

Advancing Alzheimer's Disease and Related Dementias Research for All Populations

Prevent. Diagnose. Treat. Care.



National Institutes of Health

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Introduction

The National Institutes of Health (NIH) is leading the federal government effort to meet an ambitious goal: Prevent and effectively treat Alzheimer's disease and related dementias by 2025. This progress report features science advances and related efforts between April 2021 and early 2022 in areas including drug development, lifestyle interventions, biomarker research, and more. Though not exhaustive, the information in the following pages provides an overview of the meaningful progress researchers are making to address the enormous health care challenges of these diseases.

The burden of Alzheimer's disease and related dementias is significant.

Alzheimer's and related dementias are complex brain disorders that slowly destroy memory and thinking skills. People living with these diseases may eventually lose the ability to live independently and, as their brain changes worsen, may be unable to carry out simple tasks such as feeding themselves. While dementia is more common in older adults, it is not a normal part of aging.

Dementia diseases cause a considerable financial burden on individuals and on society. Several independent research teams using different methods and sources of data have estimated the costs of dementia care. For example, based on Medicare claims data, health care and long-term services for dementia patients in 2021 cost an estimated \$321 billion. Unpaid care provided by family members and other care partners in 2021 is estimated at \$271.6 billion. In addition to the financial costs of Alzheimer's and related dementias, these diseases place

a heavy emotional burden on the people with dementia, family members, and other care partners, underscoring the urgent need for effective diagnostics, preventions, treatments, and care.

In 2022, more than 6 million Americans age 65 and older have Alzheimer's, the most common dementia diagnosis. It is likely these numbers will increase as the nation's population ages. In addition, many people are living with Alzheimer's-related dementias such as Lewy body dementia, vascular dementia, and frontotemporal dementia. While some

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individuals may experience only one form of dementia, many may have more than one type of brain pathology. Autopsy studies show that mixed dementias are the most prominent form of dementia after age 80, but they are difficult to diagnose during life, given current diagnostic tools. Similarly, it is challenging for clinicians to discriminate between different forms of dementia.

Some older adults who do not have dementia have more memory challenges or problems with thinking than other adults their age. This condition is called [mild cognitive impairment](#), or MCI. The symptoms of MCI are not as severe as those of Alzheimer's or a related dementia. People with MCI are still able to take care of themselves and perform their normal daily activities, but they are at greater risk for developing dementia. Still, not everyone who has MCI will develop Alzheimer's or a related dementia, and in many cases, the symptoms of MCI may stay the same or even improve.

NIH leads the nation's dementia research strategies.

NIH drives the nation's research to better understand the complex causes of Alzheimer's and related dementias, identify early signs of disease, develop effective interventions to prevent or delay disease progression, and improve care and support for those living with dementia as well as their caregivers. The [National Institute on Aging](#) (NIA) and [National Institute of Neurological Disorders and Stroke](#) (NINDS) conduct and fund the vast majority of NIH research on Alzheimer's and related dementias.

In recent years, NIH has received significant increases in funding for dementia research. This was catalyzed by the development of the [National Plan to Address Alzheimer's Disease](#), which arose from the [National Alzheimer's Project Act \(NAPA\)](#). The National Plan, first issued in 2012 and updated annually, outlines goals including preventing and effectively treating Alzheimer's and related dementias by 2025, as well as strategies to meet those aspirations.



Thanks to generous federal funding increases, Alzheimer's and related dementias research has advanced at a remarkable pace. Researchers have identified new genetic, behavioral, and lifestyle risks and protective factors for dementias and developed improved diagnostic tools to pinpoint the cause of a person's dementia symptoms. As the U.S. federal government leader in medical research, NIH has expanded dementia research initiatives and resources including platforms for data sharing and interdisciplinary collaborations, new research models and methodologies, and policies to ensure our clinical trials reflect the diversity of our population.

NIH Research Implementation Milestones track progress and guide future directions.

NIH informs the scientific community about its interests and priorities for Alzheimer's and related dementias research through its [Research Implementation Milestones](#) database. The milestones, which span the research spectrum from basic science to clinical implementation, were developed based on research gaps and opportunities identified by more than 350 leading academic and industry experts, innovators, and public advocates participating in [strategic research planning summits](#). These milestones reflect a framework for achieving the national goal of preventing and effectively treating Alzheimer's and related dementias by 2025.

RESEARCH SPOTLIGHT

A long-term NIH study broadens understanding of the trajectory of Alzheimer's.

One of the key challenges in designing clinical studies to test interventions for Alzheimer's is fully understanding the complexity of the disease. A greater understanding of the prevalence of this disease across populations is an important step. To this end, a recent analysis of data from more than 17,000 participants from the NIH-funded [Framingham Heart Study](#), a long-term study that has followed the health of thousands of people since 1948, has shown that more than 1,000 people in this sample had been diagnosed with Alzheimer's or [mild cognitive impairment](#) (MCI). Among people with Alzheimer's, 50.4% had mild disease, 30.3% had moderate disease, and 19.3% had severe disease. Understanding that half of



Dr. Dawber, Director of Framingham Heart Study, Dr. Tedeschi, Pathologist. Credit: NIH History Office

the people living with Alzheimer's [may have mild rather than moderate or severe disease](#) can help in balancing future research initiatives across disease stages, and it may aid the government and public health sectors in better targeting programs to support these individuals and their families.

This 2022 NIH Scientific Progress Report details major advances in dementia research.

In the following report, you will read about advances across a robust and diverse research pipeline — from molecules to populations and from the laboratory bench to the clinic. This is the eighth year that [NIH has published a scientific progress report](#) describing notable advances in Alzheimer's and related dementias research made possible through NIH funding.

In 2021 and 2022, scientists reported significant progress in Alzheimer's and related dementias research. Researchers have added to the growing list of genetic factors and molecular pathways involved in these disorders, such as DNA damage, [cellular senescence](#), and energy dysfunction. They have developed a new generation of research tools to identify, explore, and validate disease mechanisms and a variety of potential drug targets. Scientists have also made progress in determining how behavioral and lifestyle factors affect dementia risk.

During this period, results from NIH-funded population studies have shown the depth of [disparities](#) in dementia risk, prevalence, and care among various populations, such as in traditionally underserved communities. Study results have suggested steps to improve health equity, including the importance of partnering with diverse participants in clinical trials. Data from diverse, population-representative groups will serve as the basis for a more precise, person-centered approach to dementia prevention and treatment that takes into account an individual's sex, race and ethnicity, lifestyle, socioeconomic status, and specific environmental exposures, among other factors.

All these advances would not be possible without collaborations among researchers, clinicians, individuals living with dementia, their care partners, their families, and the support of the American public. Together, we are accelerating the momentum of research on Alzheimer's and related dementias and creating a path forward toward effective prevention, diagnostic, treatment, and care options.



Drug Development

Due in part to the substantial increases in funding referenced above, the pipeline of potential dementia treatments is more robust and diverse than ever. NIH is currently conducting and/or supporting research into all aspects of drug development: basic research to drug discovery, preclinical studies, and early- to late-stage clinical trials. The goal is new treatment options that will prevent, slow, or reverse the development of dementia.

NIA-supported basic research contributed to anti-amyloid drugs for dementia treatment.

