of developing effective prevention and treatment strategies, [NIH invests in research to better understand these various disorders](#), including why several distinct dementia-related brain changes can develop simultaneously.

Magnitude of the burden from dementia

According to a [recent NIH-funded analysis](#), an estimated 6.25 million Americans are now living with Alzheimer's disease, based on symptoms such as memory loss and difficulty thinking. Of these, most are women. The estimate increases to about 12.7 million Americans with Alzheimer's in 2050 and to more than 13.8 million in 2060.

Many people also have other forms of dementia, such as Lewy body disease, frontotemporal disorder, and vascular cognitive impairment. It remains challenging to determine exactly how many people have Alzheimer's dementia versus other forms, but through NIH investments, researchers are improving diagnostics.

This recent analysis also demonstrates that the burden of dementia is rising among racial and ethnic minority groups. Between 2021 and 2060, the number of Black/African Americans with Alzheimer's is expected to increase from about 1.1 million to 3.1 million people. During that same time frame, the number of Hispanic/Latino Americans with Alzheimer's is expected to increase from about 0.76 million to 3.7 million people. The increasing dementia incidence underscores the need for research participants who reflect the diversity of the U.S. population.

Deaths from Alzheimer's and related dementias are a leading cause of mortality in the United States. According to a recent estimate from the Centers for Disease Control and Prevention, each year [more than 260,000 Americans die from Alzheimer's and related dementias combined](#).

Of further concern, people with dementia experience significantly higher costs of care compared with those without dementia, and [the burden of those higher costs falls disproportionately on people with dementia and their families](#), according to another recent NIH-funded study.

NIH information about Alzheimer's and related dementias

NIH offers general information about dementia:

- [What Is Dementia? Symptoms, Types, and Diagnosis](#)
- [Dementia Information Page](#)
- [The Dementias: Hope Through Research](#)

We also provide information about specific kinds of dementia:

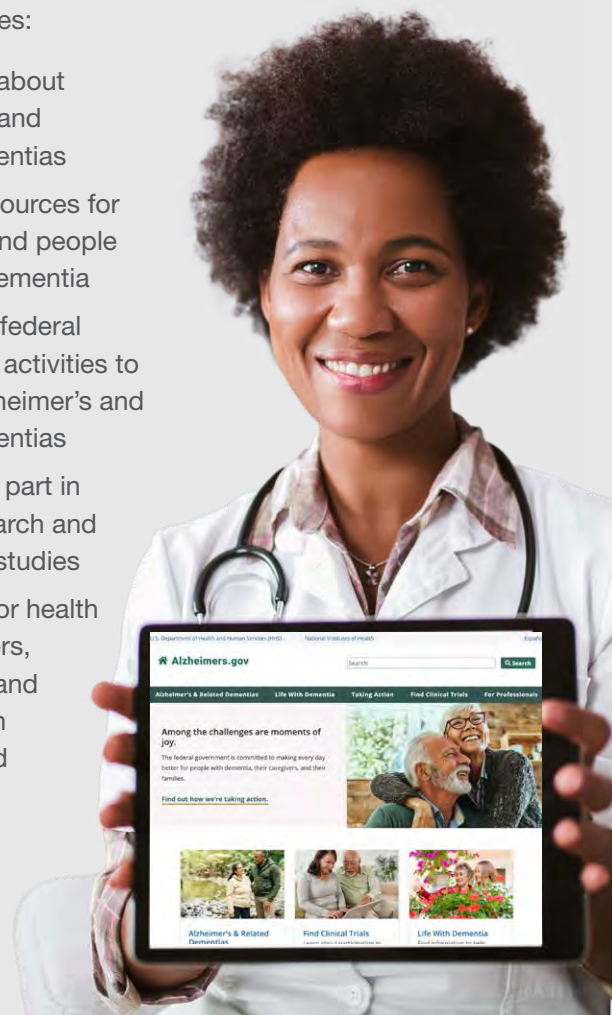
- [Basics of Alzheimer's Disease and Dementia](#)
- [What Are Frontotemporal Disorders?](#)
- [What Is Lewy Body Dementia?](#)
- [What Is Mixed Dementia?](#)
- [Vascular Contributions to Cognitive Impairment and Dementia](#)

New web portal for materials about Alzheimer's and related dementias

Working with other federal agencies, the National Institute on Aging (NIA) recently led efforts to update and enhance the [Alzheimers.gov](#) website. This new

portal to federal government information and resources launched February 2021. It features:

- Information about Alzheimer's and related dementias
- Tips and resources for caregivers and people living with dementia
- Updates on federal government activities to address Alzheimer's and related dementias
- How to take part in clinical research and how to find studies
- Resources for health care providers, community and public health workers, and researchers



Alzheimer's research investment pays off in unexpected ways

In 2020, the coronavirus pandemic presented new challenges for older adults with dementia and their caregivers. As a result, NIH and the broader research community began to consider new areas of research with relevance to Alzheimer's and related dementias. For example, people living with dementia in nursing homes and long-term care facilities are especially vulnerable to COVID-19 infection, but little was known initially about how to reduce their risk or improve their care. Because of NIH's broad

investments in dementia and related research, researchers were able to more quickly design meaningful studies, such as the following, to advance understanding:

- **People with dementia in the community:** Not only were older adults with dementia at enhanced risk of contracting COVID-19, but a study funded in part by NIH showed that they [were more likely to have severe illness, be hospitalized, and die](#). Results from this analysis of nearly 62 million Americans, which included 1 million people with dementia, showed that 59% of people

with dementia versus 25% of people without dementia were hospitalized within six months of their COVID-19 diagnosis. Of those with dementia, 73% of Black/African Americans and 54% of white Americans were hospitalized within that same time frame. The study underscores the need to vigilantly protect older adults with dementia from COVID-19, and it also highlights the pressing need to address health disparities.

- **People with cognitive impairment in nursing homes:** A related study, which also was funded in part by NIH, confirmed the findings that people with cognitive impairment are more vulnerable to COVID-19. The research team found that [nursing home residents with moderate to severe cognitive impairment were more likely to die](#) from COVID-19 than residents without cognitive impairment.

Purpose of this professional judgment budget

This professional judgment budget estimates the additional funding needed during FY 2023 to help reach the research goal of the [National Plan to Address Alzheimer's Disease](#) — to effectively treat and prevent Alzheimer's and related dementias by 2025.

NIH presents this budget estimate in accordance with Public Law No. 113-235, the Consolidated and Further Continuing Appropriations Act, 2015, Sec. 230. This law states:

Hereafter, for each fiscal year through fiscal year 2025, the Director of the National Institutes of Health shall prepare and submit directly to the President for review and transmittal to Congress, after reasonable opportunity for comment, but

Annual research summits

The research component of the National Plan to Address Alzheimer's Disease 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 living with these diseases. Experts routinely analyze and assess research progress and rechart strategies as needed given the evolving scientific evidence.

To obtain input from the broader scientific community and other stakeholders, NIH now hosts national research summits each year. Summit organizers invite hundreds of scientific experts representing widely diverse fields of dementia and other research, people living with dementia and those who care for them, members of the advocacy community, and policymakers.



Goals include:

- Review scientific progress
- Identify research gaps and opportunities
- Prioritize 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

The focus rotates on a three-year schedule:

- **Alzheimer's:** The [2021 NIH Alzheimer's Research Summit](#) was held virtually April 19 to 22. The final report is in progress.
- **Care, Services, and Supports:** The [2020 National Research Summit on Care, Services, and Supports for Persons Living with Dementia and Their Caregivers](#) resulted in this [final report](#).
- **Related Dementias:** The 2019 Alzheimer's Disease-Related Dementias Summit resulted in this [final report](#). Plans are underway for the 2022 event.

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 the annual budget estimate proposal is provided directly to the President and to Congress outside of the traditional annual federal budget process for NIH, the estimate is known as a "bypass budget" proposal.

Broad NIH support for Alzheimer's and related dementias research

Increased investment in Alzheimer's and related dementias has enabled enhanced collaboration and coordination across NIH. Representatives from all 27 Institutes and Centers are invited to participate in annual NIH-wide planning meetings to focus on opportunities for scientific partnerships.

As part of these coordination efforts, NIA has supported a supplement program since fiscal year 2018 that

allows scientists with grants from any NIH Institute, Center, or Office (ICO) to apply for supplemental funding for projects relevant both to Alzheimer's and related dementias as well as to their existing research initiatives. In FY 2020, the following ICOs were provided a total of 312 supplemental grants:

- [National Institute of Neurological Disorders and Stroke](#) (34)
- [National Heart, Lung, and Blood Institute](#) (25)
- [National Institute of Diabetes and Digestive and Kidney Diseases](#) (25)
- [National Institute of Mental Health](#) (25)
- [National Institute of General Medical Sciences](#) (24)
- [National Cancer Institute](#) (20)
- [National Center for Complementary and Integrative Health](#) (18)
- [National Institute on Deafness and Other Communication Disorders](#) (18)
- [National Institute of Allergy and Infectious Diseases](#) (18)
- [National Institute on Minority Health and Health Disparities](#) (17)
- [National Eye Institute](#) (14)
- [National Institute of Nursing Research](#) (14)
- [National Institute of Biomedical Imaging and Bioengineering](#) (14)
- [National Institute on Alcohol Abuse and Alcoholism](#) (13)
- [NIH Office of the Director](#) (8)
- [National Institute on Drug Abuse](#) (7)
- [National Human Genome Research Institute](#) (6)
- [Fogarty International Center](#) (4)
- [Eunice Kennedy Shriver National Institute of Child Health and Human Development](#) (3)
- [National Institute of Environmental Health Sciences](#) (2)
- [National Institute of Arthritis and Musculoskeletal and Skin Diseases](#) (2)
- [National Institute of Dental and Craniofacial Research](#) (1)

Research implementation milestones

Through its [Research Implementation Milestones database](#), NIH informs the research community about its interests in and priorities for funding Alzheimer's and related dementias research projects. The milestones are accessible and for use by all NIH stakeholders as a basis for independent but relevant research pursuits and for collaborations.

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.

Budgeting for FY 2023 Alzheimer's and related dementias research

The FY 2023 Professional Judgment Budget for Alzheimer's Disease and Related Dementias shows \$376 million in additional resources needed for new and evolving research. This estimate will be reduced by \$150 million in funding from completed projects that is now available for new research initiatives. As a result, the additional resources needed for new research in the FY 2023 budget are \$226 million. This would bring the total FY 2023 resources to \$3.4 billion, enabling NIH to be best positioned to meet the 2025 goal of effective prevention and treatment.

In addition to sustaining the momentum created by the previous increased investment in Alzheimer's and related dementias research, these funds would enhance NIH's ability to further advance research on preventing dementia and to improve the diagnostics, treatments, and care of those living with these diseases. Continued, enhanced investments would also drive efforts to develop novel biomarkers for use as screening tests and to monitor treatment

International research portfolio

In collaboration with the Alzheimer's Association, NIH launched the [International Alzheimer's and Related Dementias Research Portfolio \(IADRP\)](#) in 2010. This database, which is updated regularly, 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 international research portfolio is to help organizations identify research gaps, avoid duplication of effort, and leverage resources by coordinating funding strategies.

response, identify and test new drug candidates, advance comprehensive models of care, explore disease risk and protective factors, and improve the understanding of the role of genetics and other disease mechanisms.

References:

- Rajan KB, et al. [Population estimate of people with clinical AD and mild cognitive impairment in the United States \(2020-2060\)](#). *Alzheimer's & Dementia*. 2021. Epub May 27. doi: 10.1002/alz.12362.
- Murphy SL, et al. [Deaths: Final data for 2018](#). *National Vital Statistics Reports*. 2021; 69(13):1-83. Hyattsville, MD: National Center for Health Statistics.
- Ahmad FB and Anderson RN. [The leading causes of death in the US for 2020](#). *JAMA*. 2021;325(18):1829-1830. doi: 10.1001/jama.2021.5469.
- Kelley AS, et al. [Residential setting and the cumulative financial burden of dementia in the 7 years before death](#). *Journal of the American Geriatrics Society*. 2020;68(6):1319-1324. doi: 10.1111/jgs.16414.
- Wang Q, et al. [COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US](#). *Alzheimer's & Dementia*. 2021. Epub Feb 9. doi: 10.1002/alz.12296.
- Panagiotou OA, et al. [Risk factors associated with all-cause 30-day mortality in nursing home residents with COVID-19](#). *JAMA Internal Medicine*. 2021. Epub Jan 4. doi: 10.1001/jamainternmed.2020.7968.
- Ramos, D.M., et al. [Tackling neurodegenerative diseases with genomic engineering: A new stem cell initiative from the NIH](#). *Neuron*. 2021;109(7):1080-1083. doi: 10.1016/j.neuron.2021.03.022.

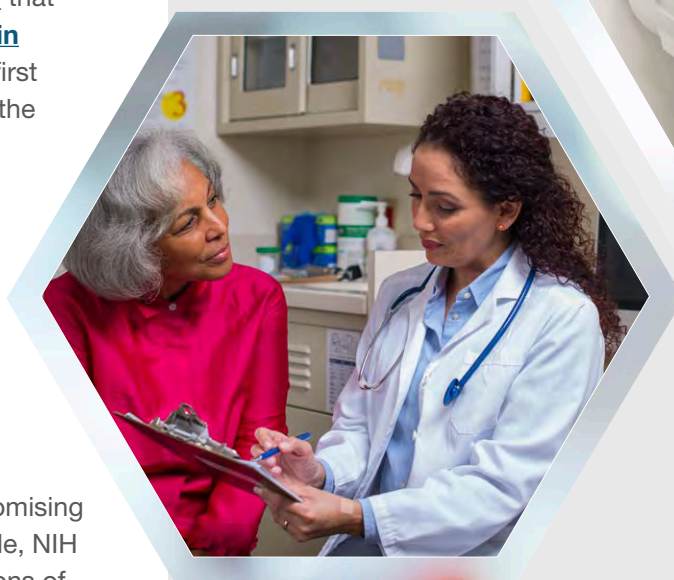
FDA approves first new Alzheimer's drug since 2003

On June 7, 2021, [FDA granted accelerated approval of aducanumab](#) for the treatment of Alzheimer's, marking a milestone in Alzheimer's research. This drug is the first treatment for Alzheimer's disease approved since 2003.

Aducanumab is an [immunotherapy](#) that targets [amyloid plaques in the brain](#) of people with Alzheimer's. It is the first approved treatment that addresses the underlying disease process to slow or reverse the progression of this condition. Previously approved Alzheimer's-related drugs addressed only the symptoms.

While NIH did not provide direct support for the development of aducanumab, years of public funding were integral to the drug's development, as well as to other promising therapeutic approaches. For example, NIH supported basic science investigations of immunotherapies similar to aducanumab, as well as translational research for next-generation immunotherapies. Additionally, the selection of participants for aducanumab clinical trials hinged on [positron emission tomography](#) (PET) scans for amyloid plaques. Amyloid PET imaging is a method that would not exist today without NIH-supported research.

The work does not stop here: NIH presses onward with its robust and diverse research portfolio for developing treatments. We will continue to evolve our understanding about Alzheimer's and to develop more ways to detect, treat, and prevent this disease.



New NIH intramural research initiative for Alzheimer's and related dementias research

In 2020, NIH broke ground on its Bethesda, Maryland, campus to construct a new intramural research facility devoted to Alzheimer's and related dementias research. This [Center for Alzheimer's Disease and Related Dementias \(CARD\)](#) will support basic, translational, and clinical research. Center initiatives will complement and enhance the work of thousands of researchers nationwide and beyond who are exploring disease mechanisms to translate scientific knowledge into ways to better prevent and treat these diseases.

CARD scientists will have the opportunity to leverage some of the unique and powerful aspects of the [NIH Intramural Research Program](#), such as coordinating early phase clinical trials at the [NIH Clinical Center](#) and high-throughput testing at the [NIH National Center for Advancing Translational Sciences](#).

While the dedicated facility is expected to fully open its doors in early 2022, CARD researchers are already building multidisciplinary collaborations among scientists on the NIH campus and in academia and industry.

In early 2021, CARD investigators and their collaborators documented efforts to [create "personalized" stem cells for studying dementia](#). This project, one of the first to be supported through CARD, is designed to engineer cell models of disease-causing gene mutations from multiple brain disorders, including:

- Alzheimer's
- Frontotemporal dementia and amyotrophic lateral sclerosis
- Dementia with Lewy bodies and Parkinson's disease dementia

The resulting library of cell lines, which will be freely available to the research community, can be used for disease modeling and drug development.

"Our immediate priorities are to quickly stand up our clinical, translational, and basic research efforts," said [Andrew B. Singleton, Ph.D., upon being named the CARD director in April 2021](#).

"Critical to this effort will be the recruitment of key positions within CARD, including leadership of translational and clinical areas.

"It is essential that we train and recruit the very best and brightest scientists with an emphasis on creating a diverse and energetic culture. The aim is to accelerate our collective path to effective treatments and preventions for these devastating diseases."



Fiscal Year 2023 Professional Judgment Budget: Alzheimer's Disease and Related Dementias

Baseline Estimate, Fiscal Year 2021 Enacted Level for
Alzheimer's and Related Dementias (AD/ADRD) Research¹

\$3,201,132,093

Professional Judgment Budget FY 2023 Additional Resources Needed

Areas of Research	Amount
Molecular Pathogenesis and Pathophysiology of Alzheimer's Disease	\$54,000,000
Diagnosis, Assessment, and Disease Monitoring	\$26,500,000
Translational Research and Clinical Interventions	\$102,750,000
Epidemiology	\$43,375,000
Care and Caregiver Support	\$27,375,000
Research Resources	\$74,950,000
Alzheimer's Disease-Related Dementias	\$37,598,611
Staffing Needs and Administrative Support	\$9,437,500
Total Costs for New AD/ADRD Research	\$375,986,111
Less: Funding from completed projects that is now available for new Alzheimer's and related dementias research	(\$150,000,000)
Additional FY 2023 Resources Needed for New AD/ADRD Research²	\$225,986,111

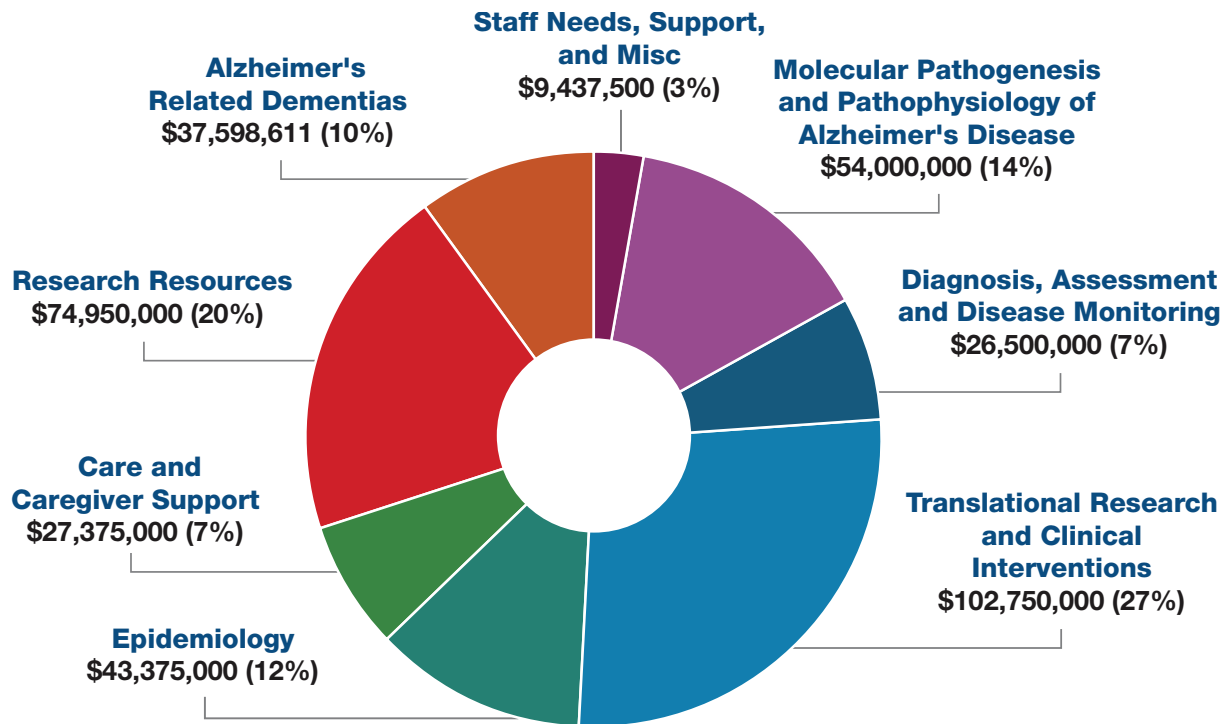
Professional Judgment Budget FY 2023 Total Resources Needed

Factors	Amount
FY 2021 Enacted Level for AD/ADRD Research (baseline estimate)	\$3,201,132,093
ADDITIONAL FY2023 Resources Needed for New AD/ADRD Research	\$225,986,111
Total FY 2023 Resources Needed for AD/ADRD Research	\$3,427,118,204

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/funding/categorical-spending#/>.

² In FY 2023, 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 \$376 million. This estimate will be reduced by \$150 million in funding from completed projects that is now available for new AD/ADRD research initiatives. As a result, the additional resources needed for new research in the FY 2023 budget is \$226 million.

Distribution of FY 2023 Total Projected Costs Across Research Areas



Total Projected Costs:
\$375,986,111*

**Additional Resources
Needed for New Research:**
\$225,986,111

** In FY 2023, the projected cost of resources needed for new and evolving research to meet the 2025 treatment/prevention goal is \$376 million. This estimate will be reduced by \$150 million in funding from completed projects that is now available for new research initiatives. As a result, the additional resources needed for new research in the FY 2023 budget are \$226 million.*

The background is a complex, abstract composition. It features several overlapping hexagonal shapes in various shades of blue, teal, and orange. These shapes are semi-transparent, allowing a blurred image of a person's face and upper body to be visible underneath. The person appears to be wearing a light-colored shirt and has their hand near their face. The overall effect is a modern, scientific, and artistic aesthetic.

Scientific Progress Report



This progress report is a snapshot of scientific advances and new programs initiated over the past year (2020/2021) thanks to NIH investments in Alzheimer's and related dementias research. The report summarizes achievements in the following areas:

- [**Biomarker Research**](#)
- [**Research on Tools to Detect Cognitive Changes**](#)
- [**Clinical Study Recruitment Initiatives to Enhance Diversity**](#)
- [**Drug Candidates**](#)
- [**Lifestyle, Behavior, and Cognitive Training Intervention Research**](#)
- [**Care and Caregiver Support Studies**](#)
- [**Population Studies and Health Disparities**](#)
- [**Disease Mechanisms**](#)
- [**Research Enterprise**](#)

More detail about scientific progress is provided through embedded hyperlinks to additional resources and information, including:

- [**NIH news releases**](#) about scientific findings and new research programs
- [**NIH Research Matters**](#), a weekly newsletter about new journal articles
- [**NIA Featured Research Articles**](#)
- [**Inside NIA**](#), a Blog for Researchers
- [**NINDS Director's Messages**](#)
- [**NIH PubMed.gov abstracts**](#) of papers reporting scientific advances

In addition, the report links to NIH fact sheets and videos that describe Alzheimer's and related dementias and explain scientific terms and concepts.

A list of relevant journal articles is included at the end of each section that features recent scientific findings.

NIH inspires students to pursue research careers

By offering programs aimed at research trainees at many points along the career trajectory, NIH demonstrates its commitment to expanding the research workforce dedicated to Alzheimer's and related dementias research. For example, [NIH's Advancing Diversity in Aging Research \(ADAR\) through Undergraduate Education](#) encourages college students to pursue research careers that may involve (but are not

limited to) dementia-related research. Students are eligible to apply for NIA ADAR-funded programs if they are from economically, socially, culturally, or educationally disadvantaged backgrounds. Applicants include students from underrepresented racial and ethnic groups and those who have vision, hearing, or other physical challenges. The experiences of three recent research trainees are highlighted in this report's "Investing in the Future" sections:

- [Udell Holmes III](#)
- [Parveer Kaur](#)
- [Jose Sandoval](#)



Biomarker Research



When effective treatments for Alzheimer's and related dementias become available, doctors will need reliable tests for early detection and diagnosis. To this end, NIH invests in the development of easier-to-use, less expensive testing methods. This investment led to significant advances in 2020, particularly in the further development of blood and imaging tests.

For example, since fall 2020, [physicians in clinical practice can now order a blood test for amyloid protein](#), a hallmark sign of Alzheimer's, for an individual who is not participating in a study. Several other blood tests are in development. In addition, there were advances in brain imaging, most notably the [FDA approval of the first PET scan product](#) to detect [tau tangles in the brain](#), another hallmark sign of Alzheimer's.

However, the current ability to obtain an Alzheimer's and related dementias diagnostic test in a doctor's office is still quite limited, and biomarker imaging and lab tests are mainly used today by researchers to study people who volunteer to take part in related studies. NIH continues to fund multiple studies to discover and validate additional testing options.

(continued on page 21)

What is a biomarker?

A **biomarker** is an indicator of disease that can be measured in blood, cerebrospinal fluid, other body fluids, or tissues. For example, the hallmark signs of Alzheimer's are detected with brain imaging tests and lab tests of cerebrospinal fluid or blood:

- Plaques of amyloid protein
- Tangles of tau protein

Before scientists developed biomarker tests for Alzheimer's in the early 2000s, the only sure way to know whether a person had the disease was by studying their brain tissue after they died. Today, brain imaging methods such as PET scans and lab tests of spinal fluid and blood are available to help diagnose people living with the disease.

Methods of diagnosing the various causes of dementia are still undergoing research and development. Learn more:

- [Biomarkers for Dementia Detection and Research](#)
- [Diagnosing Frontotemporal Dementia](#)
- [Diagnosing Lewy Body Dementia](#)

After using these biomarker tests for many years with research participants, scientists now realize that brain changes may begin decades before memory loss or other symptoms appear. Now they are working to find ways to slow or prevent the changes that lead to dementia, and biomarker tests are essential for these projects.



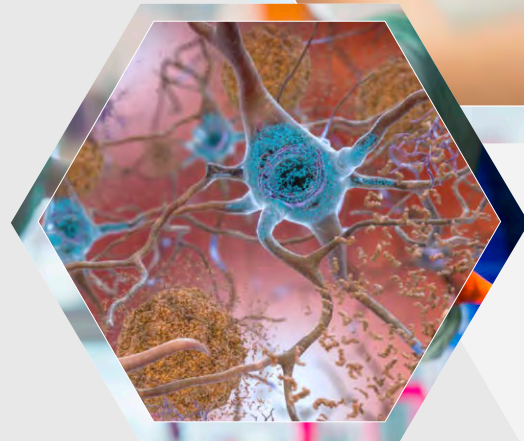
Science Spotlight

First blood test of amyloid, a biomarker for Alzheimer's, now available to doctors

Thanks in part to NIH funding, researchers at C2N Diagnostics developed the [PrecivityAD blood test](#). This is the first amyloid blood test to become available to doctors, who can send blood samples to C2N's lab to analyze blood for amyloid. While this test does not diagnose Alzheimer's per se, it can help doctors evaluate their patients with cognitive disorders.

C2N's lab measures the [concentrations of amyloid 42 and 40](#) and checks for the presence of [apolipoprotein E](#). From these measures, C2N's automated method generates an Amyloid Probability Score to suggest the likelihood of amyloid plaques in the brain. A high score is consistent with a high level of amyloid plaques found on a PET scan.

Although C2N has demonstrated that their lab provides accurate and reliable test results for blood samples, studies are needed to further evaluate this method with people who have symptoms of Alzheimer's, including diverse populations. C2N has multiple NIH grants, including small business grants.



As Alzheimer's develops, clumps of beta-amyloid (shown in orange) slowly build up between neurons.

Science Spotlight

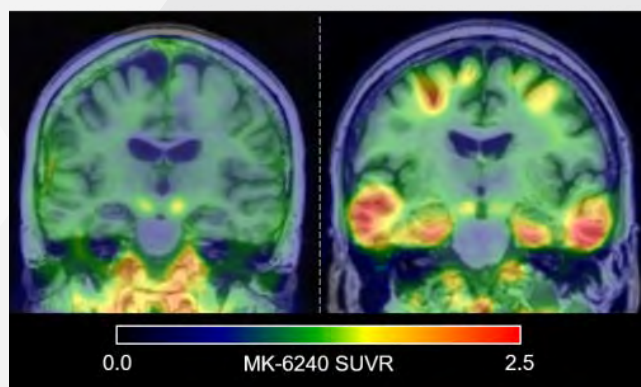


FDA approves first diagnostic agent for tau tangles

In 2020, **FDA approved flortaucipir — the first diagnostic agent** for measuring tau tangles on a PET scan of the brain. This approval is a major technological advance in biomarker tests for Alzheimer's.

The radioactive diagnostic agent flortaucipir binds to dense areas of tau tangles, which appear bright red on a PET brain scan. An NIA-funded project **demonstrated a high degree of similarity** between the amount and location of tau tangles detected with the brain scan while research participants were alive and in an examination of brain tissue after death.

Before FDA approval of flortaucipir, determining the distribution and density of tau tangles in the brain was possible only through autopsy. The new diagnostic agent fills an important missing piece of the diagnostic puzzle. Results from a tau PET scan, when combined with results from an amyloid PET scan, can help doctors evaluate a person who has cognitive impairment. Previously, FDA approved three PET scan diagnostic agents for detecting amyloid plaques in people who have Alzheimer's.



On left, no tau biomarker detected on the PET brain scan. On right, tau biomarker detected (shown in red).

Credit: S.C. Johnson, Ph.D., and T.J. Betthauser, Ph.D., Wisconsin Alzheimer's Disease Research Center

(continued from page 18)

In the continuing quest for new biomarkers of Alzheimer's and related dementias, researchers recently identified various proteins and other substances that have potential:

- **Tau tangles:** When tau tangles collect in the brain, various tau forms can also be found in the spinal fluid and blood. Over the past year, NIH-supported projects have made progress with the tau form known as ptau217, and two research teams devised and tested methods of [measuring ptau217 in blood samples](#). Both teams reported that ptau217 was better than [ptau181](#) at detecting signs of Alzheimer's and that ptau217 had the potential to rival PET imaging and spinal fluid testing at Alzheimer's detection. Researchers continue to further develop blood test methods that detect ptau217.
- **Protein groups:** Researchers supported by the [NIH Accelerating Medicines Partnership Alzheimer's Disease](#) (AMP AD) program measured 3,500 proteins in spinal fluid and 12,000 proteins in brain samples from people with Alzheimer's and from cognitively normal study participants. The research team identified [groups of proteins that were associated with Alzheimer's](#), an advance that lays the foundation for the discovery of new fluid biomarkers for Alzheimer's.
- **Neurofilament light chain:** The presence of the biomarker known as neurofilament light chain protein is an indicator that neurons have been injured or destroyed. A team of researchers funded in part by NIH found further evidence to support the [development of a blood-based biomarker test for neurofilament light chain](#) for the inherited form of Alzheimer's. More research is needed to better understand whether neurofilament light chain would be a useful biomarker for those with the more common form of Alzheimer's disease, meaning the type that is not inherited.
- **Lipids:** A team of international researchers analyzed the entire set of lipids (fatty substances) in blood plasma samples from about 2,000 people, including participants in the [NIA-supported](#)

[Alzheimer's Disease Neuroimaging Initiative.](#)

The team discovered that [certain lipids are linked to Alzheimer's](#), signifying that these substances have potential as fluid biomarkers.

Recent studies have also noted that people with Alzheimer's may have changes with their eyes or vision and that they may experience sleep disturbances, which are two more avenues of study for biomarkers:

- **Eyes and vision changes:** Recent NIH-supported studies have suggested that [retina changes](#) and [vision and pupil changes](#) might serve as biomarkers of Alzheimer's and related dementias.
- **Sleep disturbance:** Three recent studies explored the relationship between [sleep deprivation and abnormal deposits of certain proteins](#), such as [tau tangles](#) and amyloid plaques. One of the research teams suggested that measuring sleep activity with wearable devices may have potential as an easy and safe way to predict the abnormal accumulation of proteins in the brain before cognitive decline and other symptoms of brain disease develop.



PROGRAM SPOTLIGHT

What is the role of white matter lesions in cognitive impairment and dementia?

In October 2020, University of California, Davis (UC), received NIH funding for a new project called [**White Matter Lesion Etiology of Dementia in Diverse Populations \(Diverse VCID\)**](#). Part of [**NIH's Vascular Contributions to Cognitive Impairment and Dementia \(VCID\) program**](#), the project is focused on health disparities in diverse racial and ethnic populations.

Abnormally bright white areas on brain images — also known as white matter lesions or white matter hyperintensities — indicate injury. They are very common and can occur from a stroke, normal aging, or other causes. Researchers have linked having high levels of the bright white areas to dementia. The UC Davis project will analyze both age-related and disease-related white matter lesions for their possible link to dementia.

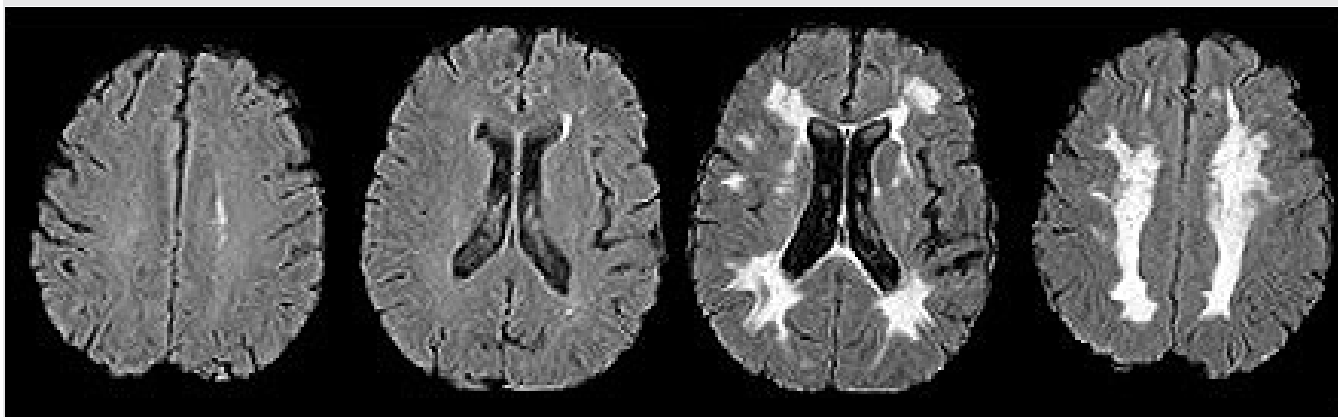
This will be the first large study of a diverse population on the long-term effects of white

matter lesions on thinking and dementia risk. By recruiting participants that represent the diversity of the U.S. population, the scientists leading the project aim to lay the groundwork for creating reliable standards for assessing, diagnosing, and treating people with cognitive problems and white matter lesions.

By analyzing MRI scans and other measures, the research team will study the role of vascular factors, particularly white matter lesions in cognitive impairment and dementia. The project will identify whether white matter lesions differ by race, ethnicity, and sex.

Recruitment of participants is expected to begin in late 2021 at UC Davis and at a minimum of 10 other locations throughout the U.S.

This project supports 27 investigators at 12 institutions, and it will leverage resources from the NIH-funded [**MarkVCID**](#) initiative, through which researchers have developed and validated several VCID biomarker kits.



On left, brain scans with normal level of age-related white matter lesions. On right, brain scans with high level of age-related white matter lesions. Credit: Charles DeCarli, M.D., FAAN, FAHA, UC Davis Health

PROGRAM SPOTLIGHT

Alzheimer's Biomarkers Consortium — Down Syndrome

People living with Down syndrome are at high risk of developing Alzheimer's. By about age 40, nearly all adults with Down syndrome have a hallmark sign of Alzheimer's — amyloid plaques in their brain. Experts estimate that at least **50% of people with Down syndrome** will develop Alzheimer's dementia as they age.

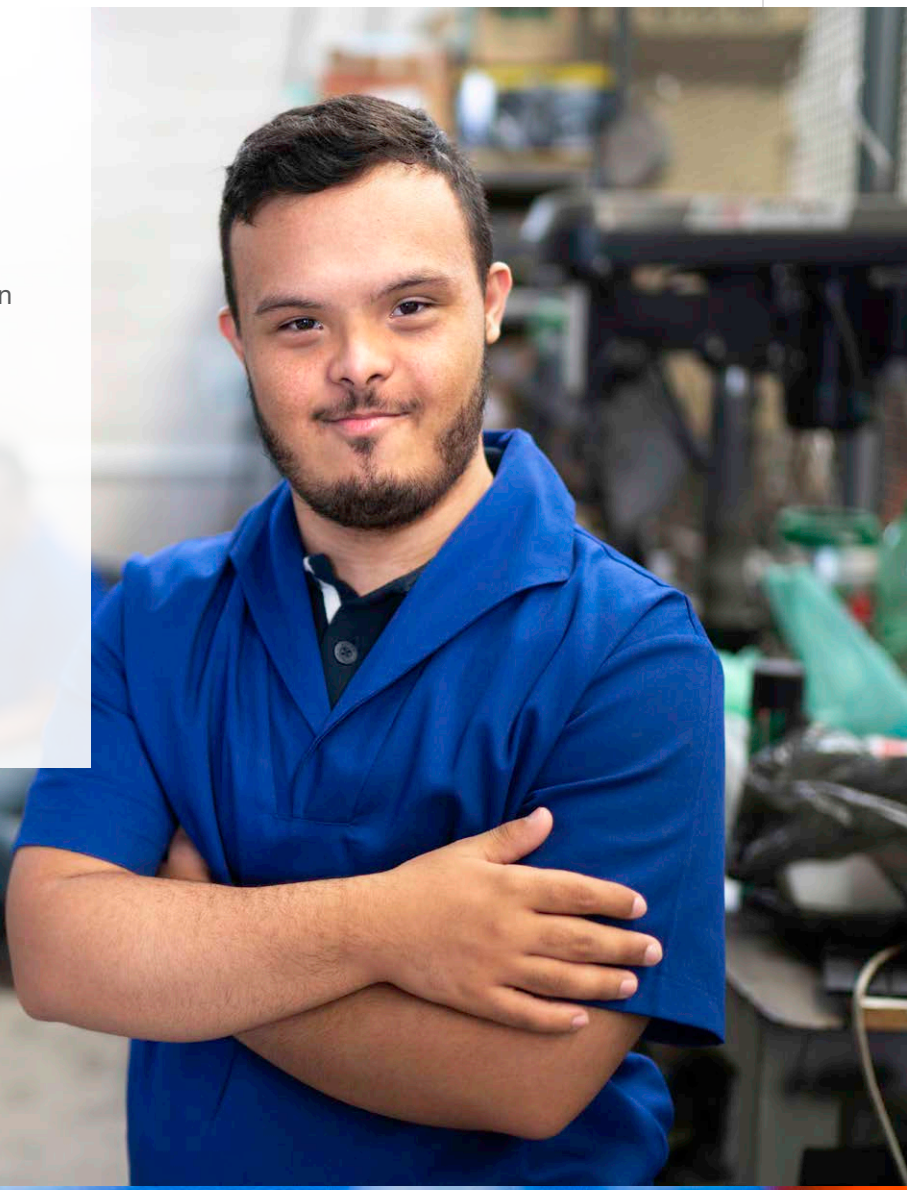
NIH is funding **Alzheimer's Biomarkers Consortium — Down Syndrome** (ABC-DS), a multi-institution research team led by the University of Pittsburgh, to expand research on the biomarkers of Alzheimer's in adults with Down syndrome.