In Alzheimer's disease, beta-amyloid clumps together to form plaques in the brain. One possible strategy to treat or prevent Alzheimer's is to reduce these plaques with monoclonal antibodies (antibodies made in the laboratory) that bind to beta-amyloid. One of these antibody drugs, [aducanumab](#), received U.S. Food and Drug Administration (FDA) [accelerated approval](#) in 2021, based on the effect of treatment on biomarkers such as brain imaging. While NIH did not directly fund the development of aducanumab, the agency did support critical foundational research leading to the discovery of antibody drugs.

Work to better understand the impact of anti-amyloid therapies has continued: In 2021, NIA scientists analyzed results from clinical trials of aducanumab and similar antibodies to obtain a more comprehensive view into the efficacy of these antibody drugs. Overall, these drugs [may slightly improve brain function and be treatment options that are somewhat effective](#) for

people living with Alzheimer's by reducing plaques in the brain. But the drugs also raise the risk of certain brain abnormalities.

Additionally, a recent NIA-funded study showed that treatment with either gantenerumab or solanezumab (other anti-amyloid antibodies) [did not slow cognitive decline](#) in people who have a rare, early-onset form of Alzheimer's called dominantly inherited Alzheimer's disease. However, gantenerumab reduced certain [biomarkers](#) of the disease such as brain cell damage and tau levels, indicating that higher doses and longer treatment times may be worth further study.

Also, a rare genetic variant causes early-onset autosomal dominant Alzheimer's disease (ADAD), characterized by even greater beta-amyloid accumulation than non-inherited forms of the disease. A 2022 NIA-funded study found that the anti-amyloid antibody [crenezumab did not prevent or slow cognitive impairment](#) in people with ADAD. While disappointing, these studies provided important insights into the genetic causes of Alzheimer's and models for future studies on treatments for individuals at substantially higher genetic risk.



What happens to the brain in Alzheimer's disease?

The healthy human brain contains tens of billions of neurons, specialized cells that transmit messages between different parts of the brain and between the brain and other parts of the body, such as muscles and organs. In Alzheimer's disease, [toxic changes](#) can disrupt communication among neurons. Researchers believe this process involves abnormal forms of certain proteins.

In people with Alzheimer's, abnormal levels of the beta-amyloid protein clump together to form plaques that slowly build up between neurons. Abnormal forms of the tau protein accumulate in neurons, eventually forming tangles inside the neurons.

Ultimately, beta-amyloid plaques and tau tangles spread throughout the brain and prevent neurons from functioning properly. As many neurons stop functioning, they lose connections with other neurons and may die. Researchers are working to discover how other factors, such as inflammation, the brain's blood supply, and brain changes caused by proteins other than beta-amyloid and tau (including alpha-synuclein and TDP-43, which are discussed later in this report) may also contribute to Alzheimer's and related dementias.

A new vaccine may prevent beta-amyloid accumulation.

Scientists are also developing vaccines to potentially delay or prevent Alzheimer's and related dementias. Based on lessons learned from previous work, NIH-funded research has resulted in a [DNA-based vaccine, called AV-1959D](#), which triggers an immune response against beta-amyloid. Studies in animal models have shown that AV-1959D is safe and effective at preventing beta-amyloid accumulation and brain cell death. As a result of their preclinical studies, [NIA awarded a grant to test AV-1959D](#) in clinical trials with individuals with early-stage MCI or Alzheimer's. The trial is slated to begin in late 2022.

A new drug treatment strategy targeting protein malfunction is being tested in clinical trials.

Molecules called chaperones help proteins form correctly inside cells. In Alzheimer's, chaperones stop working normally, causing proteins in the cell to take on the wrong shape and interact with each other in ways that can cause disease. In 2021, NIA-funded research led to the development of a small molecule called PU-AD that [targets the malfunctioning chaperones](#).

A Phase 1 trial showed that PU-AD is safe in healthy volunteers, and future clinical trials will assess whether this drug is an effective treatment for Alzheimer's.

NIH-funded research is accelerating the discovery of new dementia drugs.

Through its [Alzheimer's Disease Drug Development Program](#), NIA supports research aimed at discovering new drug candidates that target various biological processes involved in Alzheimer's and related dementias. Since its inception in 2006, this initiative has supported 47 drug development projects and resulted in 12 new, disease-modifying dementia drug candidates that have advanced to testing in human trials. Highlights of ongoing NIA-funded drug development projects include the following:

- » It is understood that brain inflammation increases the risk of Alzheimer's and related dementias. One cause of this inflammation is deposits of fibrin, a protein which helps to form blood clots. NIA is funding a study focused on developing [an antibody against fibrin](#) as a potential treatment for Alzheimer's.

RESEARCH SPOTLIGHT

An anti-beta-amyloid vaccine shows promise in people living with Down syndrome.



People living with Down syndrome have a high risk of developing Alzheimer's. They are born with an extra copy of chromosome 21, which carries a gene that produces a specific protein. This protein, called APP, leads to a buildup of beta-amyloid clumps in the brain.

Researchers have developed a vaccine called ACI-24 that causes the body to make antibodies against these clumps in the hope of preventing harmful plaques from forming in the brain. An [NIA-funded Phase 1 clinical trial](#) found that the vaccine was safe and well-tolerated in adults with Down syndrome and was effective at inducing the production of anti-beta-amyloid antibodies. The vaccine will be tested in Phase 2 trials to validate these results in a larger group of participants.

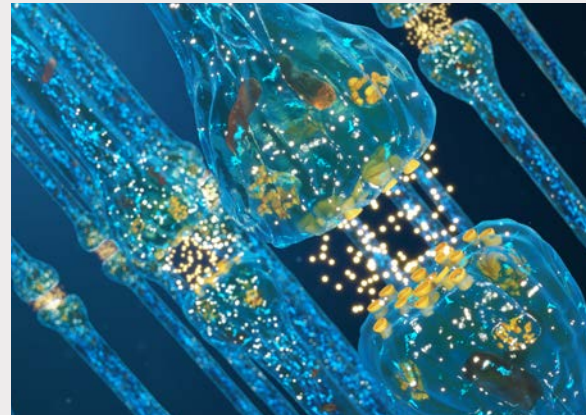
PROGRESS SPOTLIGHT

Support via multiple NIA funding opportunities bolsters promising Alzheimer's drug.

In early clinical trials, a small molecule called CT1812 has shown promise for protecting the connections between brain cells. CT1812 [removes toxic beta-amyloid clumps](#) between brain cells and may prevent cell damage. NIA-funded grants supported data collection to confirm the safety of CT1812. Subsequently,

NIA awarded the start-up company developing this drug a [Small Business Innovation Research \(SBIR\)](#) grant, leading to an FDA Fast Track designation in 2017 for the treatment of people living with Alzheimer's.

A [Fast Track SBIR award to the company](#) further resulted in three ongoing early-phase clinical trials of CT1812 and enhanced partnership opportunities. With additional support from a five-year NIA grant, CT1812 is now being tested in a Phase 2 trial in collaboration with the NIA-funded [Alzheimer's Clinical Trials Consortium \(ACTC\)](#).