The increased risk of Alzheimer's in this population may stem from the fact that people with Down syndrome have three rather than two copies of a key gene that produces amyloid. By learning the biological mechanism that explains the increased risk, researchers may devise methods of prevention and treatment not just for those with Down syndrome, but also for other adults at risk of developing Alzheimer's.

A recent analysis of data from the NIH-supported ABC-DS study suggests that **people with Down syndrome show similar changes in metabolic processes as people with late-stage Alzheimer's**. The same pattern of metabolic changes occurs for people with Down syndrome who go on to

develop Alzheimer's and people with late-stage Alzheimer's. The findings suggest that measures of metabolic substances may have potential as blood-based biomarker tests.

Launched in 2018, the **NIH INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome) Project** is a related research initiative for individuals with Down syndrome. Because one of the conditions of special interest for the INCLUDE Project is Alzheimer's, it supports the Alzheimer's Biomarkers Consortium — Down Syndrome.



Developing biomarkers for Parkinson's disease dementia and dementia with Lewy bodies

Biomarker development goes beyond Alzheimer's: Many NIH-supported projects are aimed at finding new biomarkers and developing diagnostic tests for Alzheimer's-related dementias, such as Parkinson's disease dementia and dementia with Lewy bodies. For example, clumped forms of the [alpha-synuclein protein](#) are found in the brains of people with Parkinson's disease and Lewy body dementias, and a [test of spinal fluid](#) can detect the protein.

To develop a diagnostic test that would be easier than the spinal fluid test, an NIH-supported project is working on a skin test for this biomarker. The team reported recently that they detected [deposits of the clumped protein in skin samples](#) from people with Lewy body dementias but not in healthy people. The skin test results were comparable to spinal fluid tests for alpha-synuclein.

To further our understanding of potential biomarkers for Parkinson's and other Lewy body dementias, NIH has been supporting several projects and programs including the [Accelerating Medicines Partnership \(AMP\) Parkinson's Disease](#). In addition, NIH recently released a [new funding opportunity to support the identification of biomarkers for Lewy body dementia](#). Through this new opportunity, NIH seeks research projects that will increase our understanding of how clinical information from people with Lewy bodies corresponds with abnormal areas observed in brain tissue collected after death.

New initiative to address health disparities through biomarker research

To meet the pressing need to better understand the prevalence, progression, and clinical impact of Alzheimer's among Mexican Americans, [NIH awarded additional funding in 2020 for more PET scan and other biomarker measures](#) to the ongoing Health and Aging Brain Among Latino Elders (HABLE) study. The additional funding will support the Health and Aging Brain Among Latino Elders-Amyloid, Tau, and Neurodegeneration (HABLE-AT(N)) study, which enables researchers to collect amyloid and tau PET imaging and other biomarker measures. The goal is to better understand health disparities of brain aging and Alzheimer's between Mexican Americans and non-Latino whites. An additional benefit of HABLE and HABLE AT(N) will be the ability to better classify/categorize participants into groups by type of dementia and stage of the disease. This will help facilitate potential enrollment in future studies.



Creating a legacy through brain donation

To help encourage the public to take part in brain donation for ongoing research efforts, NIH developed and released a [feature article](#) and [social media toolkit](#) last year. These materials are designed to be shared broadly and to spark discussions about this important topic.

The article focuses on why brain donors are needed and explains the steps in developing a donation plan. The social media toolkit includes image cards, sample social media posts, a flyer, an infographic, and drop-in language for grantee and other newsletters. Available in both English and Spanish, the toolkit is already being used by the [NIA-supported Alzheimer's Disease Research Centers](#) and others to spread the word about the importance of brain donation.

These brain donation materials also explain how people can enroll to donate to the [NIH NeuroBioBank](#), which is supported by several parts of NIH:

- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
- National Institute of Mental Health
- National Institute of Neurological Disorders and Stroke
- National Institute on Aging
- National Institute on Drug Abuse

Through its NeuroBioBank, NIH distributes thousands of samples of human brain tissue to the research community each year to help spur research progress in understanding dementia. Many more donors are needed, however, because progress in understanding dementia relies on donors who represent the diversity of the U.S.



Talk with a loved one about leaving a **lasting legacy.**

One donated brain makes a huge impact.



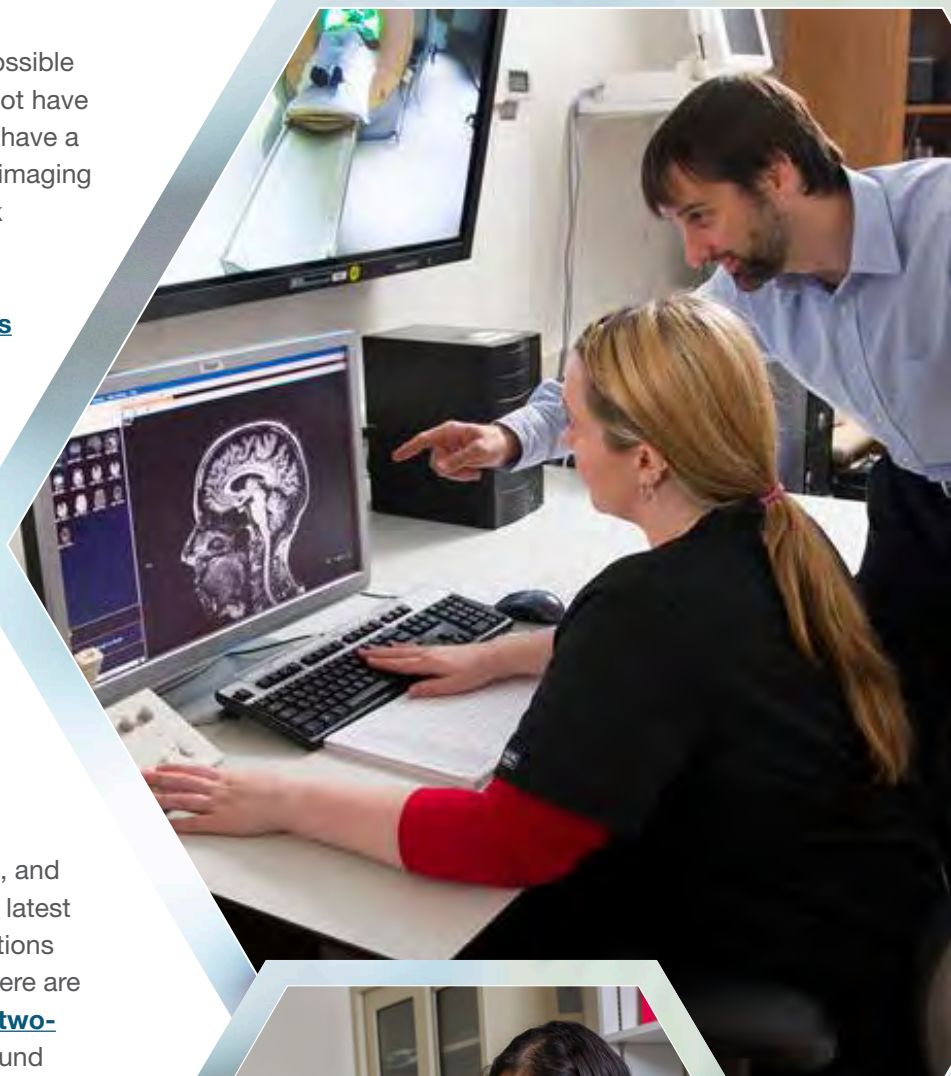
#braindonation



Behavioral research and biomarkers

Researchers have begun to investigate the possible psychological effects on individuals who do not have symptoms of dementia but who are told they have a biological sign of Alzheimer's based on brain imaging tests for amyloid plaques, one of the hallmark signs of Alzheimer's. Two independent teams of behavioral and social scientists recently reported that [learning biomarker test results does not cause serious distress](#) among Alzheimer's research participants. However, further research with more diverse populations is needed to examine the short-term and lasting psychological effects of learning biomarker test results of dementia risk, as well as how physicians can best communicate results to lessen the chance of serious distress.

Studies on other possible effects from biomarker tests in people without symptoms are also being conducted. In June 2021, the National Academies of Sciences, Engineering, and Medicine invited leading thinkers to share the latest research results to evaluate the many implications of diagnosing people with dementia before there are symptoms. The goals of the [NIA-sponsored two-day workshop](#) were to advance dialogue around this issue, explore new ideas, and discuss possible solutions to challenges arising from the use of biomarker tests. Participants considered the clinical implications of early detection of dementia using biomarkers, as well as the impact on behavioral and social research. They shared their thoughts about the ethical implications of early diagnosis, how to ensure health equity in studies of individuals who have not developed symptoms of dementia, and the economic impact of diagnostic biomarkers on health services.



INVESTING IN THE FUTURE:

Research Trainee: Udel Holmes III

Providing funding for research training is one way that NIH nurtures the next generation of scientists. At Columbia University, investigators recruit students from underrepresented groups to conduct research projects with neuroimaging data for their NIA-funded [Summer of Translational Aging Research for Undergraduates \(STAR U\)](#). The trainees are helping to develop brain images as biomarkers of dementia through [NIA's Advancing Diversity in Aging Research \(ADAR\) through Undergraduate Education](#) program.

An example of a STAR U trainee is Udel Holmes III, who in 2020 earned a bachelor of arts degree in psychology with honors from Cleveland State University. Holmes conducted an independent research project studying the default mode network, a group of areas in the brain that is active when an individual is not focused on the outside world. Neuroscientists study it with imaging methods such as brain MRI.

Holmes set out to determine whether the default mode network can be developed as a biomarker for detecting subjective cognitive decline. Subjective decline is an individual's perception that their memory or thinking skills are worse than for other people their age, but standard diagnostic tests do not detect any difference. Researchers have wondered whether it may be a stage before cognitive decline progresses to dementia. If the default mode network has the potential to be a biomarker, then it could be developed into an objective test of early cognitive decline.

Holmes analyzed MRI scans from 22 healthy older adults and observed that the front region of the default mode network might be correlated with subjective cognitive decline.

"I really want to do research, and I also want to be a practitioner as well, working with either hospitals or university hospitals to help patients," he said.

Investing in research trainees like Holmes is one way that NIA inspires the next generation of scientists to focus on Alzheimer's and related dementias. In the fall of 2021, Holmes will begin his graduate program at the University of Florida, pursuing a Ph.D. in clinical neuropsychology.



"I really want to do research, and I also want to be a practitioner as well, working with either hospitals or university hospitals to help patients."



Magnetic resonance imaging of areas of the brain in the default mode network.

Credit: John Graner, Duke University

References:

- Schindler SE, et al. [High-precision plasma \$\beta\$ -amyloid 42/40 predicts current and future brain amyloidosis](#). *Neurology*. 2019;93(17):e1647-e1659. doi: 10.1212/WNL.0000000000008081.
- Fleisher AS, et al. [Positron emission tomography imaging with \[\$^{18}\$ F\]flortaucipir and postmortem assessment of Alzheimer disease neuropathologic changes](#). *JAMA Neurology*. 2020;77(7):829-839. doi: 10.1001/jamaneurol.2020.0528.
- Palmqvist S, et al. [Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders](#). *JAMA*. 2020;324(8):772-781. doi: 10.1001/jama.2020.12134.
- Barthélemy NR, et al. [Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease](#). *Journal of Experimental Medicine*. 2020;217(11):e20200861. doi: 10.1084/jem.20200861.
- Higginbotham L, et al. [Integrated proteomics reveals brain-based cerebrospinal fluid biomarkers in asymptomatic and symptomatic Alzheimer's disease](#). *Science Advances*. 2020;6(43): eaaz9360. doi:10.1126/sciadv.aaz9360.
- Quiroz YT, et al. [Plasma neurofilament light chain in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: A cross-sectional and longitudinal cohort study](#). *Lancet Neurology*. 2020;19(6):513-521. doi: 10.1016/s1474-4422(20)30137-x.
- Huynh K, et al. [Concordant peripheral lipidome signatures in two large clinical studies of Alzheimer's disease](#). *Nature Communications*. 2020; 11(1):5698. doi: 10.1038/s41467-020-19473-7.
- Shi H, et al. [Identification of early pericyte loss and vascular amyloidosis in Alzheimer's disease retina](#). *Acta Neuropathologica*. 2020;139(5):813-836. doi: 10.1007/s00401-020-02134-w.
- Risacher SL, et al. [Visual contrast sensitivity is associated with the presence of cerebral amyloid and tau deposition](#). *Brain Communications*. 2020;2(1):fcaa019. doi: 10.1093/braincomms/fcaa019.
- Adams JW, et al. [Association of probable REM sleep behavior disorder with pathology and years of contact sports play in chronic traumatic encephalopathy](#). *Acta Neuropathologica*. 2020;140(6):851-862. doi: 10.1007/s00401-020-02206-x.
- Winer RJ, et al. [Sleep disturbance forecasts \$\beta\$ -amyloid accumulation across subsequent years](#). *Current Biology*. 2020;30(21):4291-4298.e3. doi: 10.1016/j.cub.2020.08.017.
- Barthélemy NR, et al. [Sleep deprivation affects tau phosphorylation in human cerebrospinal fluid](#). *Annals of Neurology*. 2020;87(5):700-709. doi: 10.1002/ana.25702.
- Mapstone M, et al. [Metabolic correlates of prevalent mild cognitive impairment and Alzheimer's disease in adults with Down syndrome](#). *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2020;12(1):e12028. doi: 10.1002/dad2.12028.
- Wang Z, et al., [Skin \$\alpha\$ -synuclein aggregation seeding activity as a novel biomarker for Parkinson disease](#). *JAMA Neurology*. 2020;78(1):1-11. doi: 10.1001/jamaneurol.2020.3311.
- Grill JD, et al. [Short-term psychological outcomes of disclosing amyloid imaging results to research participants who do not have cognitive impairment](#). *JAMA Neurology*. 2020. Epub Aug 10. doi: 10.1001/jamaneurol.2020.2734.
- Largent EA, et al. [Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results](#). *PLOS One*. 2020;15(2):e0229137. doi: 10.1371/journal.pone.0229137.

Research on Tools to Detect Cognitive Changes



At the same time biomarker tests are being developed to detect physical signs of Alzheimer's and related diseases, NIH is supporting researchers who are [developing tests to detect cognitive changes](#). Of special interest are [tools that are inexpensive, easy to use in the community, and culturally appropriate](#). Recent progress includes:

- **Expanding the NIH Toolbox:** To further develop a brief but comprehensive assessment tool, researchers are expanding the [NIH Toolbox for the Assessment of Neurological and Behavioral Function](#). Now available in English and Spanish, the tool was released in 2012 to screen for a decline in cognitive health. To date, more than 200 clinical studies are using the NIH Toolbox, and more than 250 peer-reviewed articles have been published. The NIH-supported Advancing Reliable Measurement in Alzheimer's Disease and Cognitive Aging study is investigating the use of the NIH Toolbox measures for people with Alzheimer's. Through this effort, researchers are expanding the toolbox so that it will be valid to use with ethnically and racially diverse adults and in adults 86 and older. The study is being conducted with the [National Alzheimer's Coordinating Center](#), which NIA established more than two decades ago to facilitate research at the [NIA-funded Alzheimer's Disease Research Centers](#), as well as to share data and support research in the broader field.
- **Enrolling diverse participants in the DetectCID consortium:** There is an urgent need to provide caregivers in primary care settings with better ways to easily, quickly, and accurately determine whether people have cognitive impairment and dementia. Through the [NIH-supported national Consortium for Detecting Cognitive Impairment, Including Dementia \(DetectCID\)](#), researchers are developing, testing, and validating cognitive impairment detection tools that can be used by general practitioners to provide follow-up recommendations for the patient. With trials now in Phase 2, scientists are enrolling a larger number of research participants with at least 50% from racial and ethnic minority groups. Although investigators are still analyzing assessments to determine effectiveness and cultural appropriateness, preliminary data are encouraging.
- **Assessing the usefulness of a combination of tests:** Researchers recently reported the [development and validation of a combination of tests](#) to assess mild cognitive impairment. The combination of tests, which are being used in the NIH-sponsored [EXERT clinical trial of exercise](#), measure thinking skills such as planning, working memory, time management, and organization.
- **Analyzing financial skills:** Another method under development for detecting signs of cognitive decline is [monitoring financial data](#), financial decision-making capacity, and susceptibility to financial exploitation. People with Alzheimer's disease and related dementias [may start having trouble handling money and paying bills](#) years before diagnosis, according to a recent NIH-funded study.
- **Interpreting writing samples:** Analyzing writing for certain [patterns of language](#) is yet another method under development for predicting a future Alzheimer's diagnosis in people who are cognitively normal. Researchers found that short and simple phrases, repeated words, spelling errors, and missing punctuation were associated with a diagnosis of Alzheimer's several years later.



References:

Snitz BE, et al. **Associations between NIH Toolbox Cognition Battery and in vivo brain amyloid and tau pathology in non-demented older adults**. *Alzheimer's & Dementia (Amsterdam)*. 2020;12(1):e12018. doi: 10.1002/dad2.12018.

Jacobs DM, et al. **Development of a novel cognitive composite outcome to assess therapeutic effects of exercise in the EXERT trial for adults with MCI: The ADAS-Cog-Exec**. *Alzheimer's & Dementia (New York)*. 2020;6(1):e12059. doi: 10.1002/trc2.12059.

Nicholas LH, et al. **Financial presentation of Alzheimer's disease and related dementias**. *JAMA Internal Medicine*. 2021;181(2):220-227. doi: 10.1001/jamainternmed.2020.6432.

Eyigoz E, et al. **Linguistic markers predict onset of Alzheimer's disease**. *EClinicalMedicine*. 2020;28:100583. doi: 10.1016/j.eclinm.2020.100583.



Clinical Study Recruitment Initiatives to Enhance Diversity



To ensure that prevention and treatment interventions will be effective for all people with Alzheimer's and related dementias, investigators must recruit research participants from more diverse populations, including Black/African Americans and Hispanics/Latinos, who are at higher risk of dementia than white Americans. As a federal agency, NIH is helping to coordinate, collaborate, and fund a range of activities to achieve this goal.

In 2018, NIA, in collaboration with the Alzheimer's Association and many other stakeholders, developed and released the [National Strategy for Recruitment and Participation in Alzheimer's and Related Dementias Clinical Research](#). The main goal of the national strategy is to engage broad segments of the public in the Alzheimer's and related dementias research enterprise. Recruitment is particularly focused on the inclusion of underrepresented communities who are disproportionately affected by the disease. By enrolling and retaining diverse participants, researchers will be able to gain a better understanding of these diseases so that someday they can be managed much more successfully.

Since the launch of the national strategy, NIA has implemented several activities to facilitate and enhance clinical study enrollment and retention:

- **Enhancing outreach targeted to specific underrepresented groups:** NIA has been conducting focus groups, surveys, and stakeholder interviews to tailor recruitment materials for clinical studies to reach underrepresented populations more effectively. Using the findings from this research, NIA in 2020 developed a set of materials and messaging, including videos and other multimedia, print ads, posters, and social media, tailored to Spanish-speaking communities and available in both English and Spanish. A similar approach was used in 2019 to develop materials for Black/African American audiences. Additional

communication activities to improve outreach to other underrepresented populations is underway, including the development of clinical study recruitment materials and messaging for Chinese Americans, Filipino Americans, and Indian Americans in English, Mandarin, Tagalog, and Hindi.

- **Providing a web-based tool for recruitment:** NIA is developing a web-based communication tool, called Outreach Pro, to enable health care professionals to more easily produce and brand tailored clinical trial recruitment materials and strategies. Designed to help reach multiple cultures and those who do not speak English, the tool is to launch in 2021. It will enable the research community to access, adapt, and personalize materials that NIA has developed — and will continue to create — for underrepresented communities.
- **Tracking enrollment progress:** A key factor for improving enrollment is to help researchers monitor actual recruitment against planned milestones. To achieve the ability to track, report, and manage enrollment data, NIA recently awarded a contract to develop a unified Clinical Research Operations & Management System (CROMS). Through CROMS, NIA will track, manage, and report enrollment data and activities made possible via the NIA-funded clinical research portfolio. CROMS will provide critical and real-time information to ensure that NIA-supported clinical studies are making appropriate progress toward reaching their inclusion recruitment goals related to multiple underrepresented groups, including minorities. Using data from CROMS, NIA can then implement and enforce policies to address studies that perform poorly with respect to minority enrollment, as well as track studies that successfully enroll participants to identify and disseminate best practices to other grantees.

Database of hundreds of resources for researchers to use for recruitment

NIH invests in strategic clinical trial recruitment and retention initiatives, including a web-based repository of resources called [Alzheimer's and Dementia Outreach, Recruitment, and Engagement \(ADORE\)](#). Established in 2019, the repository is an online, searchable database of resources for engagement, recruitment, and retention of study participants. For example, ADORE has resources to engage and encourage Asian/Pacific Islander, Black/African, and Hispanic/Latino Americans to participate in clinical studies.

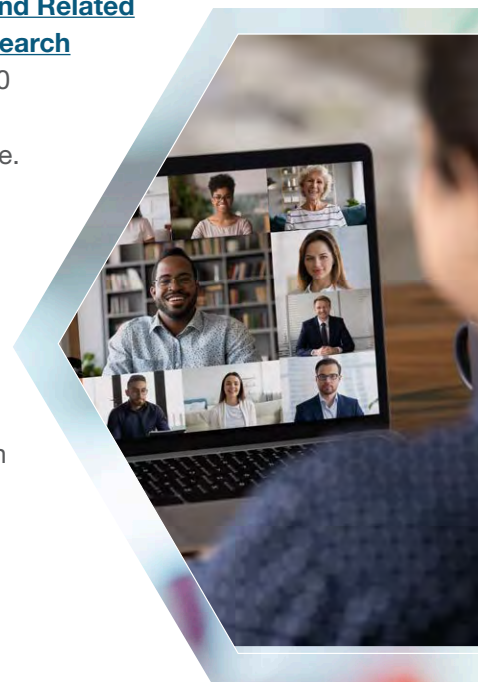
Researchers can browse the repository, which now has hundreds of resources, by main categories or A-Z topics, search by keyword, or explore by tags. The repository has evolved as researchers have nominated their resources for NIA's consideration.

Enhancing and developing the science of recruitment

A crucial piece of NIA's implementation of the national recruitment strategy involves developing the science of recruitment and retention. NIA continues to direct and fund several projects with researchers to better understand the myriad challenges researchers and potential participants face in clinical trials recruitment, including:

- **Examining diversity in research:** Through the [Examining Diversity, Recruitment, and Retention in Aging Research funding opportunity](#), NIA awarded support for several projects focused on improving research tools, methods, and recruitment practices. Some examples:

- A culturally tailored registry to educate and engage Asian Americans/Pacific Islanders about research participation
- A recruitment approach that relies on different generations of people to engage older adults
- A collaborative, transdisciplinary network to engage, educate, and motivate Hispanic/Latino community members to participate in research
- **FOREVER:** NIA recently funded [Foundations of Representative Engagement, Valid, and Effective Recruitment \(FOREVER\) in Alzheimer's Research](#). Through this project, researchers are developing and implementing novel methods for recruitment, engagement, and retention of minorities into Alzheimer's and related dementia studies through community engagement and the [NIA-funded Alzheimer's Disease Research Centers](#). The research team is also developing recruitment, engagement, and retention metrics and interventions, and establishing communications frameworks to improve literacy for both general public and research communities.
- **Symposium about developing the science of recruitment:** To further underscore the importance of building a robust scientific foundation, NIA and the Alzheimer's Association collaborated to host the [Developing an Applied Science of Recruitment and Retention for Alzheimer's Disease and Related Dementia Clinical Research Symposium](#) at the 2020 Alzheimer's Association International Conference. This virtual symposium provided a broad perspective that builds on existing scientific knowledge to support the goal of ultimately accelerating and expanding research efforts on recruitment strategies for clinical trials.



Drug Candidates



Thanks to increased investments in Alzheimer's and related dementias research, scientists have identified new underlying disease pathways that can lead to these diseases. As scientific knowledge of Alzheimer's and related dementias has grown, drug development projects have evolved to reflect this complexity. Like cancer and its many subtypes, the many types of dementias will likely require targeted treatments aimed at an individual's unique disease characteristics. While the FDA's recent accelerated approval of aducanumab is a milestone in Alzheimer's research, an array of treatments will be necessary to successfully halt or reverse the effects of these diseases for everyone. A [precision medicine approach](#) would deliver specific treatments based on a person's type of dementia as diagnosed through lab and imaging tests.

As knowledge advances, scientists are developing more precise treatments and preventions aimed at specific types of Alzheimer's and related dementias. Today, many kinds of compounds

are chosen for testing and development as drug candidates. In addition to drugs aimed at a specific disease pathway, NIH-funded researchers are also exploring many variations of targets simultaneously, considering combinations of treatments, and working to repurpose existing drugs to treat these diseases.

New drug development projects in the lab

NIA recently funded several new projects (see table) through its [Alzheimer's Drug Development Program](#). Each project is focused on developing a new drug that targets a different biological process, such as brain inflammation, known to go awry during the development of Alzheimer's and related dementias. If successful, these NIH-supported preclinical drug development studies will result in new candidate drugs that could then be tested in people.

Drug candidates under study work against many different brain targets

Drug candidates now in preclinical studies target multiple aspects of the disease process. For example, some are being tested to inhibit brain inflammation, promote the health of neurons, or clear amyloid deposits.



- Amyloid-related mechanisms
- Tau-related mechanisms
- Growth factors/growth factor receptors
- Proteostasis
- Synaptic plasticity/neuroprotection
- Immune cell activity or brain inflammation
- Neurogenesis
- Vasculature
- Metabolism
- Sleep
- Multi-target
- Other

New in 2020: Examples of NIA-funded preclinical studies of drug candidates

Drug candidate	How it may work
Posiphen	INHIBITS The synthesis of the hallmark signs of Alzheimer's or related dementias: amyloid, tau, and alpha-synuclein
RASRx1902 and RASRx1911	REDUCES Brain inflammation and cellular damage
Glycosylated-Angiotensin 1-7	REDUCES Brain inflammation
MW071 and MW109	PROMOTES The health of neurons
PU.1 Inhibitory Modulators	ENHANCES Immune cell activity
EHI-16	REDUCES Brain inflammation
M3	PROMOTES The health of neurons

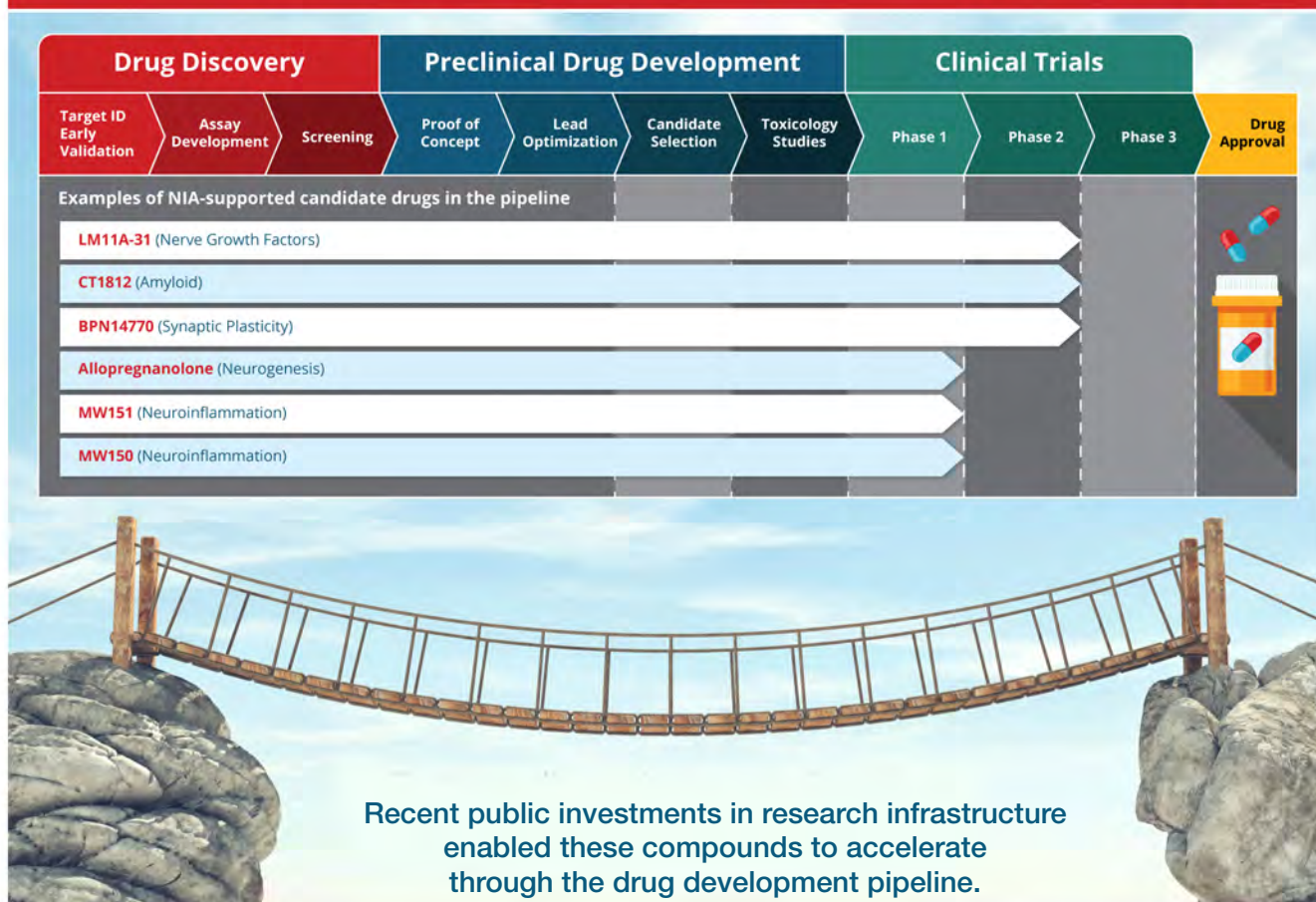
Drugs in clinical trials

As a result of the substantial research progress achieved over the last several years in understanding how Alzheimer's and related dementias develop and worsen, the drug development pipeline has never been more diverse. Drug candidates now in clinical studies target multiple aspects of the disease process. Thanks to increased investments in Alzheimer's and related dementias research, NIH-funded clinical studies extend beyond drug candidates that target amyloid plaques in the brain. The continuously updated list of [NIA-Funded Active Alzheimer's and Related Dementias Clinical Trials and Studies](#) catalogs the many different disease pathways.

NIA is supporting many [late-stage drug trials](#) and [early-stage drug trials](#) for Alzheimer's and related dementias. In addition, [several studies](#) are evaluating drug candidates for treating psychological or neurological symptoms of dementia, including apathy, agitation, and restless legs.

Drug candidates that are shown to be safe and effective in late-stage trials can then be presented to FDA. Before drugs are approved for use in people, FDA ensures that drugs work correctly and that their health benefits outweigh their known risks.

Public Funding Bridges the Gaps in Drug Discovery



PROGRAM SPOTLIGHT

New uses for FDA-approved drugs

One way NIH works to find effective ways to treat dementia is by considering drugs that FDA has already deemed safe for people with other conditions. The thinking is that some of these drugs could be repurposed to effectively prevent or treat Alzheimer's and related dementias as well.

As one example, Madhav Thambisetty, M.D., in [NIA's Clinical and Translational Neuroscience Section in the Laboratory of Behavioral Neuroscience](#), is leading the [Drug Repurposing for Effective Alzheimer's Medicines \(DREAM\)](#) study. DREAM is a collaboration with researchers at Harvard Medical School, Rutgers University,

and Johns Hopkins University School of Medicine to [repurpose FDA-approved drugs for dementia](#).

The research team recently reported that they discovered a network of about 20 biological pathways linked to abnormal brain metabolism in people with Alzheimer's and related dementias. These abnormalities may precede or influence the brain changes that lead to dementia. Next, they identified 35 FDA-approved drugs that might be active against the network of 20 pathways. Of these 35, the team selected 15 drugs as the best candidates for further analysis.

From this point, the team can analyze data collected during routine health care for the effects of a candidate drug on the development of dementia. Data sources include electronic health records from U.S. Medicare and the United Kingdom. The analysis will estimate the incidence of dementia for people treated with the candidate drug and compare it to those receiving another drug for the same disease.

(continued on page 40)



PROGRAM SPOTLIGHT

(continued from page 39)

Results from the DREAM study will help guide future research. If a drug appears to reduce the risk or severity of Alzheimer's or a related dementia, researchers could conduct lab tests to determine how the drug works against dementia, and the drugs could eventually be tested with people in clinical trials.

Research at other NIA-supported labs

NIA also funds drug repurposing research at its grantee institutions. Following are examples:

- A study published recently showed how electronic medical records from 1.7 million U.S. veterans can be used to [identify FDA-approved drugs that may have potential for Alzheimer's](#). First, the research team demonstrated that the risk of being diagnosed with Alzheimer's was greater for veterans who have a history of traumatic brain injury than those without traumatic brain injury. Next, they analyzed whether any of four classes of drugs had shown evidence of lowering the risk of Alzheimer's. They found that veterans who took a combination of medicines that lower blood pressure and cholesterol were less likely to develop Alzheimer's after traumatic brain injury. Although the analysis was promising, more studies are needed before this drug combination can be tested in people.
- A research team devised a [system of ranking 80 compounds](#), including 33 FDA-approved drugs, according to their likelihood of being active against certain Alzheimer's-

related genetic mechanisms. The researchers relied on data collected by the NIH-funded [Accelerating Medicines Partnership - Alzheimer's Disease \(AMP AD\)](#). The team concluded that their system has the potential to predict which drugs can inhibit disease.

- To build on findings like those above, NIH released a funding initiative in 2020 called [Translational Bioinformatics Approaches to Advance Drug Repositioning and Combination Therapy Development for Alzheimer's Disease](#). The goal is to leverage the power of big data and open science in advancing drug repurposing and combination therapy development.



References:

Desai RJ, et al. **Targeting abnormal metabolism in Alzheimer's disease: The Drug Repurposing for Effective Alzheimer's Medicines (DREAM) study.** *Alzheimer's & Dementia* (New York). 2020;6(1):e12095. doi: 10.1002/trc2.12095.

Li M, et al. **Beneficial association of angiotensin converting enzyme inhibitors and statins on the occurrence of possible Alzheimer's disease after traumatic brain injury.** *Alzheimer's Research & Therapy*. 2020;12(1):33. doi: 10.1186/s13195-020-00589-3.

Rodriguez S, et al. **Machine learning identifies novel candidates for drug repurposing in Alzheimer's disease.** *Nature Communications*. 2021;12(1):1033. doi: 10.1038/s41467-021-21330-0.



Lifestyle, Behavior, and Cognitive Training Intervention Research



Many of the prevention and treatment studies in progress for Alzheimer's and related dementias do not involve drug candidates that interfere with disease pathways. Instead, these NIH-funded studies are exploring [lifestyle and behavioral interventions](#) — such as cognitive training, a healthy diet, and exercise, as well as combinations of these strategies — as ways to help prevent dementia or slow the progression from mild cognitive impairment to dementia.

Carefully controlled clinical trials randomly assign research participants to an intervention, such as increased physical activity or a healthy diet, and compare their rate of dementia to a group that did not have that intervention. Clinical trials designed to investigate certain lifestyle choices and behavioral patterns are based on previous [population studies](#) that identified groups of people who seemed to have a lower risk of dementia because of certain healthy behaviors. After a population study has identified a strong association between a lifestyle factor and dementia, a next step in research is to test an intervention in a controlled clinical trial. Clinical trials are a way of testing whether certain lifestyle habits and behaviors really explain why a group of people has a lower rate of dementia.

NIH is funding multiple studies of healthy behaviors to reduce the risk of dementia. Examples of recent progress include:

- **Analysis of previous cognitive training clinical trials:** A recent NIA-supported meta-analysis of 215 clinical trials showed that the various cognitive training tools under study can help older adults who are healthy or have mild cognitive impairment to [improve cognitive health](#) and perhaps their everyday functioning. The research team also found that the overall benefits of cognitive training, while modest in size, were similar for both healthy older adults and those with mild cognitive impairment. This may mean that some forms of cognitive training can help reduce or delay the development of cognitive impairment and dementia.

- **Clinical trial to test computerized games to improve brain speed:** NIA is funding a [clinical trial to test the usefulness of computerized brain games](#) designed to accelerate how fast the brain works. Specifically, this study is testing whether this kind of brain training can reduce mild cognitive impairment or dementia. It is also exploring whether an individual's risk factors for Alzheimer's — such as [having amyloid plaques in the brain](#) or [having the APOE ε4 gene](#) — can make brain games less likely to work.

- **Clinical trial of taking aspirin for brain health:** A recent analysis of the Aspirin in Reducing Events in the Elderly (ASPREE) trial found that [daily low-dose aspirin did not reduce the risk of dementia](#), mild cognitive impairment, or cognitive decline among ASPREE trial participants. ASPREE is a large clinical trial supported in part by NIH and designed to determine the risks and benefits of daily low-dose aspirin in more than 19,000 healthy older adults without signs of heart disease. Among people with heart disease, aspirin may reduce the risk of stroke, but it was unknown whether aspirin would benefit healthy adults. The research team noted that a limitation of the five-year study is that not many cases of dementia were detected during that time, making it difficult to compare the aspirin and placebo groups. The ASPREE team continues to monitor trial participants to assess longer-term outcomes, including the effects of aspirin on cognitive function and dementia.



- **Funding opportunities for studies of the motivation for choosing healthy behaviors:** Determining how to get people to engage in and sustain healthy behaviors, such as [controlling high blood pressure and getting enough exercise](#), that may prevent or delay cognitive decline, mild cognitive impairment, and Alzheimer's and related dementias continues to be an NIH research priority. Recognizing that these behaviors may need to start decades before disease onset, understanding the factors that support long-term adherence to lifestyle change will be critical. In early 2021, NIA released new funding opportunities to support [research](#), including behavior change [clinical trials](#), on the psychology of motivation, value-based decision-making, and social support. The hope is that findings from this line of research will help investigators develop ways to help people choose and sustain healthy behaviors over many years.