- » A drug called mebendazole, used to treat parasitic infections in humans, has been shown to reduce the buildup of tau tangles in most research models of Alzheimer's. NIA is funding a [study aimed at changing the chemical structure of mebendazole](#) and transforming it into a new drug candidate that can reduce tau pathology and improve the memory deficits in people living with Alzheimer's.
- » A protein called TDP-43 accumulates in the brain of older adults with dementia. Initial research identified small molecules that bind to TDP-43 and prevent its accumulation. NIA-funded drug development studies will optimize these [small molecules into a drug candidate](#) for the treatment of Alzheimer's and related dementias. NIA advances efforts to repurpose existing drugs for other conditions to treat dementias.

NIA advances efforts to repurpose existing drugs for other conditions to treat dementias.

Researchers are leading studies to determine whether drugs currently used to treat other conditions can help prevent or treat Alzheimer's. This strategy, called drug repurposing, is an alternative to traditional drug development research. In 2021 and 2022, drug repurposing studies made several important discoveries, including:

- » [NIA researchers](#) are using an animal model to test drugs with similar structures to thalidomide, known as thalidomide analogs, as a way to reduce brain inflammation associated with Alzheimer's and related dementias. Thalidomide is an FDA-approved drug that reduces inflammation and is currently used to treat skin conditions such as leprosy and some types of cancer, including multiple myeloma. One study found that the [thalidomide analog DP](#) reduces brain inflammation, prevents brain cell death, and improves motor and behavioral functions in mice with beta-amyloid plaques. Another study

found that the [thalidomide analog NAP promotes recovery from severe brain injuries](#), which can increase the risk of developing Alzheimer's.

- » In cell culture experiments, [two drugs](#), an FDA-approved treatment for myeloid leukemia called dasatinib and an experimental treatment for liver cancer, C188-9, were able to correct distinct molecular abnormalities associated with Alzheimer's pathogenesis. These drugs may target proteins in the brain that appear to be altered early in the course of Alzheimer's. The study included samples from participants in the NIA-led [Baltimore Longitudinal Study of Aging](#) and the NIA-funded [Religious Orders Study](#).
- » Bumetanide, a common diuretic, [may lower the risk of Alzheimer's](#) in people who have a genetic risk for this disease. Scientists obtained these results by analyzing data from databases of brain tissue samples and FDA-approved drugs. The researchers mapped individuals' genetic risk for disease against the pathologies in

their brains, cross-referenced with the prescription drugs they took. This effort demonstrates how data-driven research can help identify drugs that can be repurposed to prevent or treat dementia diseases. This is one of more than 30 projects that NIA funds through its [Drug Repositioning and Combination Therapy Development initiative](#).

Ritalin reduced apathy in an Alzheimer's clinical trial.

Apathy, a loss of interest or motivation, is common among people with Alzheimer's disease and is associated with increased medical costs, mortality, and caregiver burden. In 2021, a multicenter trial that NIA funded through its Alzheimer's disease clinical trials program, showed that [two daily doses of the drug methylphenidate](#) (commonly known by the brand name Ritalin) safely reduced apathy among adults living with Alzheimer's. This drug could help improve the quality of life of dementia patients.

RESEARCH SPOTLIGHT

A recently launched clinical trial will test gene therapy for Alzheimer's and MCI.

Gene therapy is an emerging technology that treats or reverses conditions by correcting problems with DNA. This technology may offer an exciting potential treatment option for Alzheimer's and related dementias. NIA funds cutting-edge research in this area through its [Alzheimer's Drug Development Program](#). In addition, via its [Alzheimer's disease clinical trials program](#), NIA launched a first-in-human (Phase 1) clinical trial to test a [gene therapy to increase levels of brain-derived neurotrophic factor \(BDNF\)](#). BDNF is a brain growth factor that reduces cell death and promotes connections between brain cells; previous studies have found reduced BDNF levels in people with Alzheimer's.

The trial is enrolling people with early Alzheimer's or MCI, which can be a precursor to dementia. As a Phase 1 trial, the goal is to test the safety, tolerability, and preliminary efficacy of BDNF gene therapy. The researchers are hopeful that this treatment will prevent and possibly even reverse the loss of brain cells in people with dementia.



Biomarker Research

A timely and accurate diagnosis is crucial for determining the best treatment options for people living with Alzheimer's or a related dementia. In the past, the only sure way to know whether a person had a specific type of dementia was through autopsy. Today, NIH-funded biomarker research has led to more reliable, more affordable, and less invasive tests that help diagnose and differentiate among the types of dementia.

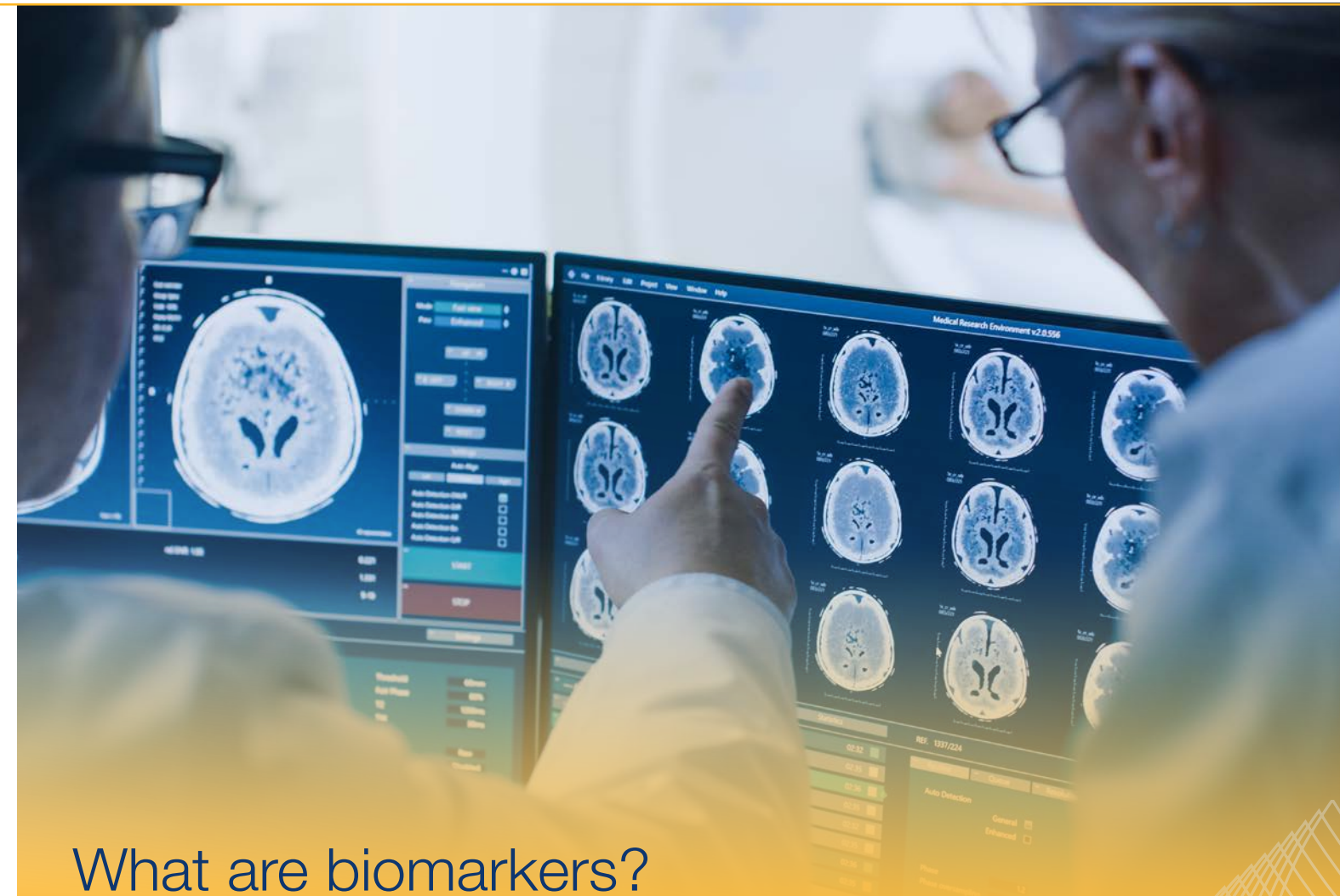
In people with dementia, changes in the brain begin many years before the start of any noticeable symptoms. Effective biomarkers could improve dementia research and care by:

- » Identifying people who are most likely to develop dementia later in life and who would benefit most from preventive interventions
- » Detecting the earliest signs of dementia to help start treatment as soon as possible
- » Distinguishing different forms of dementia from one another
- » Determining what stage of dementia a patient has and monitoring changes, including disease progression and treatment response
- » Screening and selecting participants for clinical trials based on their risk or early signs of dementia

NIH supports an extensive range of research that is helping to identify new biomarkers and improve upon existing tests.

Biomarker tests for dementia can depend on brain imaging methods such as PET scans, or lab tests of spinal fluid and blood, and are usually combined with cognitive tests to assess a person's memory and thinking skills. Currently, these tests are mostly used in research settings, although they are also available to a limited number of doctors and their patients. NIH supports an extensive range of research that is helping to identify new biomarkers and improve upon existing tests. The goal is to promote broad access to accurate, easy-to-use, affordable, and minimally invasive tests that are easily accessible to health care providers nationwide and effective in broad, diverse populations.

In the future, biomarkers are expected to help health care providers deliver the right medicine in the right place at the right time to each person with dementia.



What are biomarkers?

Biomarkers are measurable indicators of what is happening in the body. They can be found in blood and other bodily fluids, organs, and tissues and can be measured by laboratory and imaging tests. Biomarkers can help doctors and scientists diagnose diseases and health conditions, find health risks in a person, monitor responses to treatment, and track how a disease or health condition changes over time.

Progress Update

First blood test for a biomarker of Alzheimer's now validated in clinical trials.

NIA's small business research program funding supported the initial development of the [PrecivityAD™ blood test](#), which is the first blood test for biomarkers of Alzheimer's to become more broadly available to some doctors, dependent on state-specific availability reflecting FDA guidelines. The test, developed by [C₂N Diagnostics](#), can help physicians evaluate patients who have cognitive impairment. C₂N's laboratory measures the [concentrations of two forms of the amyloid protein: amyloids 42 and 40](#). The test also checks for the presence of a protein called [apolipoprotein E](#). C₂N uses these measures to calculate an Amyloid Probability Score, which can be used to estimate the likelihood of amyloid plaques in the brain.

In 2022, C₂N Diagnostics published new findings from two independent studies that compared results from the PrecivityAD™ blood test with results from imaging tests in a total of 686 participants. The studies showed the [PrecivityAD™ blood test is 81% accurate in predicting the presence of amyloid plaques in the brain](#). These results reaffirm the test as an important tool to help diagnose Alzheimer's. Researchers from the NIA-funded [AHEAD Study](#) plan to use the PrecivityAD™ blood test to help select participants for this [clinical trial](#). The AHEAD Study is testing whether a new drug called lecanemab — another anti-amyloid antibody — can slow down or stop Alzheimer's-related brain changes in people who have a high risk for this condition but do not have any symptoms.



Neurons in Alzheimer's disease. 3D illustration showing amyloid plaques in brain tissue.

New blood-based biomarker tests help clinicians more easily and accurately diagnose dementia.

Some proteins from the brain can be measured by sensitive blood tests. The levels of certain proteins in the blood can change when someone has Alzheimer's or a related dementia, and researchers are developing new methods to detect these changes. In the past year, NIH-funded science has led to these discoveries:

- » [A new blood test can accurately predict the presence of beta-amyloid plaques in the brain](#). This test could help lower the cost of accurately diagnosing Alzheimer's or another dementia and expand availability of accurate, sensitive tests for dementia to more people.
- » Two forms of the tau protein, called ptau217 and ptau181, have both been found to be [accurate blood-based biomarkers for Alzheimer's](#). Additionally, evidence suggests ptau217 may be an especially [accurate indicator of Alzheimer's in diverse populations](#).
- » The level of a protein called neurofilament light chain (NfL) in the blood can [more accurately predict remaining lifespan in late life](#) than currently used estimates based on physical and cognitive function.

» Among people who have a genetic risk of [frontotemporal dementia](#), those who have [high levels of NfL in the blood are more likely to develop symptoms of this condition](#). Blood tests for NfL could help identify people who have the highest risk of developing this type of dementia and might benefit from early interventions.

Advances in brain imaging technology are improving dementia diagnosis.

Brain imaging, also known as brain scans, can help detect changes in the brain that are linked to dementias. Advanced brain imaging techniques can identify tau tangles and beta-amyloid plaques, which are hallmarks of Alzheimer's disease, and can help rule out other causes of cognitive impairment, such as a brain tumor. Recent NIH-funded discoveries in brain imaging technology for dementias include the following:

» In people living with Alzheimer's, a small area of the brain called the [locus coeruleus might show signs of the disease before any other brain area](#). The locus coeruleus communicates with other areas of the brain, affecting many functions including memory, wakefulness and attention, and

response to stress. Changes in this region could serve as a biomarker for early diagnosis of the disease.

» A new tracer designed to detect living synapses (connections between nerve cells) that can be used together with brain imaging technology can help researchers [study the connections between nerve cells in the brain](#). This new technique will help clarify how interrupted connections between nerve cells contribute to dementia diseases.

Biomarkers for dementia-related vascular damage gain momentum.

Scientists are uncovering considerable knowledge about [vascular contributions to cognitive impairment and dementia](#) (VCID). Damage to the brain's vascular system — the collection of arteries and blood vessels that supply oxygen and other nutrients to the brain — often occurs early and contributes to the severity of Alzheimer's disease and other dementias. To help improve VCID detection, NINDS and NIA fund and help lead the [MarkVCID Consortium](#) with the goal of identifying biomarkers that indicate problems with blood vessels in the brain.

In 2021, MarkVCID Consortium scientists published promising results from several candidate [cerebrospinal fluid- and blood-based biomarkers](#) as well as [imaging-based biomarkers](#) of VCID. The researchers also developed standardized, well-documented procedures to help with the large-scale rigorous validation of these candidate biomarkers. They are now testing the most promising biomarkers in larger-scale clinical trials in diverse populations.



RESEARCH SPOTLIGHT



A breakthrough test can help diagnose multiple types of dementia.

Thanks in part to NIA funding, [Amprion®](#), a biotechnology company, launched the [SYNTap™ Biomarker Test](#). The test, which was granted FDA breakthrough device designation earlier this year, detects abnormal forms of the alpha-synuclein protein in cerebrospinal fluid samples. Alpha-synuclein is misfolded in Lewy body dementia, but its presence is typically not confirmed until autopsy. Once FDA approved, the test will aid early diagnosis of these diseases and help detect the co-occurrence of Lewy bodies in people with Alzheimer's disease, in whom it is thought to accelerate disease progression. Amprion is currently seeking FDA approval for the biomarker test.

Lewy body dementia biomarkers are advancing through rapid research.

[Lewy body dementia](#) is characterized by abnormal brain deposits of a protein called alpha-synuclein. These deposits affect how brain cells function and can lead to cognitive impairment. In 2021, NINDS renewed and expanded its [Biomarkers for Lewy Body Dementia](#) initiative to identify indicators within the body to help scientists diagnose and monitor the progression of this disease.

Digital cognitive biomarkers can help predict cognitive decline.

NIH supports research to develop minimally invasive strategies that help detect pre-symptomatic or early-stage Alzheimer's. For example, digital cognitive biomarkers assess how well a person completes learning- and memory-related tasks on a digital device. Funded in part by NIA, [newly developed and validated digital cognitive biomarkers for Alzheimer's](#) can help predict which seemingly healthy people may experience cognitive decline in the future.

PROGRAM SPOTLIGHT

Supporting the biomarker research infrastructure remains a high priority.

The NIA-funded [Alzheimer's Disease Neuroimaging Initiative \(ADNI\)](#) is an innovative public-private partnership established to accelerate the development of biomarkers to diagnose and monitor Alzheimer's. Since its inception in 2004, teams of ADNI researchers from several research facilities have collected participant samples and imaging data to study normal brain aging processes and the development of mild cognitive impairment and Alzheimer's. ADNI makes this data, which has contributed to [more than 3,500 peer-reviewed publications](#), available through the University of Southern California Laboratory of Neuro Imaging's [Image & Data Archive](#).

Research using ADNI data led to the development of methods for early detection of Alzheimer's, and many clinical trials running today are using biomarkers first identified by ADNI. ADNI has also contributed to understanding the patterns and rates of

change in dementia biomarkers over time and in different areas of the brain, helping researchers to identify promising areas to target for potential therapies and interventions. ADNI's unique partnership model and data sharing approach have been replicated around the world and have inspired similar initiatives in Parkinson's and multiple sclerosis research.

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Scientists are identifying biomarkers for Alzheimer's in people with Down syndrome.

People who have Down syndrome have a high risk of developing Alzheimer's disease: Almost all adults with Down syndrome have Alzheimer's-related brain changes by age 40. NIA funds and helps guide the [Alzheimer's Biomarkers Consortium-Down Syndrome \(ABC-DS\)](#), through which researchers identify early biomarkers of Alzheimer's in adults with Down syndrome. ABC-DS is a longitudinal study that is funded in collaboration with the [Eunice Kennedy Shriver National Institute of Child Health and Human Development](#) and the [NIH INCLUDE Project](#). In 2021, based in part on ABC-DS data, researchers discovered that people who have Down syndrome have a [profile of biomarkers highly similar](#) to people with a gene variant that causes an inherited form of Alzheimer's. Results from this project will help doctors and scientists better understand the onset and progression of Alzheimer's in people who have Down syndrome and will aid in therapy development.



*Amyloid beta clusters (red) build up among neurons (green) in a mouse model of Alzheimer's disease.
Credit: [Strittmatter Laboratory, Yale University](#)*

Researchers are using next-generation approaches to develop new animal models for dementia.

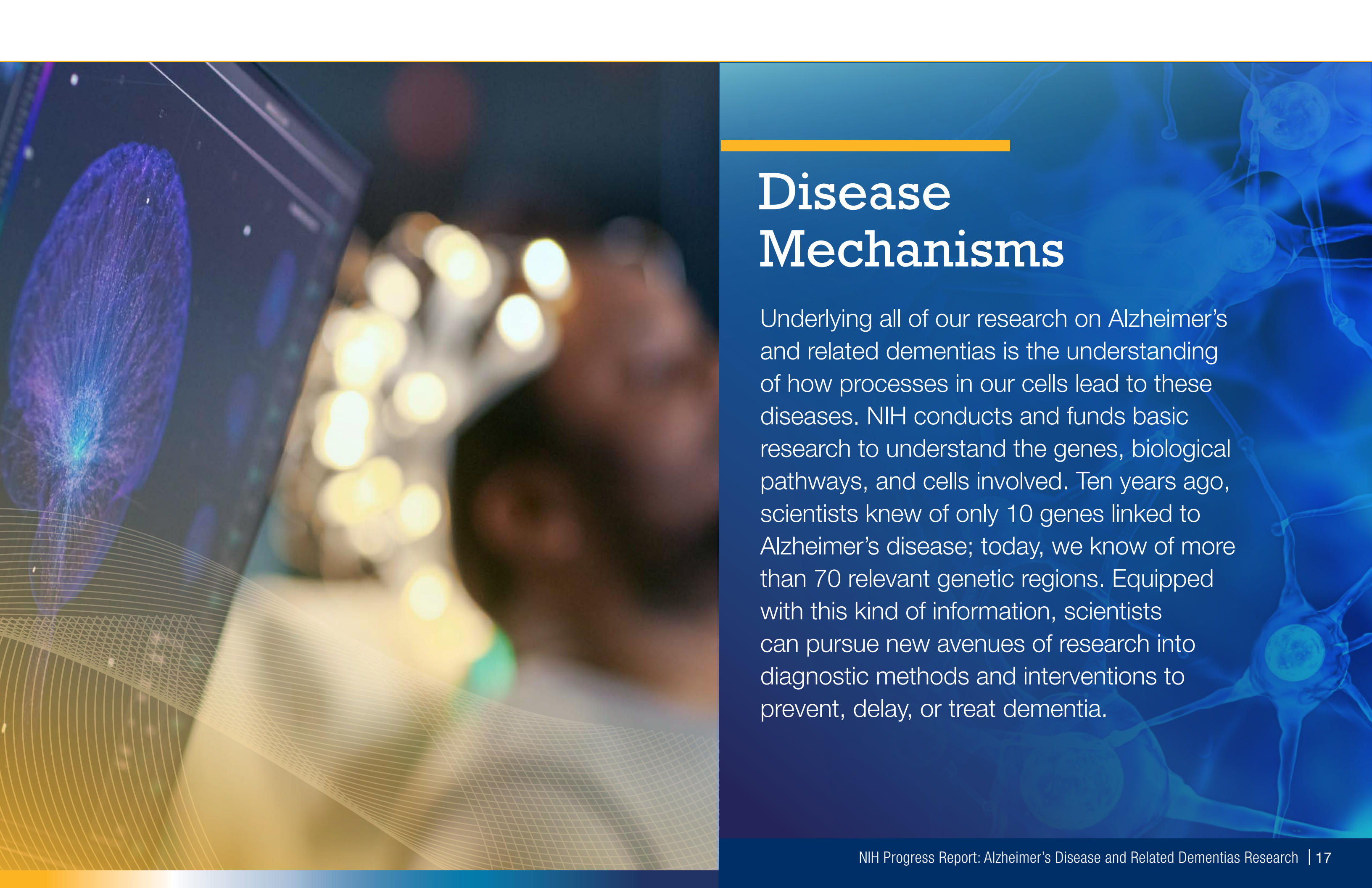
Through the NIA-funded [MODEL-AD \(Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease\) consortium](#), researchers work to develop novel models of Alzheimer's based on human data to guide drug development for Alzheimer's and help increase the likelihood that findings in these models can be replicated in humans. Consortium scientists are developing new mouse models for Alzheimer's and [conducting detailed characterizations of the most promising ones](#) by comparing biomarkers in brain and blood samples from these mice with biomarkers in people living with the disease. This research is yielding animal models that more faithfully replicate the biology of Alzheimer's in humans.