Science Spotlight

Choosing healthy lifestyle behaviors to reduce risk

Before controlled clinical trials are designed to test the impact of healthy behaviors on dementia, researchers consider findings from population studies. A recent NIH-funded analysis of data from two population studies found that people who practice several **healthy lifestyle behaviors** are at substantially lower risk for Alzheimer's disease.

In this study of nearly 3,000 adults, those who reported adhering to four or five of the following healthy behaviors had the least risk of developing the disease:

- Getting at least 150 minutes per week of physical activity
- Not smoking
- Limiting alcohol use
- Choosing a high-quality diet, such as one that is plant-based
- Keeping the mind active, even later in life

This study provides more evidence on how practicing a combination of healthy behaviors may reduce the risk of Alzheimer's. This evidence adds to the basis for conducting controlled clinical trials to directly test the ability of interventions to slow or prevent development of Alzheimer's.

NIA funds many clinical trials on behavior and lifestyle factors and dementia, including combinations of healthy behaviors. Visit the NIA website for a list of current **[NIA-supported trials testing healthy behaviors](#)**.



References:

Basak C, et al. [Differential effects of cognitive training modules in healthy aging and mild cognitive impairment: A comprehensive meta-analysis of randomized controlled trials](#). *Psychology and Aging*. 2020;35(2):220-249. doi:10.1037/pag0000442

Ryan J, et al. [Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline](#). *Neurology*. 2020;95(3):e320-e331. doi: 10.1212/WNL.0000000000009277.

Knopman DS, Petersen RC. [The quest for dementia prevention does not include an aspirin a day](#). *Neurology*. 2020;95(3):105-106. doi: 10.1212/WNL.0000000000009278.

Dhana K, et al. [Healthy lifestyle and the risk of Alzheimer's dementia: Findings from 2 longitudinal studies](#). *Neurology*. 2020;95(4):1-10. doi: 10.1212/WNL.0000000000009816.



Care and Caregiver Support Studies



Alzheimer's and related dementias have an enormous impact on family caregivers, long-term care facilities, health care providers, health care systems and infrastructure, and the communities in which we all live. Although it is difficult to estimate the financial toll of dementia, NIH-supported researchers have estimated that total health care spending for people with dementia at the end of life is far more than for people with heart disease or cancer.

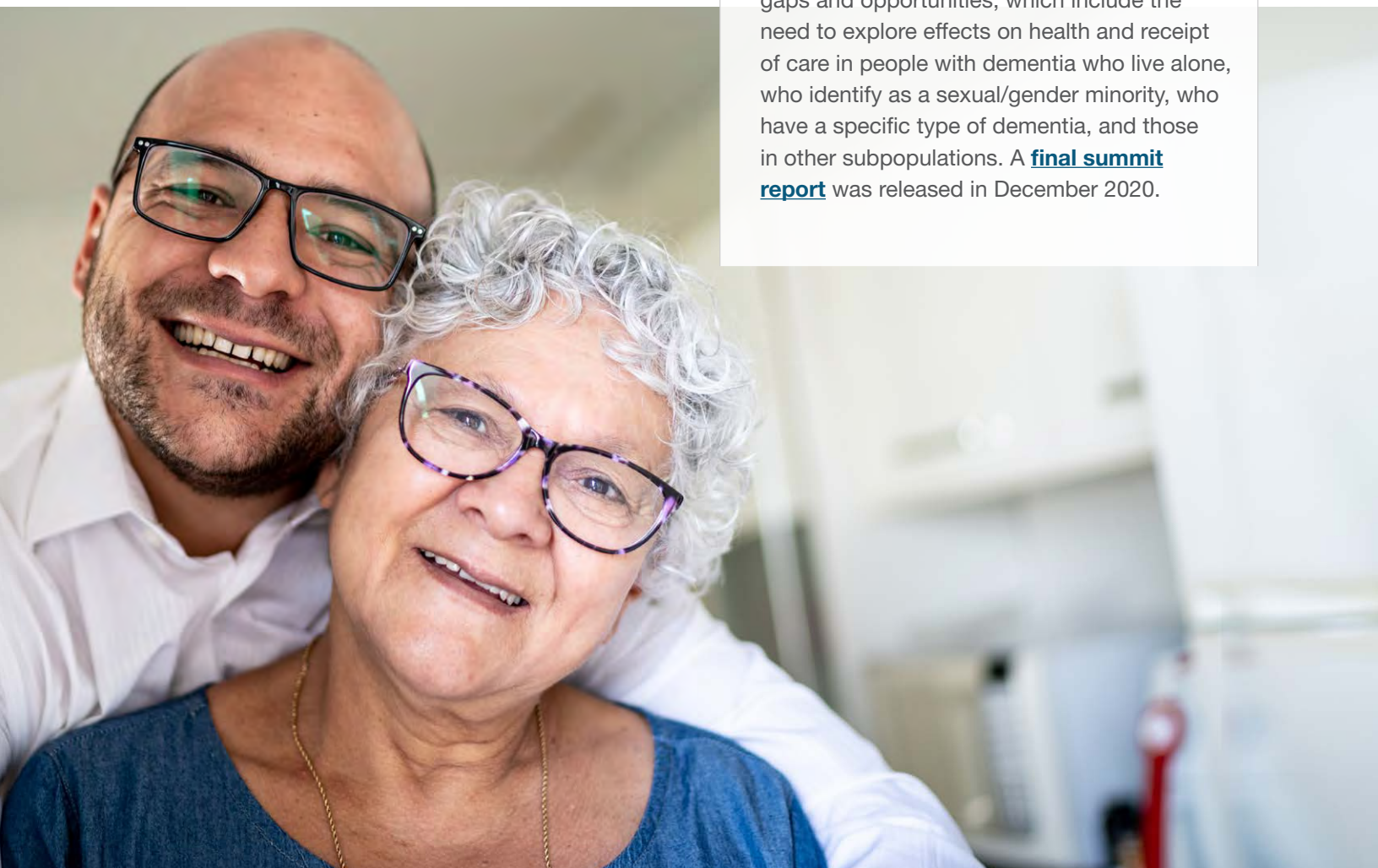
To support people living with dementia, caregivers, and health providers, NIH has made large investments in research to improve the quality of care and care coordination. Already, research efforts have contributed to improvements in the quality of care — as well as in the resulting health, well-being, and quality of life — for those living with dementia. In addition, NIH support has enabled the development of resources designed to help ease burdens on care providers.

PROGRAM SPOTLIGHT

2020 Dementia Care, Caregiving, and Services Research Summit

NIH and the broader HHS hosted a virtual meeting series for the [2020 National Research Summit on Care, Services, and Supports for Persons with Dementia and Their Caregivers](#), which was the second one on this topic. The first was held in 2017.

The summit brought together researchers, people living with dementia, care partners and providers, and advocates. Goals included evaluating evidence-based programs, strategies, approaches, and other research to improve the quality of care and of life for those living with dementia and their caregivers. The event also provided a platform for identifying gaps and opportunities, which include the need to explore effects on health and receipt of care in people with dementia who live alone, who identify as a sexual/gender minority, who have a specific type of dementia, and those in other subpopulations. A [final summit report](#) was released in December 2020.



As one example of NIH investments to facilitate care research, the National Academies of Sciences, Engineering, and Medicine (NASEM) released [**“Meeting the Challenge of Caring for Persons Living with Dementia and Their Care Partners and Caregivers: A Way Forward.”**](#) The report is the culmination of a collaboration among NIA, the Agency for Healthcare Research and Quality, and NASEM to develop a comprehensive understanding of the evidence base, for essential care and caregiving interventions for the millions of people living with dementia and their caregivers.

Dementia Collaboratory's Impact on COVID-19 Research

In 2019, NIH funded the [**IMbedded Pragmatic Alzheimer's Disease and AD-Related Dementias Clinical Trials \(IMPACT\) Collaboratory**](#), which is designed to spur innovation to meet the challenges of the complex care management for people living with Alzheimer's and related dementias. Collaboratory researchers are partnering with scientists at other universities with health care and long-term care systems to test care interventions in real-world settings. To date, the collaboratory has supported multiple pilot projects and career development awards for researchers from varied disciplines. Examples of [**IMPACT-supported projects**](#) include:

- Working to improve Alzheimer's and related dementias care management across interdisciplinary teams
- Designing mobile apps to help adult day service centers prevent minor health issues from escalating to medical emergencies
- Empowering bedside nurses in emergency departments to improve detection of dementia in patients

With its previously established network of partnering health care systems, in 2020, the IMPACT Collaboratory was crucial in helping researchers quickly pivot and effectively respond to the coronavirus pandemic with new studies. Given its goal of finding novel ways to deliver high-quality, evidence-based care to people living with dementias

and their caregivers, the collaboratory's infrastructure was primed and ready to rapidly support the development of and conduct studies to assess the pandemic's acute impact on older adults, particularly people living with dementia. One outcome was an analysis showing that [**cognitive impairment is linked to elevated death rates in nursing home residents with COVID-19.**](#)

Creating resources that help caregivers

NIA develops articles and other materials for caregivers to help them be effective care providers while also taking care of themselves. Many of these materials provide [**tips specifically for those who provide care to people with Alzheimer's**](#). Health tips from NIA are based on evidence from research results.

Caregivers can learn how to provide everyday care for someone living with dementia, respond to changes in communication and behavior, and get help when needed. NIA resources include:

- [**Coping with Agitation and Aggression in Alzheimer's Disease**](#)
- [**6 Tips for Managing Sleep Problems in Alzheimer's**](#)
- [**Wandering and Alzheimer's Disease**](#)
- [**When a Person with Alzheimer's Rummages and Hides Things**](#)

Caregiving can be rewarding but exhausting. NIA also offers articles about how caregivers can take care of themselves — physically, mentally, and emotionally. Resources include:

- [**Getting Help with Alzheimer's Caregiving**](#)
- [**Alzheimer's Caregiving: Caring for Yourself**](#)
- [**Taking Care of Yourself: Tips for Caregivers**](#)
- [**Frequently Asked Questions About Caregiving**](#)

In addition, [**caregivers can sign up**](#) to receive NIA's updates and resources delivered by email.

In response to COVID-19 and its devastating effects on people living with dementia and their families and caregivers, NIA awarded the IMPACT Collaboratory with [several supplements](#), including:

- [Improved Testing for COVID-19 in Skilled Nursing Facilities](#)
- [COVID-19 Serology Strategies in Skilled Nursing Facilities](#)
- [Effect of a COVID-Specific Advance Care Planning Intervention on Documentation of Advance Directives and Goals of Care](#)
- [Evaluation of a State-wide Effort to Improve COVID-19 Infection Control in Massachusetts Nursing Homes](#)

In addition, through two NIA supplemental awards — [Designing a Real Time COVID-19 vaccination Adverse Event Monitoring System for Nursing Home Residents](#) and [Monitoring Medicare Beneficiaries' Response to COVID Vaccines \(CVS Project\)](#) — researchers are supporting the development of data sharing and reporting systems, and data infrastructure, to monitor the effects of the COVID-19 vaccines administered to frail older adults, including people living with dementia. These initiatives will provide near real-time insight into the use, effects, and outcomes related to use of COVID-19 vaccines among this population.

Roybal Center for Translational Research to Improve Health Care for the Aging

The goal of the [Edward R. Roybal Centers for Translational Research in the Behavioral and Social Sciences of Aging](#) is the translation and integration of basic behavioral and social research findings into interventions to improve the lives of older adults and the capacity of institutions to adapt to societal aging. The Roybal Centers are structured within the conceptual framework of the

multidirectional, translational [NIH Stage Model](#) to produce potent and implementable principle-driven behavioral interventions.

This model provides structure in six stages for how researchers develop behavioral interventions, from basic research through testing and dissemination. The purpose of the stages is to create interventions that are highly effective at improving health and well-being.

Of the 15 currently funded centers, four are a part of the [Roybal Centers for Translational Research on Dementia Care Provider Support](#). These are focused on:

- Transforming residential palliative care for persons with dementia
- Using technologies to improve care support intervention development
- Decreasing care provider loneliness and isolation
- Strengthening informal caregiving mastery

Dementia-related COVID-19 care and caregiving projects

In further response to the COVID-19 pandemic, NIA supported [more than 30 administrative supplements](#) to address the challenges experienced by persons living with dementia and their care partners. Projects have included research on:

- Transitioning dementia care interventions to virtual formats
- Developing online family caregiving courses
- Conducting epidemiology studies on the COVID-19 outbreak among persons living with dementia
- Studying the effects of stay-at-home and social distancing requirements on community-dwelling adults, their care partners, and those with Alzheimer's and related dementias who reside in nursing homes and assisted living communities

Roybal Centers for Translational Research in Behavioral and Social Sciences of Aging: Dementia Research

Center	2020 Progress
<u>Penn Roybal Center On Palliative Care In Dementia</u> at the University of Pennsylvania	- Initiated two new pilots in 2020, including one on promoting advance care planning among persons with advanced dementia and another on improving uptake of tele-palliative care for persons with dementia in long-term care facilities during COVID-19 - Held a virtual symposium on palliative care in dementia, which highlighted their pilot projects, the use of behavioral economics and data science to improve dementia care, and opportunities for collaboration
<u>Rochester Roybal Center for Social Ties and Aging Research</u> at the University of Rochester	- Introduced two new pilot projects on promoting social connections among Hispanic/Latino caregivers and mindfulness training for dementia caregivers - Held a research symposium to share progress on pilot studies
<u>The Emory Roybal Center for Caregiving Mastery</u> at Emory University	- Initiated <u>four new pilot projects</u>, including teaching care skills to dementia caregivers - Began developing an online course for mastering the challenges of dementia family caregiving in a time of COVID-19 (a COVID-19 research supplement)
<u>Oregon Roybal Center for Care Support Translational Research Advantaged by Integrating Technology</u> at Oregon Health & Science University	- Began work on a new pilot to develop an intervention to support couples in planning for changing dementia care needs - Continued further testing on a technology called Tele-STELLA to advance education and support for families caring for loved ones with dementia
<u>Midwest Roybal Center for Health Promotion and Translation</u> at the University of Illinois at Chicago	- Initiated a pilot program to preserve functioning and prevent cognitive decline among community-dwelling older adults - Began pilot study to develop a walking program using physical activity monitors and social network for older adults with intellectual disabilities

INVESTING IN THE FUTURE:

Research Trainee Parveer Kaur

People with cognitive challenges and dementia are at risk of losing their ability to live independently as dementia worsens. Washington State University investigators are trying to help these individuals by developing a daily organizational tool and memory aid called the Digital Memory Notebook. A tablet application, the notebook is being tested with older adults who have thinking and memory challenges.

Through [NIA's Advancing Diversity in Aging Research \(ADAR\) through Undergraduate Education](#) program, the investigators are recruiting students from underrepresented groups to conduct research to help improve the app. Their [Gerontechnology-Focused Summer Undergraduate Research Experience](#) program requires undergraduate research trainees to have a background in computer science and programming languages.

One of the trainees selected was Parveer Kaur. She shadowed clinicians as they trained older adults aged 65 to 81 to use the Digital Memory Notebook. Kaur used statistical programs to compare the research participants to determine why certain adults were more likely to adopt the app and gain high mastery. Her analysis enabled the research team to target older adults who are most likely to benefit from the Digital Memory Notebook, as well as continue to improve the app.

"I was so grateful to participate in the research experience at Washington State University because I realized that I enjoy working with the aging population, especially when I got to shadow the clinicians," said Kaur.

In May 2020, Kaur earned a bachelor of arts degree in neuroscience and behavior with departmental honors from Vassar College in Poughkeepsie, New York, and in May 2021 earned a bachelor of engineering degree from Dartmouth College in Hanover, New Hampshire. Her long-term career goals include becoming an academic physician so that she can teach and continue doing research.



"I was so grateful to participate in the research experience at Washington State University because I realized that I enjoy working with the aging population, especially when I got to shadow the clinicians."

Reference:

Panagiotou OA, et al. [Risk factors associated with all-cause 30-day mortality in nursing home residents with COVID-19](#). *JAMA Internal Medicine*. 2021;181(4):439-448. doi: 10.1001/jamainternmed.2020.7968.

Population Studies and Health Disparities





Large, long-term population studies have enabled scientists to examine the influence of a spectrum of risk and protective factors for developing Alzheimer's and related dementias. Because of scientific progress made possible by NIH investments in this research, scientists have discovered that these conditions usually develop from the combined effects of certain behaviors and lifestyle choices, as well as genetic, social, economic, educational, and environmental factors.

NIH-supported population studies are part of the overall effort to find ways to prevent and treat Alzheimer's and related dementias. These large studies explore the health of populations over a long period of time, which helps researchers determine why some people develop these diseases while others do not.

For this research, scientists aim to involve a large group of people who represent the diversity of the U.S. population. The ongoing analysis of risk and protective factors will help [precision medicine](#) researchers develop interventions that can address underlying disease processes, as well as symptoms, and that can be tailored to a person's unique disease risk profile.

Identifying new genetic factors for dementia

Large-scale analyses of data collected from population studies have been revealing the many possible genetic risk factors for Alzheimer's and related dementias. These large datasets have enabled the discovery and analysis of many genetic

variants. Ten years ago, we knew of only 10 genes associated with Alzheimer's. Today scientists are studying more than 50 genes — that's a 400% advancement in this area!

NIH's [Genetics of Alzheimer's Disease Portfolio](#) supports research to discover long-term treatments for the disease by the identification of risk factor and protective genes and the underlying molecular pathways. Within this portfolio, the [Alzheimer's Disease Sequencing Project](#) supports studies to discover genes involved in Alzheimer's. This project involves more than 150 international investigators at 33 institutions. Data come from more than 60 cohorts of research participants. The aim of the sequencing project is to identify — in diverse populations — genes that increase risk for Alzheimer's and those that confer protection, as well as to provide insight into why some people with known risk factor genes do not develop the disease. Through this effort, researchers also aim to identify potential avenues to prevent and treat Alzheimer's.

Genetic discoveries provide more possible avenues for scientific exploration into preventing and treating Alzheimer's and related dementias. Over the past year, multiple research teams reported results from studies of genetic factors that may influence the risk of developing these diseases:

- **Potential genes for Alzheimer's discovered:**
A research team reported finding [11 genes \(ACE, CARHSP1, CTSH, DOC2A, ICA1L, LACTB, PLEKHA1, RTFDC1, SNX32, STX4, and STX6\)](#) that might contribute to Alzheimer's. The team analyzed more than 8,000 proteins generated

from about 400 brain samples from the [NIA-supported Religious Orders Study and Memory and Aging Project](#) (ROSMAP), and integrated results with a genetic dataset from about 72,000 people with Alzheimer's. Scientists can build on these findings by exploring how these 11 genes might play a role in this disease.