EVENT SPOTLIGHT

NIH funds an expert workshop to address the implications of preclinical diagnosis of dementia.

In June 2021, NIA sponsored a [virtual workshop](#) to discuss the behavioral and social science research questions raised by the use of biomarkers for diagnosing dementia in people at early, preclinical stages. Hosted by the [National Academies of Sciences, Engineering, and Medicine](#), the event brought together researchers from various fields to discuss the benefits and possible complications of early detection of dementia, including the impact of early diagnosis on affected individuals and their families.

Attendees also discussed steps to promote health equity in biomarker development to ensure that biomarkers are effective in all populations and that everyone has equal access to improved diagnostic methods for dementias. Discussion outcomes were published in a publicly available [detailed report](#).



Disease Mechanisms

Underlying all of our research on Alzheimer's and related dementias is the understanding of how processes in our cells lead to these diseases. NIH conducts and funds basic research to understand the genes, biological pathways, and cells involved. Ten years ago, scientists knew of only 10 genes linked to Alzheimer's disease; today, we know of more than 70 relevant genetic regions. Equipped with this kind of information, scientists can pursue new avenues of research into diagnostic methods and interventions to prevent, delay, or treat dementia.

Details emerge on TDP-43 link to multiple neurodegenerative diseases.

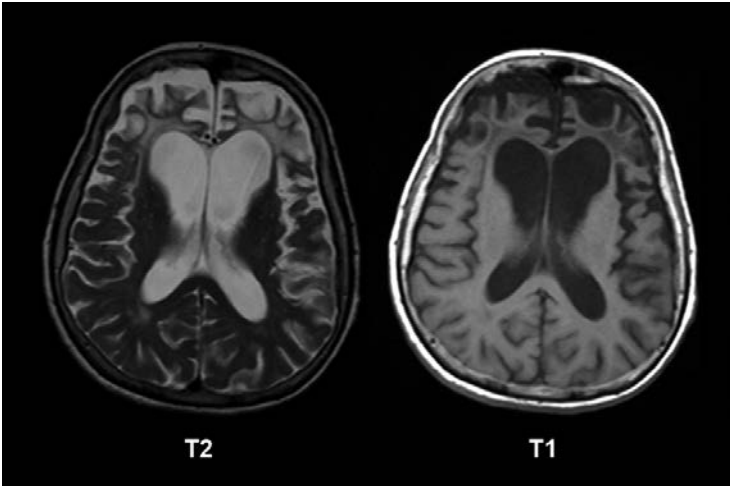
NIA and NINDS fund basic research into the many types of dementia, including under-recognized forms involving a protein called TDP-43. Abnormal, misfolded forms of TDP-43 play a role in the development of a number of brain diseases, including amyotrophic lateral sclerosis (ALS),

frontotemporal dementia, and a recently recognized brain disorder that mimics the clinical features of Alzheimer’s disease, called [limbic-predominant age-related TDP-43 encephalopathy \(LATE\)](#). A recent study found that people in the advanced stages of LATE are more likely to have certain types of [small blood vessel disease in the brain](#). The study analyzed data from the NIA-funded

[Religious Orders Study and Memory and Aging Project \(ROSMAP\)](#) and [Minority Aging Research Study \(MARS\)](#). In early 2022, NIA hosted a [workshop on LATE](#) to share the newest research findings as well as to stimulate discussion and consider future directions.

Researchers have also discovered that TREM2, a protein found on certain immune cells, helps [protect the brain from TDP-43-related harm](#). The results suggest that treatments that enhance the activity of TREM2 might be helpful for people with ALS and FTD.

TDP-43 is usually found in the nucleus, where genes are activated. However, misfolded forms of this protein cannot enter the nucleus. Two independent research teams discovered how having TDP-43 in the wrong place [alters the genetic instructions for a gene called UNC13A](#). *UNC13A* is important for maintaining connections between neurons, and changes to this gene can raise the risk of both ALS and FTD.



Brain MRI of a female of 65 years with frontotemporal dementia. Credit: [Mikhail Kalinin under CC BY-SA 3.0](#)

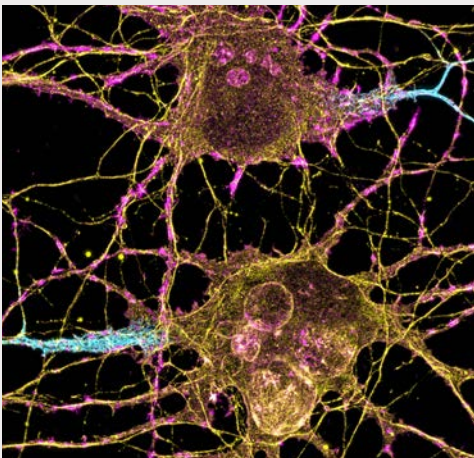
Specific forms of the tau protein are linked to different brain diseases.

Abnormal tangles of the tau protein form harmful structures in Alzheimer’s, frontotemporal dementia, and a number of other diseases, known collectively as tauopathies. Researchers have recently been able to describe the [3D structures of these tau forms](#), identifying distinct structures in different tauopathies. The findings could help scientists develop biomarkers that differentiate between diseases.

PROGRAM SPOTLIGHT

A NINDS initiative harnesses the power of single-cell technologies.

In 2021, NINDS launched a new basic research initiative for [identifying cellular signatures of Alzheimer’s and related dementias](#), such as frontotemporal dementia and Lewy body dementia. The aim is to encourage researchers to use cutting-edge technologies to examine disease-associated changes at the level of a single cell. This could help them identify how the most vulnerable brain cells change in the earliest stages of these dementias, which could ultimately better guide the development of biomarkers and therapies for these conditions.



Neurons. Credit: [Leterrier, NeuroCyto Lab, INP, Marseille, France](#)

The immune system contributes to brain aging.

Inflammation is part of the immune system's natural response to infection or injury, but it can also cause problems if it is not responding properly in specific circumstances. Recent research findings have linked inflammation and issues with the immune system to the development of Alzheimer's and related dementias.

- » Scientists discovered a process that [switches immune cells](#) from protecting the brain to driving inflammation. They found a way to block this process, improving cognition in older mice and suggesting a potential treatment for Alzheimer's and other cognitive diseases.
- » Another team of researchers identified "immune hubs" around the brain where the peripheral [immune system monitors the brain](#). In those hubs, cellular waste leaving the brain interacts with immune cells; this may initiate the inflammatory responses seen in Alzheimer's and other neurodegenerative diseases. The finding points to new ways to target brain inflammation.