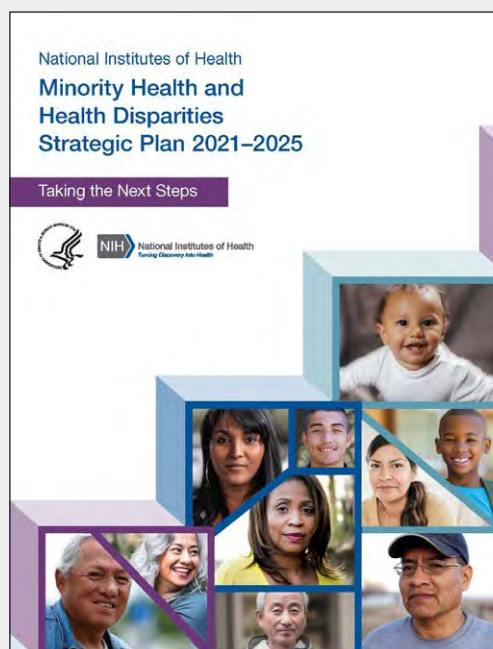
- **APOE ε2 gene variant appears to lower risk:** A recent study of more than 4,000 autopsy-confirmed Alzheimer's cases from the [NIA-funded Alzheimer's Disease Genetics Consortium](#) suggests that having two copies of the [APOE ε2 gene variant](#) may lower risk even more than previously thought. An improved understanding of how gene variants can be protective can help scientists develop better strategies for treatment and prevention.
- **KLOTHO gene variant and APOE ε4:** Having one copy of a [KLOTHO gene](#) variant [reduced the risk of Alzheimer's](#) among those who also had the APOE ε4 gene variant, despite the fact that APOE ε4 usually increases risk. In addition, people with one copy of the KLOTHO variant had lower levels of amyloid in the brain and spinal fluid. Data for this large-scale analysis included more than 20,000 people from these NIA-supported studies: the [National Alzheimer's Coordinating Center, Religious Orders Study and Memory and Aging Project \(ROSMAP\)](#), and the [Alzheimer's Disease Neuroimaging Initiative](#).
- **Genetic risk for Alzheimer's among Black/African Americans:** Genetic risk can differ substantially between racial and ethnic groups, and identifying the differences might partially explain health disparities. A recent study provided new insights about the [biological pathways and genetic factors that contribute to the development of Alzheimer's in Black/African Americans](#). The researchers also found a link between kidney system development and Alzheimer's risk in Black/African Americans, suggesting another novel disease mechanism to explore to better understand unique differences in disease risk among ethnic groups — which is essential to developing effective treatments.

(continued on page 58)

Charting the way forward for the science of minority health and health disparities

March 2021 marked the release of the [NIH-Wide Minority Health and Health Disparities Strategic Plan 2021-2025: Taking the Next Steps](#), underscoring NIH's commitment to these vital topics. The plan's goals for advancing minority health and health disparities research and promoting health equity include:

- Scientific research, such as advancing the understanding of the root causes of health disparities
- Research-sustaining activities, such as strengthening the national research capacity to address minority health and health disparities, especially in minority-serving institutions
- Outreach, collaboration, and dissemination, such as cultivating and expanding the community of minority health and health disparities researchers and advocates



Science Spotlight

High blood pressure and health disparities

When a stroke, high blood pressure, or other conditions damage the blood vessels in the brain, the flow of blood may be impaired. When blood flow is partially or completely blocked, the brain may not get enough oxygen. That cascade of events can lead to brain injury and ultimately, cognitive impairment, including dementia, in this case a form of [vascular dementia](#).

Over time, high blood pressure can injure the blood vessels in the brain and make them narrower. In 2020, an NIH-supported study found that [high blood pressure is linked to faster rates of cognitive decline among adults](#). This study of about 20,000 people suggested that controlling high blood pressure, especially in midlife, may be an effective approach to preventing cognitive decline and dementia. In addition, the analysis confirmed previous findings from other studies that Black/African Americans experienced cognitive decline earlier than white Americans, and it also showed that uncontrolled high blood pressure may account for the cognitive decline.

In a separate NIH-supported study published recently, researchers reported that [control of high blood pressure is worsening in the U.S.](#) This study of 18,000 participants found that awareness about whether they had high blood pressure had declined compared with a similar analysis in 2013. The proportion of those with controlled high blood pressure had also fallen during that time.

To help raise awareness about the link between high blood pressure and the risk of dementia and

stroke, NINDS developed the [Mind Your Risks® public education campaign](#). Mind Your

Risks encourages talking to health care providers about using medicines that lower blood pressure as well as choosing behavior and lifestyle habits to reduce the risk of dementia.

In 2021, NINDS is updating the Mind Your Risks campaign to place an even stronger messaging focus on reducing health disparities in blood pressure control. A goal is to reach more Black/African Americans, particularly men, who are most likely to have high blood pressure that is not managed.



**NOBODY'S GOT YOU,
LIKE YOU GOT YOU.**

MindYourRisks®  National Institute of
Neurological Disorders
and Stroke

MINDYOURRISKS.NIH.GOV

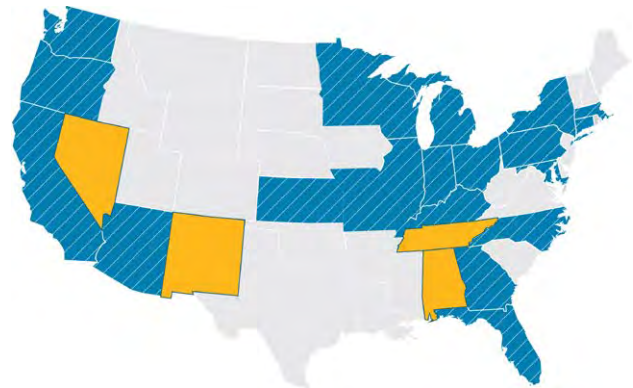
The NINDS Mind Your Risks campaign raises awareness that stroke and dementia are more likely to affect people with high blood pressure.

PROGRAM SPOTLIGHT

NIH expands capacity for health disparities research

The [NIA-funded Alzheimer's Disease Research Center \(ADRC\) network](#) has long been one of the cornerstones of NIH's Alzheimer's and related dementias research infrastructure. Building on the success of the ADRCs, NIA in 2020 added [four new exploratory centers](#) to the network. The new centers are enhancing research initiatives with underrepresented populations, such as Black/African Americans, Native Americans, and those in rural communities. The four centers also expand the network's reach into new geographic areas with locations at:

- Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada
- University of Alabama at Birmingham
- University of New Mexico, Albuquerque
- Vanderbilt University in Nashville, Tennessee

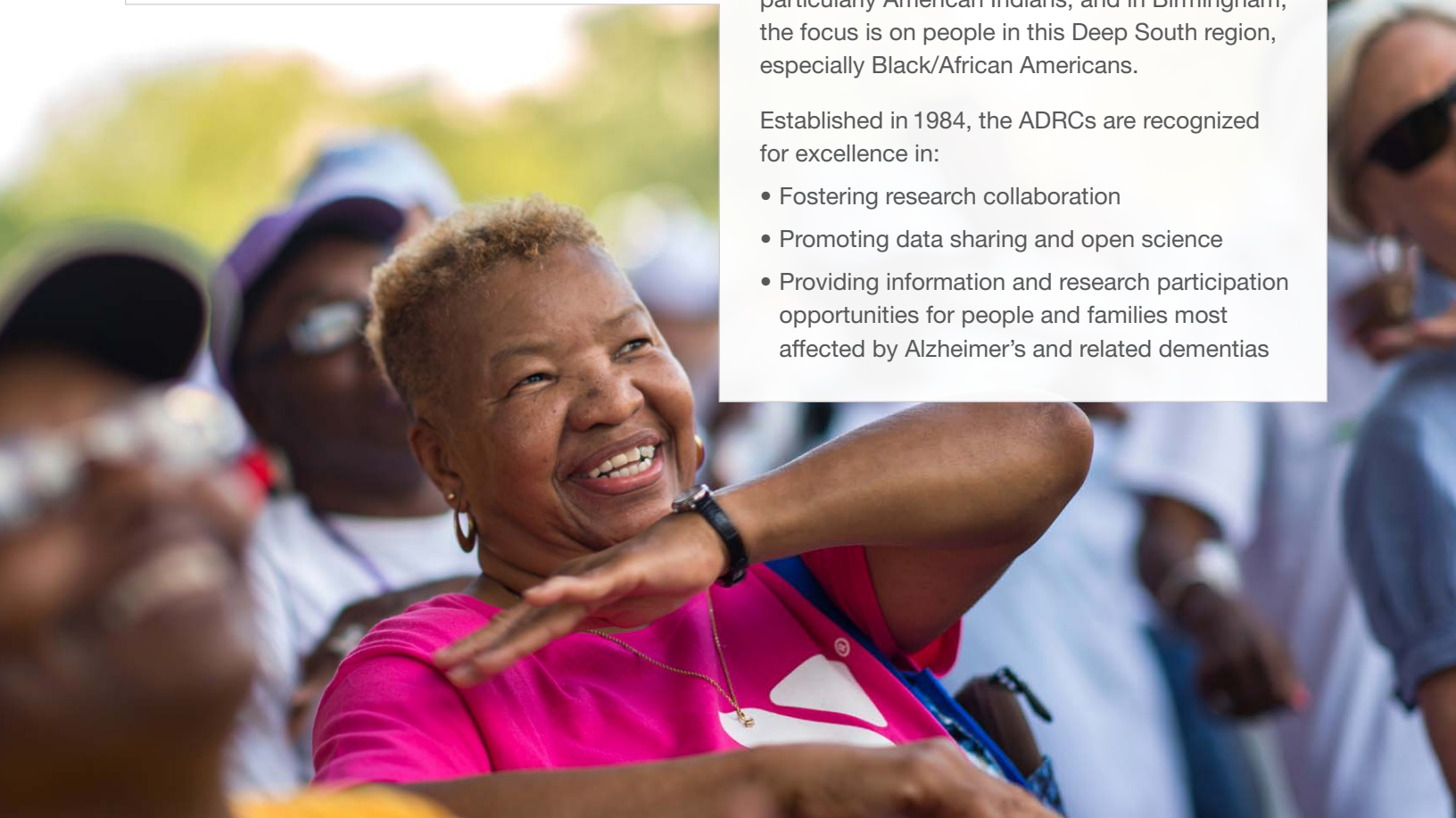


- State With NIA-Designated Center(s)
- State With Exploratory Center

Each exploratory center is designed to address regional health disparities. In Las Vegas, researchers are collecting high-quality standardized clinical data from people in rural settings, and in Nashville, they focus on vascular risk factors among Black/African Americans. The Albuquerque center prioritizes rural communities, particularly American Indians, and in Birmingham, the focus is on people in this Deep South region, especially Black/African Americans.

Established in 1984, the ADRCs are recognized for excellence in:

- Fostering research collaboration
- Promoting data sharing and open science
- Providing information and research participation opportunities for people and families most affected by Alzheimer's and related dementias



(continued from page 55)

- **Genetic variants and cognitive resilience:** Three genetic variants linked to [cognitive resilience](#) were identified near the *ATP8B1* gene, which is involved in the process of breaking down fats to produce energy for the body. The scientists also found that the level of resilience — whether it was high or low — was associated with genetic patterns for traits related to years of education, cardiovascular disease risk, and some mental health disorders such as obsessive-compulsive disorder. For example, people with genetic traits linked to more years of education showed higher cognitive resilience.

Exploring social and economic factors for dementia

In 2020, NIH-supported population studies found new evidence about social and economic factors linked to a decline in the ability to clearly think, learn, and remember, and linked to dementia:

- **Cognitive decline and lower wealth:** A study of more than 5,000 adults in the United Kingdom found that while everyone had a decline in cognitive function over time, the largest drops occurred in people with the [least wealth](#). These results add to the growing evidence showing that social and economic status can affect physical and mental health over time.
- **Memory loss and less education:** Findings from a large sample of older adults in New York suggested that [having fewer years of education](#) is associated with worse memory later in life. This study suggests that having more years of education could play an important role in protecting the brain from age-related cognitive decline and dementia.
- **Faster memory decline among women who did not have jobs:** An analysis of 6,000 women taking part in the [NIA-supported Health and Retirement Study](#) showed that [women who were not in the workforce during early adulthood and midlife](#) had faster rates of memory decline than those who were employed. This study adds to evidence that participation in the workforce may be a protective factor for cognitive health later in life.

Also during the past year, NIA invited researchers to design studies and [apply for research grants to examine sex and gender differences](#) in the risk, development, progression, diagnosis, and clinical presentation of Alzheimer's and related dementias.

To address the economic and health impacts of these diseases with population studies, NIA has expanded long-standing investments in the [demography and economics of aging](#) to support three new centers:

- [Center to Accelerate Population Research in Alzheimer's](#)
- [Hopkins' Economics of Alzheimer's Disease and Services Center](#)
- [Center for Advancing Sociodemographic and Economic Study of Alzheimer's Disease and Related Dementias](#)

Researchers at these centers examine health care delivery, quality, and disparities, as well as the role of technology diffusion and care needs of Alzheimer's.

Linking physical and other characteristics with dementia

Many researchers use data from population studies to analyze whether certain characteristics are common among people with dementia. Results over the past year from NIA-funded research suggest that dementia risk might be associated with many different physical factors, including:

- **Slower walking speed:** An international research team led by NIA analyzed data from more than 8,000 older adults in multiple long-term studies of aging, including the [NIA's Baltimore Longitudinal Study of Aging](#). The team reported that people who have both a [decline in memory and walking speed](#) were at increased risk of dementia.
- **Impaired vision:** An NIA-supported study of about 1,000 women showed that [impaired vision](#) may increase the risk of mild cognitive impairment or dementia.

- **Gum disease:** NIA scientists analyzed data from more than 6,000 people who took part in the National Health and Nutrition Examination Survey, a large population study. The results suggest that [bacteria that cause gum disease](#) may also be associated with the development of Alzheimer's and related dementias, especially vascular dementias.
- **Obesity:** Confirming findings from other population studies, NIA-supported researchers in the United Kingdom found that participants who were [overweight or obese](#) were more likely to develop dementia.
- **Pain:** A research team funded in part by NIH analyzed data from the Whitehall II study of more than 10,000 British civil servants collected over 27 years. The team reported that people who were later diagnosed with dementia had [pain that was increasing rapidly](#) in the years before cognitive decline or other obvious symptoms of dementia.

It is important to keep in mind that when a population study detects a physical characteristic that is linked to dementia, the results can suggest an association but do not prove causation. Additional research, especially through clinical trials, can provide stronger evidence.

Examining health disparities for dementia

Before NIH can work to reduce or eliminate health disparities for Alzheimer's and related dementias, [scientists must learn more](#) about the many factors that make certain groups more vulnerable to developing these conditions. NIH-supported discoveries have already shown that the development of dementia can be associated with race, ethnicity, sex, level of education, geography, and social and economic factors. Not only do these research findings help NIH progress toward the goal of reducing health disparities, but research findings that explain how and why many diseases affect diverse communities in different ways are crucial for the discovery of tailored treatments and prevention methods for Alzheimer's and related dementias.

- **DISCOVERY:** NIH funds several large initiatives and research consortia with a special focus on populations that experience health disparities, including a new study called [Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on Recovery \(DISCOVERY\)](#). This six-year prospective clinical research study was designed to determine the specific kinds of stroke events that cause cognitive impairment and dementia and which events do not. The investigators are studying people who have had a stroke to determine which clinical factors and conditions, along with the characteristics of the stroke itself, contribute to cognitive impairment and dementia outcomes. Because the study was designed to address these important questions in racial and ethnic minority groups, the research team is developing clinical and recruitment tools that are culturally appropriate and effective across all populations.
- **Health and Retirement Study:** To further facilitate health disparities research, the [NIA-funded Health and Retirement Study](#), a nationally representative study of more than 20,000 U.S. residents age 50 and older, added 2,000 additional racial and ethnic minority respondents. By continuing to diversify this cohort, researchers using Health Retirement Study data will be better able to design studies that provide insights into potential racial/ethnic differences in the incidence, prevalence, and impact of Alzheimer's and related dementias. Health and Retirement Study researchers gather cognitive testing results using the Harmonized Cognitive Assessment Protocol. They also collect DNA and blood samples that are critical to ensuring that the biomarkers being developed will be applicable to the widest range of people possible.
- **National Health and Aging Trends Study:** NIH also increased the number of diverse participants in other studies to enhance health disparities research on other aspects of Alzheimer's and related dementias. The nationally representative [National Health and Aging Trends Study](#) and the associated [National Study of Caregiving](#) provide data on the health and function of people in the U.S. age 65 and older and their caregivers. Supplemental funding is enabling the

researchers to include an additional 2,000 Hispanic/Latino participants, primarily of Mexican and Puerto Rican origin. The researchers are collecting new cognition and health data on study participants as well as conducting interviews with caregivers to support research on disparities in caregiving.

- **Longitudinal Aging Study in India:** To foster research on cross-national disparities, NIH also supports studies in many other countries that harmonize with the [NIA-funded Health and Retirement Study](#) in the U.S. One notable example is the [Longitudinal Aging Study in India \(LASI\)](#), which includes the Diagnostic Assessment of Dementia (LASI-DAD). LASI's nationally representative core study is supplemented by a sample of 4,100 community-residing older adults from 19 states in India, representing about 92% of the ethnically diverse population that receives LASI-DAD. Innovations in LASI-DAD include measurement of personal exposure to air pollution. In addition, NIA has funded the genetic study of about 2,700 participants in LASI-DAD to search for gene variants associated with Alzheimer's and related dementias.



References:

- Levine DA, et al. [Association between blood pressure and later-life cognition among black and white individuals](#). *JAMA Neurology*. 2020;77(7):810-819. doi: 10.1001/jamaneurol.2020.0568.
- Muntner P, et al. [Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018](#). *JAMA*. 2020;324(12):1190-1200. doi: 10.1001/jama.2020.14545.
- Wingo AP, et al. [Integrating human brain proteomes with genome-wide association data implicates new proteins in Alzheimer's disease pathogenesis](#). *Nature Genetics*. 2021;53(2):143-146. doi: 10.1038/s41588-020-00773-z.
- Reiman EM, et al. [Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study](#). *Nature Communications*. 2020;11(1):667. doi: 10.1038/s41467-019-14279-8.
- Belloy ME, et al. [Association of Klotho-VS heterozygosity with risk of Alzheimer disease in individuals who carry APOE4](#). *JAMA Neurology*. 2020;77(7):849-862. doi: 10.1001/jamaneurol.2020.0414.
- Kunkle BW, et al. [Novel Alzheimer disease risk loci and pathways in African American individuals using the African Genome Resources Panel: A meta-analysis](#). *JAMA Neurology*. 2020;78(1):102-113. doi: 10.1001/jamaneurol.2020.3536.
- Dumitrescu L, et al. [Genetic variants and functional pathways associated with resilience to Alzheimer's disease](#). *Brain*. 2020;143(8):2561-2575. doi: 10.1093/brain/awaa209.
- Steptoe A, et al. [Lower socioeconomic status and the acceleration of aging: An outcome-wide analysis](#). *Proceedings of the National Academy of Sciences U S A*. 2020 Jun 15:201915741. doi: 10.1073/pnas.1915741117.

Zahodne LB, et al. [The role of education in a vascular pathway to episodic memory: brain maintenance or cognitive reserve?](#) *Neurobiology of Aging*. 2019;84:109-118. doi: 10.1016/j.neurobiolaging.2019.08.009.

Mayeda ER, et al. [Association of work-family experience with mid- and late-life memory decline in US women](#). *Neurology*. 2020;95(23):e3072-e3080. doi: 10.1212/WNL.00000000000010989.