- » The lymphatic system is a series of vessels running alongside blood vessels to carry immune cells and waste to lymph nodes. A recent study points to the importance of this [drainage system in removing amyloid buildup](#) in Alzheimer's. The findings suggest that anti-amyloid immunotherapies may be more effective if the drainage function of the lymphatic system is improved with certain therapies.
- » B cells are immune cells that make immunoglobulin, which could in theory target beta-amyloid plaques to slow the progression of Alzheimer's. However, researchers found that B cells [actually contributed to Alzheimer's progression](#) in mice because the cells penetrate the brain and deposit immunoglobulin around beta-amyloid plaques. Depleting B cells with a therapeutic antibody improved many aspects of the disease, suggesting a therapeutic strategy for humans.
- » In Lewy body dementia, abnormal deposits of alpha-synuclein protein form in the brain. Recently, researchers identified how a specific type of T cell involved in autoimmune diseases [may travel to the brain to destroy neurons](#). Their findings indicate that drugs already used to treat certain autoimmune diseases may block this undesirable T cell activity.

SCIENCE SPOTLIGHT

A specific hormone may be key to sex differences in Alzheimer's.

Women are at greater risk than men of developing Alzheimer's over their lifetimes. The disease also tends to get worse faster in women, who experience a broader range of cognitive symptoms.

One possible explanation for this difference in risk is follicle-stimulating hormone (FSH), which rises sharply in women around the time of menopause. In 2022, researchers found that giving FSH to both female and male mouse models of Alzheimer's [sped up the disease's progression](#). In contrast, blocking the hormone improved Alzheimer's symptoms in mice. NIA-funded research will expand on these initial results by conducting preclinical research to [test the safety and efficacy of humanized FSH-blocking antibodies](#).

- » The gene apolipoprotein E ϵ 4 (APOE4) is one of the most significant genetic risk factors for Alzheimer's and has been linked to several related dementias, but how it promotes neuron death is unclear. Using data from the NIA-funded [Alzheimer's Disease Knowledge Portal](#) and [ROSMAP](#), as well as mouse studies, researchers have found that high levels of [APOE4 in neurons trigger an immune pathway](#), leading to tau tangles and cell death.
- » Normally, APOE4 is made mainly by a type of brain cell called an astrocyte. In a study, selectively [deleting APOE4](#) in astrocytes lowered inflammation and neuron damage in mice, even after tau tangles had started to form. The results suggest that targeting APOE4 or its downstream effects could be a treatment strategy for Alzheimer's.

SCIENCE SPOTLIGHT

Understanding DNA repair in neurons has implications for Alzheimer's disease and related dementias.

Unlike other cells, neurons generally cannot be regenerated, making it especially important for our bodies to be able to repair damage to DNA in neurons. But the ability to repair DNA tends to decline with age. To learn more about how neurons maintain their DNA, NIA-funded scientists developed a technique called Repair-seq. Using Repair-seq, they found that when repairing DNA, [neurons prioritize certain “hot spots” in the genome](#) that contain essential genes.

When they examined the proteins made from the genes associated with hot spots, the researchers discovered that some of these proteins showed changes similar to those seen in Alzheimer's. This finding suggests that problems with DNA repair may contribute to the onset or progression of the disease. Repair-seq offers a powerful new tool for exploring the role of DNA repair during the aging process.

Exercise may help protect against brain inflammation.

Evidence suggests exercise may help slow cognitive decline in older adults and may be associated with a lower risk of Alzheimer's disease. Findings from two new studies have helped clarify how inflammatory pathways may link exercise and brain health:

- » An [anti-inflammatory protein called clusterin](#) rises in the blood in people who have exercised regularly. Clusterin binds to the blood vessels in the brain and reduces the expression of genes associated with inflammation.
- » In a mouse model of Alzheimer's, [mice engineered to make a hormone called irisin](#), which is induced by exercise, performed better on cognitive tests and had less brain inflammation than mice without the hormone. These results suggest that irisin could have a therapeutic benefit in Alzheimer's and other cognitive disorders.

The brain's “cleaning system” declines during Alzheimer's disease.

The body has a system for clearing out damaged proteins from cells. But scientists found that this process [declines in a mouse model of Alzheimer's](#), growing worse as the disease advances. Encouragingly, an experimental drug developed by the team to boost this process reduced Alzheimer's symptoms in these mice.



Lifestyle, Behavior, and Cognitive Training Intervention Research

As scientists continue to develop and test new interventions for Alzheimer's and related dementias, they recognize that non-drug approaches such as healthy lifestyle behaviors may play important roles in prevention, treatment, and care. NIH funds research on ways to prevent or slow these diseases without drugs.

Clinical trials on non-drug interventions show promise in preventing or slowing the development of Alzheimer's and related dementias.

Dementia-related changes in the brain start a decade or more before symptoms appear. Lifestyle, behavioral, and cognitive training interventions may help people lower their risk of dementia earlier in life and [protect their brain health](#) as they age.

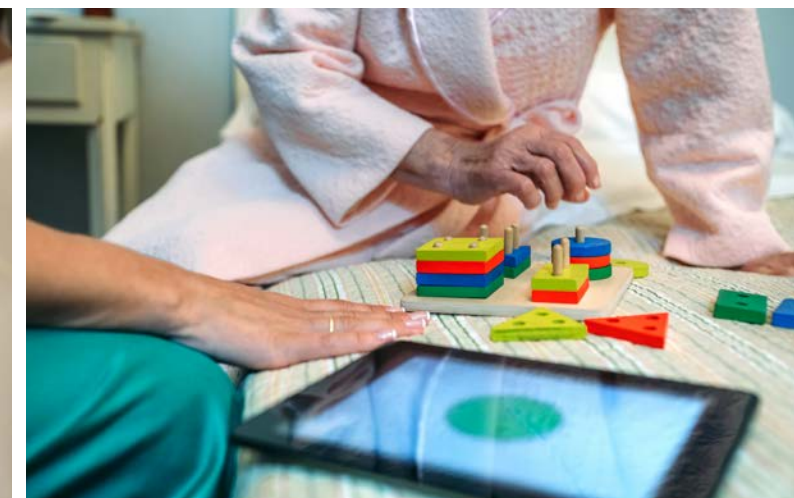
NIH is dedicated to further studying the impact of blood pressure control, regular exercise, and other non-drug interventions on dementia prevention and care. The agency currently funds [more than 130 clinical trials](#) testing these types of approaches in the following broad areas:

- » Physical activity
- » Cognitive (e.g., memory) training
- » Neurostimulation, which involves electrical stimulation to specific areas in the brain
- » Sleep-related interventions
- » Diet and dietary supplements
- » Combination therapy, which involves the use of two or more interventions

Compared to drug options, many non-drug interventions are less invasive and less expensive and may be less likely to cause harmful side effects. When a population

study identifies a strong association between a lifestyle factor and dementia, one of the next steps is to test the intervention in a clinical trial. This can shed light on whether the lifestyle factor reduces risk of dementia in people who adopt it. The following are some examples of non-drug interventions currently being tested in NIH-funded clinical trials:

- » [Cognitive training to improve brain function](#) in older adults with Alzheimer's or a related dementia and delirium
- » Personalized computerized cognitive training to improve brain health in [older adults with memory loss](#) or MCI
- » [Mobile-health technology](#) to motivate people with MCI to stick to game-based training at home
- » Cognitive training to [promote independent living skills](#) in older adults with MCI
- » Using a new [interactive exercise and cognitive training system](#) for in-home use to improve or maintain brain function in people with MCI



- » Using [cocoa flavanols to boost brain function](#) by reducing inflammation in healthy older adults
- » Combining [cognitive training and a diet high in polyphenols](#) to prevent or delay cognitive impairment in older adults with lower education levels

If effective, these non-drug interventions hold promise to be implemented broadly at the community level through evidence-based dissemination approaches that ensure they reach the most people possible, especially at-risk groups. This in turn could help improve health equity in dementia prevention and care.