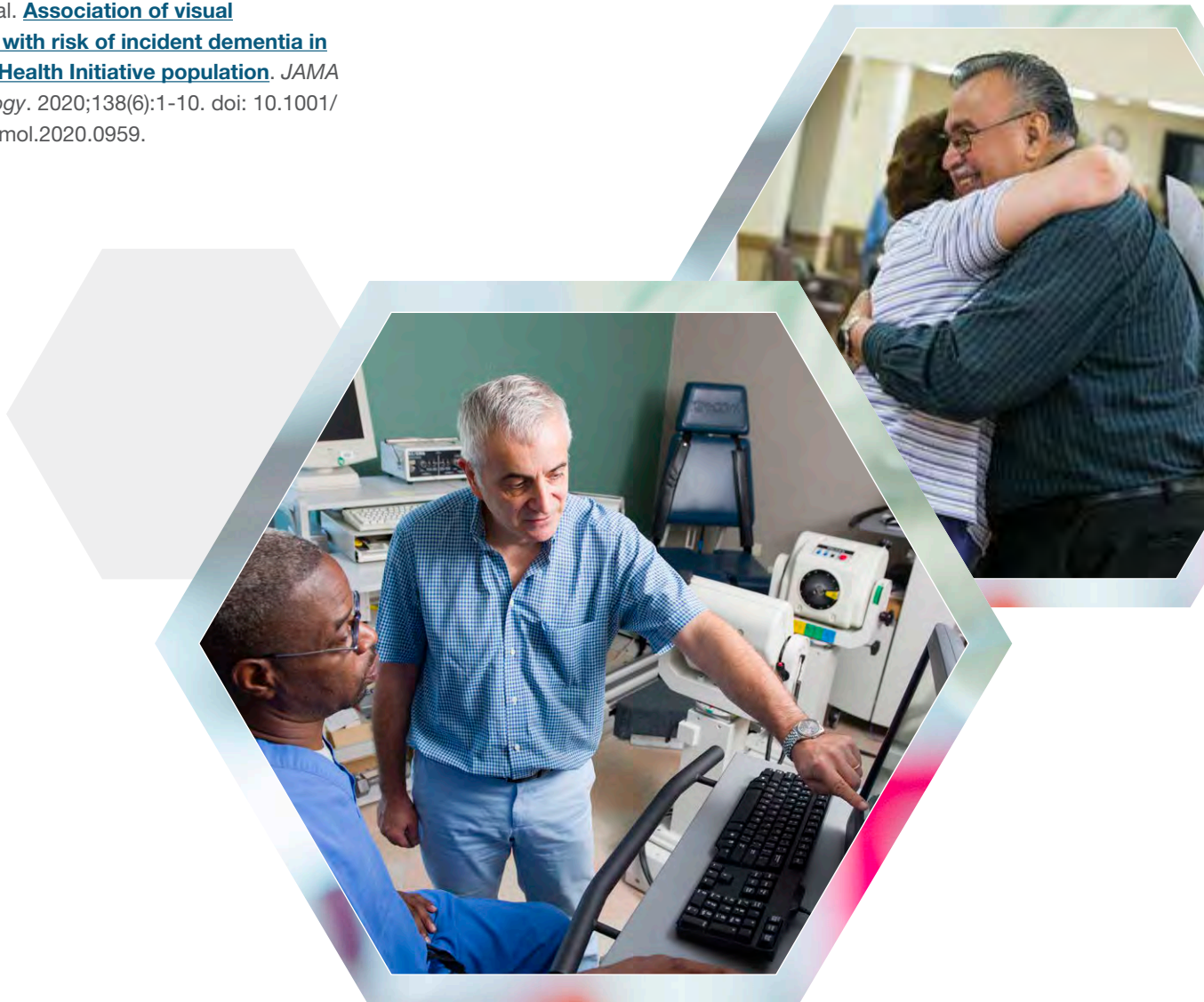
Tian Q, et al. [Association of dual decline in memory and gait speed with risk for dementia among adults older than 60 years: A multicohort individual-level meta-analysis](#). *JAMA Network Open*. 2020;3(2):e1921636. doi: 10.1001/jamanetworkopen.2019.21636.

Tran EM, et al. [Association of visual impairment with risk of incident dementia in a Women's Health Initiative population](#). *JAMA Ophthalmology*. 2020;138(6):1-10. doi: 10.1001/jamaophthalmol.2020.0959.

Beydoun M, et al. [Clinical and bacterial markers of periodontitis and their association with incident all-cause and Alzheimer's disease dementia in a large national survey](#). *Journal of Alzheimer's Disease*. 2020;75(1):157-172. doi: 10.3233/JAD-200064.

Ma Y, et al. [Higher risk of dementia in English older individuals who are overweight or obese](#). *International Journal of Epidemiology*. 2020;49(4):1353-1365. doi: 10.1093/ije/dyaa099.

Kumaradev S, et al. [Timeline of pain before dementia diagnosis: a 27-year follow-up study](#). *Pain*. 2020. Epub Sep 23. doi: 10.1097/j.pain.0000000000002080.



Disease Mechanisms



Recent increased funding for Alzheimer's and related dementias research has enabled NIH to support scientific projects designed to identify and explore the many different [biological pathways](#) leading to these diseases. Discovering which genes, proteins, and other molecules play a role in a crucial pathway provides clues for how to prevent or reverse the processes that cause dementia.

Moreover, researchers now have better and faster ways to translate their findings in the lab into drug candidates that may prevent or treat Alzheimer's and related dementias.

Discovering genetic risk factors for Parkinson's disease and Lewy body dementia

Multiple gene mutations are implicated in the development of Parkinson's disease, which is associated with the Alzheimer's disease-related Lewy body dementia. By growing the knowledge of how Parkinson's, Alzheimer's, and related dementias develop, scientists gain insights into the complexity of brain diseases. Over the past year, several NIH-funded projects led to significant progress in understanding more about the genetic causes of Parkinson's disease:

- **LRRK2 gene:** Two teams led by NIH researchers reported discovering mechanisms that suggest the biological role of [leucine-rich repeat kinase-2 \(LRRK2\) gene](#) in the development of Parkinson's disease. This means that a drug that inhibits LRRK2 might help those living with this disease. By better understanding how Parkinson's develops, researchers may be able to find new, more effective treatments for this disease.

A separate project funded in part by [NIH solved the 3D structure of the LRRK2 protein](#). Understanding [how a protein bends or twists](#) can aid researchers in exploring the role that a specific structure plays in disease development.

- **APOE ε4 gene:** Previous research has shown that the [APOE ε4 gene](#) plays a role in the cascade from amyloid plaques to tau tangles in Alzheimer's. Now two independent studies found that [APOE ε4 also directly influences the development of alpha-synuclein protein](#), the hallmark protein in Parkinson's disease and Lewy body dementia. In people with Parkinson's, those with APOE ε4 had [faster rates of cognitive decline](#). The findings suggest that APOE has direct effects on alpha-synuclein. These results reinforce the importance of APOE as a potential therapeutic target in several forms of dementia.

Connecting the microbiome with brain health

Scientists have been exploring how the community of microbes in our digestive tract — known as the gut microbiome — affects our health. Some of the substances released by the gut microbiome are beneficial to our body whereas others are harmful. Early research suggests that these substances can impact brain health. The [Alzheimer's Gut Microbiome Project](#) is an NIA-funded program exploring the role of the gut microbiome and metabolism in Alzheimer's.

Products of metabolism, such as fatty acids and bile acids, can travel through the bloodstream and enter the brain. Previous studies have linked cognitive decline and Alzheimer's to an increase in the level of certain bile acids from microbes. A recent analysis of publicly available data from the [NIA-funded Alzheimer's AD Knowledge Portal](#) of more than 2,000 brain samples provided more evidence that [microbial bile acids may play a role in Alzheimer's](#).

The Alzheimer's Gut Microbiome Project and [other NIH-supported projects](#) have only just begun to investigate the gut-brain connection and how it may play a role in cognitive impairment and dementia.

Science Spotlight

HTT gene a rare cause of FTD and ALS

In 2020, NIH researchers and their international collaborators were surprised to find that a [mutation in the *HTT* gene](#) — which causes the rare and lethal [Huntington's brain disease](#) — also causes [frontotemporal dementia \(FTD\)](#) and [amyotrophic lateral sclerosis \(ALS\)](#) in about 12 of every 100 people with FTD or ALS symptoms. However, these people do not have symptoms of Huntington's disease.

The discovery might translate into a new way of diagnosing and treating some individuals with FTD or ALS. In fact, clinical trials of gene therapy targeting the mutated *HTT* gene are already in progress with those who have Huntington's.

The investigational gene therapy may also help people with FTD or ALS who have the *HTT* gene mutation.



Advancing knowledge about multiple biological pathways

Following are examples of the wide array of recent findings from NIH-supported studies of multiple pathways potentially leading to dementia:

- **IFITM3's role in amyloid plaques:** Researchers are seeking drug candidates that can turn off the formation of the hallmark sign of Alzheimer's, which is [amyloid plaques in the brain](#). A recent report describes how interferon-induced transmembrane protein 3 (IFITM3) turns on gamma-secretase, an enzyme that [boosts the formation of amyloid](#). As people age, IFITM3 levels increase.
- **Clearing the brain of amyloid:** Scientists have not yet determined what drives the [regular clearance of wastes from the brain](#). Findings from a recent study in mice showed that proteins may flow through spaces that are very close to blood vessels, and that this flow is caused by the natural expansion and constriction of blood vessels. The research suggests that enhancing this motion may help flush from the brain the misfolded proteins thought to contribute to dementia.
- **Why certain neurons are vulnerable to changes linked to dementia:** Previous studies have noted that [tau tangles](#) develop in certain neurons in people with Alzheimer's but not in other neurons.

(continued on page 66)

Science Spotlight

Genetic study of Lewy body dementia supports ties to Alzheimer's and Parkinson's

Five genes may play a critical role in determining whether a person will develop Lewy body dementia, according to a recent study led by NIH researchers. The research team also tied Lewy body dementia to Parkinson's and noted that people who have Lewy body dementia may share similar genetic profiles with those who have Alzheimer's.

The researchers identified the five genes by comparing the genes of nearly 3,000 people with Lewy body dementia with genes of about 5,000 healthy, age-matched research participants. Three genes, called *SNCA*, *APOE*, and *GBA*, had been implicated in Lewy body dementia in previous studies. But this study was the first to implicate the other two genes, called *BIN1* and *TMEM175*, in Lewy body dementia. These two genes had previously been implicated in Alzheimer's and Parkinson's.

The findings, which suggest that Lewy body dementia is caused by a spectrum of problems that can be seen in both Parkinson's and Alzheimer's, may help researchers develop treatments for these diseases.



Genetic Risk



A new study led by NIH researchers showed that Lewy body dementia, Alzheimer's, and Parkinson's may share certain genetic causes. Credit: NINDS

(continued from page 64)

A recent paper detailed specific genes and molecular pathways that may explain the [vulnerability of certain neurons](#) and that provide insight about what may drive the development of tau tangles and Alzheimer's disease.

- **How tau tangles spread:** Two research teams recently investigated this process. The first team reported that the [spread of tangles](#) in the mouse brain depended on the shape of the long tau fibrils. The second team discovered a [mechanism for tau protein moving from cell to cell](#) in the brain. The findings from these two studies could lead to the design of treatments to prevent the spread of tau protein.
- **Linking forms of tau protein with how fast dementia worsens:** A new study found that people with Alzheimer's may worsen at [different rates because of the different physical and biochemical properties of the many forms of tau protein](#). These findings may aid the development of personalized treatments for the disease.

Accelerating drug development through the exploration of biological pathways

The [Accelerating Medicines Partnership](#) is a public-private partnership among NIH, FDA, biopharmaceutical and life science companies, and nonprofit organizations. The goal is to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets for therapeutics.

Several disease areas, including Alzheimer's and Parkinson's, are the focus of this partnership. The [Accelerating Medicines Partnership Alzheimer's Disease \(AMP AD\)](#) program has enabled participating research teams to identify unique candidate targets, including genes and proteins. These findings are shared with the broader research community to transform the speed at which new drug candidates can be identified.

Recent examples of AMP AD research findings include:

- **Discovering the importance of the *ATP6VA1* gene:** In 2020, the [ATP6VA1 gene](#) was identified as a master regulator gene of a neuronal network in Alzheimer's. With this gene, the AMP AD research team was able to improve neuronal function in lab tests with cells and flies. These findings pave the way for new drug discovery efforts targeting *ATP6VA1*.
- **Identifying the role of the *VGF* gene and protein:** Another AMP AD study identified the [VGF gene and protein](#) as having a key role in protecting the brain against Alzheimer's. This discovery provides a new target for researchers seeking to develop drugs to treat or prevent Alzheimer's.
- **Differentiating types of microglia cells in the brain:** Microglia in the brain act like trash collectors to help keep the brain healthy, and several teams are studying these cells for their potential as future treatment targets. In 2020, AMP AD researchers identified [types of microglia associated with Alzheimer's](#). One type of microglia was less abundant in the brains of people with Alzheimer's than in control brains. The next step is to design larger, more specific studies of the role of microglia types in Alzheimer's disease.
- **Describing the trajectory of the disease process:** An AMP AD team used computational approaches to make predictions about the [sequence of molecular changes](#) leading to Alzheimer's. By better understanding the sequence of changes, researchers can identify people as being in the early stages of Alzheimer's or farther along.
- **Finding molecular subtypes of Alzheimer's:** Another AMP AD team identified [several unique disease subtypes in people diagnosed with Alzheimer's dementia](#). Knowing subtypes can be useful both for developing targeted treatments and having diagnostic tests for selecting patients for those treatments.



- **Investigating why women are more likely to develop Alzheimer's:** A research team analyzed the changes in the levels of 180 metabolites in blood from more than 1,500 people who took part in the NIA-supported [Alzheimer's Disease Neuroimaging Initiative](#). The researchers reported [women who carry the APOE4 gene were more likely than men](#) to have certain metabolite changes related to known Alzheimer's biomarkers. By identifying specific pathways that go awry within specific subgroups, researchers can develop targeted treatments.

New NIH funding opportunities for researchers

NIH continues to offer the research community new funding opportunities for research projects designed to discover new biological mechanisms underlying Alzheimer's and related dementias:

- To spur research on how TDP-43 protein is involved in several kinds of dementia, NIH recently launched the [Mechanistic Basis of TDP-43-Dependent Pathobiology in Common Dementias](#) program.
- Through its [Molecular Mechanisms of Blood-Brain Barrier Function and Dysfunction](#) in Alzheimer's and related dementias initiative, NIH launched four large projects to support studies addressing how damage occurs to the blood-brain barrier and how it may contribute to cognitive impairment and dementia. The blood-brain barrier is a protective layer of cells between blood vessels and brain cells. This layer helps to control the flow of blood, oxygen, and nutrients into the brain, and block other substances.
- Through the [Center Without Walls for Molecular Mechanisms of Neurodegeneration in Frontotemporal Dementia program](#), NIH invited new applications for interdisciplinary team science support. Awarded projects aim to explore the molecular mechanisms underlying neurodegeneration in FTD in ways not possible through standard single-project approaches. The center will have a special focus on understanding mechanisms related to several known pathologies that occur in the brains of individuals with FTD, such as tau and TDP-43. A better understanding of FTD's underlying molecular mechanisms has the potential to enhance therapy development.
- To increase research on why certain brain regions are more vulnerable to abnormal proteins and damage, NIH launched [Mechanisms of Selective Vulnerability in LBD and FTD](#).
- To encourage research on how abnormal proteins spread in the brain, NIH invited researchers to develop projects for [Mechanisms of Pathological Spread of Abnormal Proteins in LBD and FTD](#).

Research on psychological changes

To better understand how psychological symptoms of Alzheimer's and related dementias differ from changes associated with normal cognitive aging, NIA has invested in a range of approaches to measure early psychological changes in the disease trajectory, as well as the behavioral and psychological symptoms of dementia. Scientists are exploring changes in affective, cognitive, social, and motivational processes in individuals with mild cognitive impairment and Alzheimer's and related dementias.

A recent study found that people with different kinds of neurodegenerative diseases [experience distinct challenges in perceiving emotion](#). The goal is to identify biological and behavioral targets for prevention and treatment approaches that will also promote social, emotional, and cognitive well-being.

NIA recently issued funding announcements to stimulate new research on changes in decision-making and emotional function that might be affected by early disease processes:

- [Integrative Studies of Neural Mechanisms and Affective Processes](#)
- [Fundamental and Translational Research on Decision Making](#)
- [Basic and Translational Research on Affective, Motivational, and Social Function](#)

NIA also encourages research that may aid the design of interventions that support decision-making. Specific areas of interest include the development of tools to assist adults with mild cognitive impairment or dementia:

- Decision-making interventions to leverage cognitive, emotional, social, and motivational strengths
- Tools to assess their ability to make decisions
- Strategies for simplifying choices
- Ways to promote timely [advance care planning](#), such as a power of attorney and living wills

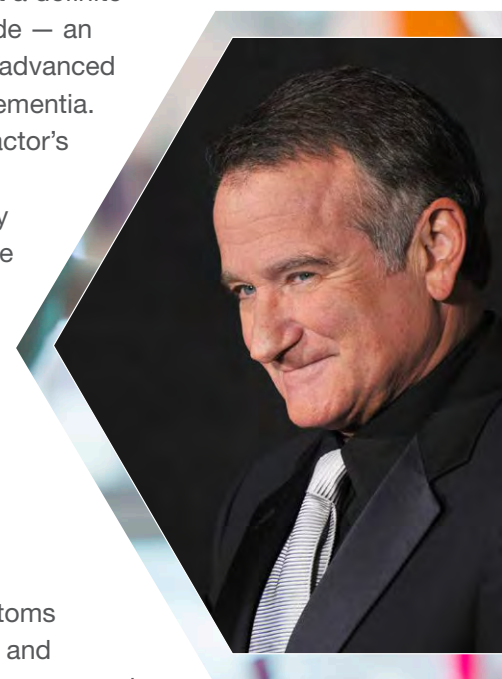
Robin's Wish

In 2020, the [documentary *Robin's Wish*](#) was released, along with a scientific version for professional audiences. The film chronicled the late comedian and actor Robin Williams' experiences with [Lewy body dementia](#).

Robin Williams experienced a puzzling pattern of behavior, including personality changes, confusion, forgetfulness, anxiety, paranoia, hallucinations, and problems with movement. It was not until after his death, however, that a definite diagnosis could be made — an autopsy demonstrated advanced stages of Lewy body dementia. This diagnosis led the actor's wife, Susan Schneider Williams, on an odyssey to learn how the disease explained Robin's symptoms and to raise awareness of the disease, which shares considerable overlap with signs of Parkinson's disease.

The film describes the disease, how the symptoms affected him personally and professionally, and current research efforts to understand and treat this cause of dementia, which, while fairly common, is not well known.

The release of the film highlights the need to understand, treat, and even prevent Lewy body dementia. Through NIH support, researchers are investigating several aspects of the disease including genetics, learning how brain cells are affected, examining environmental factors that may influence the disease, and finding biomarkers to help identify the disease early in its course. More information and research funding opportunities can be found at the NINDS [Focus On Lewy Body Dementia](#) page.



INVESTING IN THE FUTURE:

Research Trainee Jose Sandoval

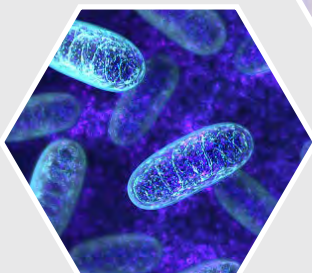
Before graduating from college, Jose Sandoval suggested to Gino Cortopassi, Ph.D., professor of molecular biosciences at the UC Davis, that they apply for an NIA grant to study the effects of [APOE ε4](#), the most common risk factor for Alzheimer's.

Cortopassi's lab studies the mechanisms of aging as well as defects in mitochondria, the energy factory of the cell. His research team also tests small molecule drugs that may treat those defects. The application was successful in receiving NIA diversity supplement funding. This type of support is geared toward eligible research trainees who desire an independent career in aging and geriatrics research and who also meet NIA's goal to [enhance diversity in the biomedical workforce](#).

In 2020, Sandoval graduated with honors with a bachelor of science in neurobiology, physiology, and behavior from UC Davis. Now he is now testing small molecule drugs to find out how to reverse the effects of the *APOE ε4* genotype on mitochondrial function, which may have implications for the treatment of Alzheimer's.

Sandoval became aware of research opportunities early on in his undergraduate career. As the first member of his family to attend college, he found a community and sense of belonging with his participation in the UC Davis Biology Undergraduate Scholars Program and later the [NIA-funded Advancing Diversity in Aging Research Program through Undergraduate Education](#).

"I credit these programs with much of my success because they helped reassure me, they helped motivate me, and they gave me the tools that I used to succeed in college and hopefully medical and Ph.D. programs," said Sandoval. "I hope to care for underserved communities disproportionately affected by metabolic disease, as well as studying that in the laboratory."



"I hope to care for underserved communities disproportionately affected by metabolic disease, as well as studying that in the laboratory."

References:

- Dewan R, et al. [Pathogenic Huntingtin repeat expansions in patients with frontotemporal dementia and amyotrophic lateral sclerosis](#). *Neuron*. 2020. Epub Nov 26. doi: 10.1016/j.neuron.2020.11.005.
- Chia, R., et al. [Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into the complex genetic architecture](#). *Nature Genetics*. 2021;53(3):294-303. doi: 10.1038/s41588-021-00785-3.
- Bonet-Ponce L, et al. [LRRK2 mediates tubulation and vesicle sorting from lysosomes](#). *Science Advances*. 2020;6(46):eabb2454. doi: 10.1126/sciadv.abb2454.
- Kim C, et al. [LRRK2 mediates microglial neurotoxicity via NFATc2 in rodent models of synucleinopathies](#). *Science Translational Medicine*. 2020;12(565):eaay0399. doi: 10.1126/scitranslmed.aay0399.
- Deniston CK, et al. [Structure of LRRK2 in Parkinson's disease and model for microtubule interaction](#). *Nature*. 2020 588(7837):344-349. doi: 10.1038/s41586-020-2673-2.
- Watanabe R, et al. [The in situ structure of Parkinson's disease-linked LRRK2](#). *Cell*. 2020;182(6):1508-1518.e16. doi: 10.1016/j.cell.2020.08.004.
- Davis AA, et al. [APOE genotype regulates pathology and disease progression in synucleinopathy](#). *Science Translational Medicine*. 2020;12(529):eaay3069. doi: 10.1126/scitranslmed.aay3069.
- Zhao N, et al. [APOE4 exacerbates \$\alpha\$ -synuclein pathology and related toxicity independent of amyloid](#). *Science Translational Medicine*. 2020;12(529):eaay1809. doi: 10.1126/scitranslmed.aay1809.
- Baloni P, et al. [Metabolic network analysis reveals altered bile acid synthesis and metabolism in Alzheimer's disease](#). *Cell Reports Medicine*. 2020;1(8):100138. doi: 10.1016/j.xcrm.2020.100138.
- Hur JW, et al. [The innate immunity protein IFITM3 modulates \$\gamma\$ -secretase in Alzheimer's disease](#). *Nature*. 2020;586(7831):735-740. doi: 10.1038/s41586-020-2681-2.
- van Veluw SJ, et al. [Vasomotion as a driving force for paravascular clearance in the awake mouse brain](#). *Neuron*. 2020;105(3):549-561.e5. doi: 10.1016/j.neuron.2019.10.033.
- Roussarie JP, et al. [Selective neuronal vulnerability in Alzheimer's disease: A network-based analysis](#). *Neuron*. 2020;107(5):821-835.e12. doi: 10.1016/j.neuron.2020.06.010.
- He Z, et al. [Transmission of tauopathy strains is independent of their isoform composition](#). *Nature Communications*. 2020;11(1):7. doi: 10.1038/s41467-019-13787-x.
- Rauch JN, et al. [LRP1 is a master regulator of tau uptake and spread](#). *Nature*. 2020;580(7803):381-385. doi: 10.1038/s41586-020-2156-5.
- Dujardin S, et al. [Tau molecular diversity contributes to clinical heterogeneity in Alzheimer's disease](#). *Nature Medicine*. 2020;26(8):1256-1263. doi: 10.1038/s41591-020-0938-9.
- Wang M, et al. [Transformative network modeling of multi-omics data reveals detailed circuits, key regulators, and potential therapeutics for Alzheimer's disease](#). *Neuron*. 2020;109(2):257-272.e14. doi:10.1016/j.neuron.2020.11.002.
- Beckmann ND, et al. [Multiscale causal networks identify VGF as a key regulator of Alzheimer's disease](#). *Nature Communications*. 2020;11(1):3942. doi:10.1038/s41467-020-17405-z.
- Olah M, et al. [Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease](#). *Nature Communications*. 2020;11(1):6129. doi:10.1038/s41467-020-19737-2.
- Mukherjee S, et al. [Molecular estimation of neurodegeneration pseudotime in older brains](#). *Nature Communications*. 2020;11(1):5781. doi:10.1038/s41467-020-19622-y.
- Neff RA, et al. [Molecular subtyping of Alzheimer's disease using RNA sequencing data reveals novel mechanisms and targets](#). *Science Advances*. 2021;7(2):eabb5398. doi: 10.1126/sciadv.abb5398.
- Arnold M, et al. [Sex and APOE \$\epsilon\$ 4 genotype modify the Alzheimer's disease serum metabolome](#). *Nature Communications*. 2020;11(1):1148. doi:10.1038/s41467-020-14959-w.
- Brown CL, et al. [Comparing two facets of emotion perception across multiple neurodegenerative diseases](#). *Social Cognitive and Affective Neuroscience*. 2020;15(5):511-522. doi: 10.1093/scan/nsaa060.

Research Enterprise



Through its open science approaches, NIH accelerates the pace and efficiency of research progress. The agency's investments in centralized data-sharing platforms and other technologies make it possible for scientists to share data, tissue samples, methods, and other crucial research

resources more broadly and effectively. The resulting large sets of data — often referred to as big data — provide the basis for discoveries that are revealing new molecular mechanisms of Alzheimer's and related dementias, providing more pathways to potential therapeutic targets and biomarkers.

PROGRAM SPOTLIGHT

Compressing the timeline for developing treatments

NIH recently announced the [next version of the Accelerating Medicines Partnership for Alzheimer's Disease \(AMP AD\)](#). During the first version, which began in 2014, the AMP AD program's open science, big data approach enabled research teams to identify and make more than 500 unique candidate targets for this complex disease publicly available. In the second version, NIA is again leading research efforts that now include funding a data coordinating center at [Sage Bionetworks, as well as funding several multi-institutional, cross-disciplinary academic research teams](#).

Since its launch seven years ago, AMP AD has made possible many new disease insights on the role of the genome, proteome, metabolome, and microbiome based on data collected from human samples and animal and cell-based models. [Recent AMP AD findings](#), described in the Biomarker Research and Disease Mechanisms sections, showcase research advances related to the discovery of new candidate targets, identification of molecular subtypes, and new potential biomarkers for a [precision medicine](#) approach to therapy development.

The [AD Knowledge Portal](#), an informatics data sharing platform that began as the data repository for the AMP AD Target Discovery Program, and the portal-linked, open-source platform [Agora](#) have enabled access to a vast amount of high-quality molecular data, analytical results, and candidate targets generated by AMP AD research teams.

The AD Knowledge Portal now includes data and resources from other NIA-supported team-science projects operating under open science principles.

The second version of AMP AD will continue to raise the standards for rigorous and reproducible research, and it will expand the characterization of Alzheimer's through the analysis of human brain samples. This will enable AMP AD research teams to refine the characterization of new targets, discover new biomarkers, define disease subtypes, and increase the understanding of causative factors and steps in disease progression. The knowledge gained will inform the development of therapies that can be tailored to an individual's unique disease risk profile.

Private sector funding partners for the second version of AMP AD include Eisai Inc., Gates Ventures, and Takeda Pharmaceutical Company Limited. In addition, the Alzheimer's Association and GlaxoSmithKline plc (GSK) — AMP AD partners since the launch of the program in 2014 — continue to participate.

Advancing research

The AMP AD program demonstrates how open science can enable the scientific community to investigate difficult scientific questions and jumpstart new drug discovery projects.

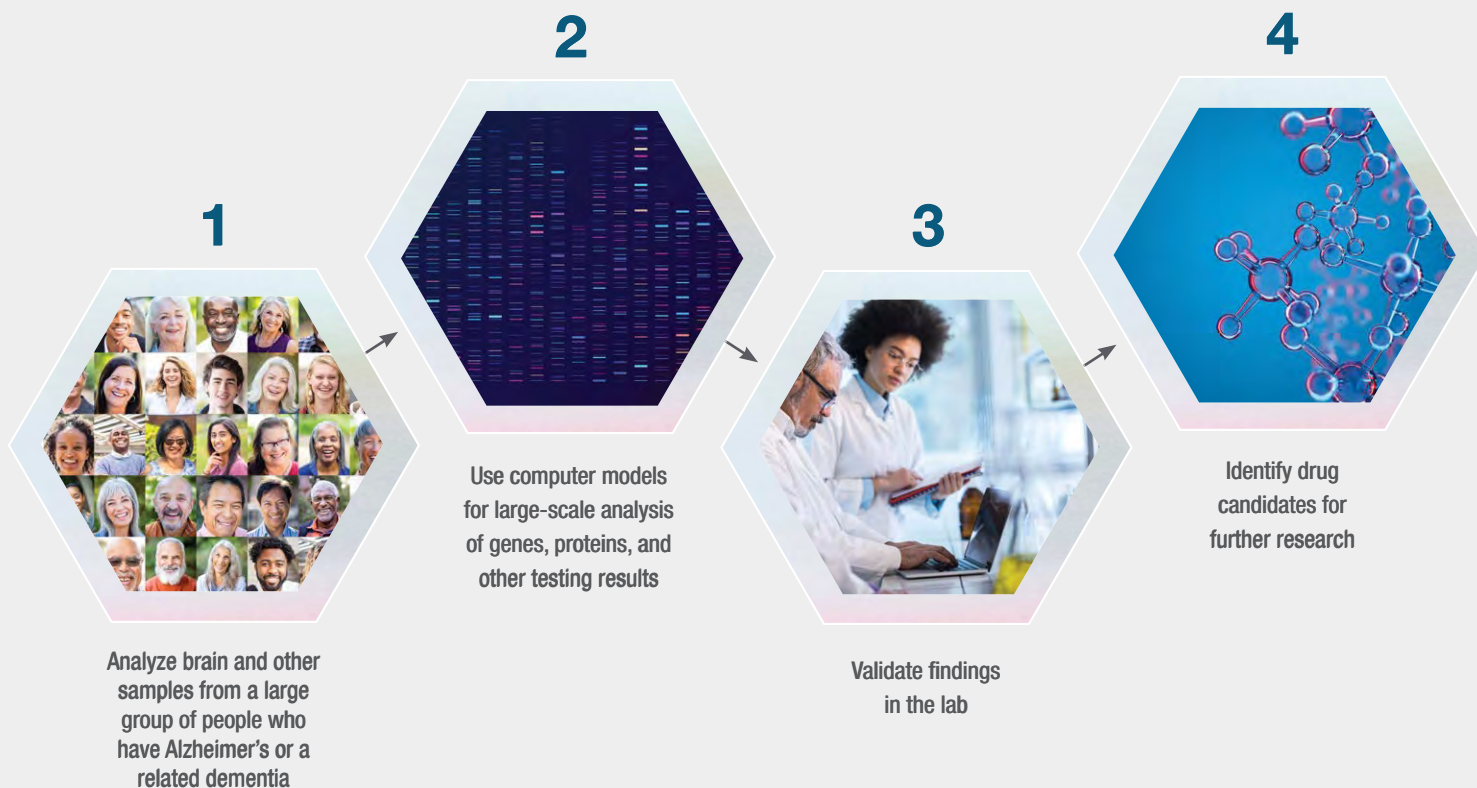
More than 3,000 researchers around the world have used the NIH-supported AD Knowledge Portal to advance research on Alzheimer's and related dementias.

NIH's ability to quickly respond to the urgent need for vaccine and treatment development for the coronavirus pandemic was made possible through experience from its already-established open science initiatives such as the [Accelerating Medicines Partnership](#) programs for [Alzheimer's](#) and [Parkinson's](#), [M²OVE-AD](#), [Resilience-AD](#), and [Psych-AD](#), [MODEL-AD](#), and [TREAT-AD](#). These and similar NIH initiatives have transformed the way that scientists collaborate rather than compete, [share their data and biological samples](#), work together to discover new biological mechanisms of disease, and find new drug candidates for testing.

Sharing population data of cognitive decline

NIH-supported behavioral studies also make data freely available to researchers. Decades of data collected from research participants about risk factors, their symptoms, and the development of cognitive impairment and dementia are available for analysis. For example, researchers share data from the NIA-supported [Harmonized Cognitive Assessment Protocol](#), through which investigators are examining cognitive change and dementia in about 3,500 older adults who already participate in the [Health and Retirement Study](#). In addition,

How to Use Big Data for Drug Discovery



similar studies are sharing data collected from research participants in Chile, China, England, the European Union, India, Mexico, and South Africa.

Developing new animal models of dementia

NIH provides new animal models for basic research or for therapy development. For example, to date, research teams that are part of the [NIA-supported Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease \(MODEL-AD\) consortium](#) have created more than 50 genetically modified mouse models. These mice are available to the research community through the [JAX AD Mouse Model Resource](#), and the data, protocols, and other resources are available through the [Experimental Tools section of the AD Knowledge Portal](#).

The MODEL-AD consortium also provides resources for rigorous preclinical efficacy testing of drug candidates. Researchers from academia and industry can apply for access to these via the [STOP-AD Portal](#).

In addition, the NINDS [Development and Validation of Advanced Mammalian Models](#) for frontotemporal disorder, vascular dementias, Lewy body disease, and mixed dementias resulted in [several new projects](#). These will help fill the critical need for next-generation animal models for many types of dementia.

Expanding the research workforce

NIH is committed to expanding the biomedical research workforce dedicated to Alzheimer's and related dementias research. As another result of increased federal investments in this area, NIA created many new funding opportunities for scientists and invited NIH-funded investigators from other research areas to apply for supplemental funding relevant to dementias. Programs are aimed at trainees at multiple points along the career trajectory, from students through early and senior investigators. Examples include:

- **Developing clinical trial experts:** Finding treatments for Alzheimer's and related dementias will depend on well-designed and expertly conducted clinical trials. To grow the number of specialized clinical trial experts, NIA supports the [Institute on Methods and Protocols for Advancement of Clinical Trials in Alzheimer's disease and related dementias](#). The comprehensive training program is designed to provide education and tools to establish a national cohort of qualified, diverse investigators to continue to enhance and improve Alzheimer's and related dementias treatment studies. Candidates are selected for their diverse demographic characteristics (such as age, race, and ethnicity), their specialties (such as physicians, psychologists, or statisticians), backgrounds (rural or urban), and career stage. The [inaugural class](#), which finished the course in 2020, included 25 female, 15 nonwhite, and six Hispanic/Latino trainees.
- **Enhancing the diversity of researchers focused on aging and dementia:** NIA recently expanded its investment in the [Resource Centers for Minority Aging Research](#) program. NIA now supports eight new resource centers focused on priority areas of social and behavioral science related to Alzheimer's and related dementias. The overarching centers' mission is to:
 - Enhance the diversity of the aging research workforce by mentoring promising scientists from underrepresented groups for sustained careers in aging research in priority areas of social, behavioral, and economic research on aging
 - Develop infrastructure to promote advances in these areas while simultaneously increasing the number of researchers focused on health disparities and the health and well-being of older adults from minority groups
- Encouraging behavioral and social sciences research skills: In March 2021, NIA released a new funding opportunity for [Short Courses on Interdisciplinary Behavioral and Social Sciences Research on Alzheimer's and Related Dementias](#). These

short courses, which are part of the [NIH Research Education Program](#), will support skills development for the Alzheimer's and related dementias workforce. The funding opportunity will also encourage the recruitment of new and diverse investigators into this area of research and to provide course participants with opportunities to interact with one another and course faculty.

According to an [analysis published by NIA in 2020](#), those new opportunities enabled many new investigators, as well as seasoned scientists from other research areas, to study Alzheimer's and related dementias.

NIH stands against structural racism in biomedical research

Within the biomedical research enterprise, [structural and institutional racism](#) has resulted in inequitable access to funding, training, and workforce opportunities, and this limits the pace of scientific progress.

In March 2021, NIH established the UNITE initiative to address structural racism and promote racial equity and inclusion within the NIH-supported and the greater scientific community.



UNITE has five committees with the following specific aims:

- U** Understanding stakeholder experiences through listening and learning
- N** New research on health disparities, minority health, and health equity
- I** Improving the NIH culture and structure for equity, inclusion, and excellence
- T** Transparency, communication, and accountability with our internal and external stakeholders
- E** Extramural research ecosystem: changing policy, culture, and structure to promote workforce diversity

[NIH is committed](#) to instituting new ways to support diversity, equity, and inclusion, and identifying and dismantling any policies and practices that may harm our workforce and our science.

References:

Greenwood A, et al. [The AD Knowledge Portal: a repository for multi-omic data on Alzheimer's disease and aging](#). *Current Protocols in Human Genetics*. 2020;108(1):e105. doi: 10.1002/cphg.105.

Oblak AL, et al. [Model organism development and evaluation for late-onset Alzheimer's disease: MODEL-AD](#). *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2020;6(1):e12110. doi: 10.1002/trc2.12110.

Berkness T, et al. [The institute on methods and protocols for advancement of clinical trials in ADRD \(IMPACT-AD\): A novel clinical trials training program](#). *Journal of Prevention of Alzheimer's Disease*. 2021;8(3):286-291. doi: 10.14283/jpad.2021.12.

Katiyar P, et al. [Attracting new investigators to Alzheimer's disease research: outcomes of increased funding and outreach](#). *Gerontologist*. 2021;61(3):312-318. doi: 10.1093/geront/gnaa056.



The background is a complex, abstract composition. It features several overlapping hexagonal shapes in various shades of blue, teal, and orange. These shapes are semi-transparent, allowing a blurred image of a person's face and upper body to be visible through them. The person appears to be looking towards the camera. The overall effect is a modern, artistic, and somewhat ethereal visual.

Moving Forward

As you have read, NIH has made tremendous progress in Alzheimer's and related dementias research in the past few years and our momentum continues to grow. With the recent accelerated approval of aducanumab, the first disease-modifying treatment for Alzheimer's, as well as other noteworthy scientific advances, now is an unprecedented time as we have never been closer to finding significant and meaningful solutions.

The research described in this professional judgment budget proposal must keep steadily moving forward with continued and expanded support. Millions of Americans are counting on us to meet the ultimate goal of preventing, diagnosing, and effectively treating Alzheimer's and related dementias. We also must find ways to provide better care and support services for those living with these devastating diseases as well as for their caregivers and families. And we must continue our work to recruit more volunteers — including an increasingly diverse range of participants — to Alzheimer's and related dementias clinical trials.

Additionally, the potential to establish the [**Advanced Research Projects Agency for Health \(ARPA-H\)**](#), if approved by Congress and appropriated for FY 2022, could provide a welcome venue for accelerating progress in Alzheimer's and related dementias research. From rapidly developing less expensive, less invasive biomarkers to launching partnerships to de-risk the drug development transition from basic and translational research early-stage clinical trials, this new agency would have the potential to spur innovation and stimulate new public-private collaboration.

Through the commitment and devotion of collaborative research teams around the world, the new trainees we recruit for our mission, and the thousands of people who take part in studies, NIH is transforming and accelerating Alzheimer's and related dementias research.



Together, we *will* succeed!