Lifestyle, behavioral, and cognitive training interventions may help people lower their risk of dementia earlier in life.

RESEARCH SPOTLIGHT **Speed of processing training may delay cognitive impairment.**

Results from a secondary data analysis of the NIH-funded [Advanced Cognitive Training and Vital Elderly \(ACTIVE\)](#) study suggested that a specific type of cognitive training, called speed of processing training (SPT), may significantly delay cognitive impairment over a 10-year period.



Based on this finding, NIA awarded a research grant to the University of South Florida to support a [large-scale, randomized controlled study](#) to clarify whether SPT reduces or delays the onset of clinically diagnosed MCI or dementia in older adults. Researchers estimate that if SPT can delay dementia onset by just one year, there would be 9 million fewer cases by 2050 than currently projected.

NIH is effectively addressing the urgent need for more research on social and behavioral interventions for dementias.

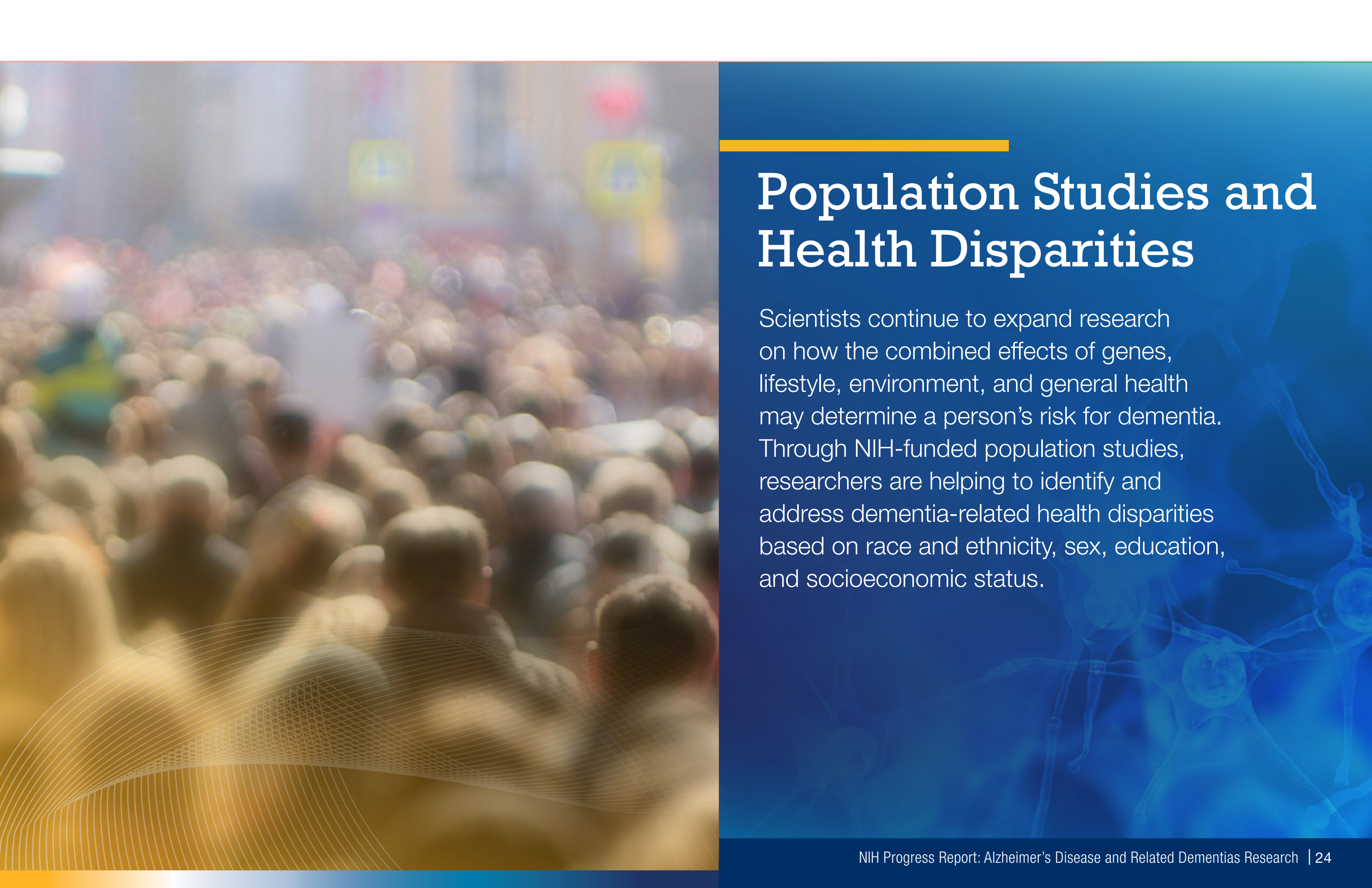
A National Academies of Sciences, Engineering, and Medicine consensus study, sponsored primarily by NIA with support from co-funders, offers a blueprint for the next decade of social and behavioral science research on Alzheimer's and related dementias. The study suggested that as many as 40% of dementia cases might be caused by risk factors that can be controlled and that social and behavioral changes could have a clear, measurable impact on dementia prevention and treatment.

This [study report, released in 2021](#), features a proposed 10-year research agenda that prioritizes the following areas, which are likely to have the greatest impact:

- » Innovative interventions that improve dementia prevention and treatment, and policies that promote the dissemination of those interventions for widespread use

- » Strategies to promote health equity across all communities
- » Policies to lower the economic burden caused by dementias, including providing affordable health care and housing, protection from financial abuse, and access to critical services
- » Approaches to improve the dementia research pipeline

Through these and related efforts, NIH's social and behavioral science research can help lower the impact of Alzheimer's and related dementias in the United States and across the world.



Population Studies and Health Disparities

Scientists continue to expand research on how the combined effects of genes, lifestyle, environment, and general health may determine a person's risk for dementia. Through NIH-funded population studies, researchers are helping to identify and address dementia-related health disparities based on race and ethnicity, sex, education, and socioeconomic status.

Program Update

An NIH genomics data program enables population studies around the world.

NIH established the [Alzheimer’s Disease Sequencing Project \(ADSP\)](#) in 2012 to sequence and analyze genomic data from large Alzheimer’s studies conducted worldwide. The 2022 overarching goals are to:

- » Identify new gene variants that increase the risk of Alzheimer’s and related dementias
- » Identify gene variants that protect against dementia
- » Provide insights into why some people with known risk factor genes do not develop dementia symptoms
- » Identify potential avenues for therapeutic approaches to prevent or treat dementias
- » Examine all of these factors in diverse populations

ADSP data have revealed several potential genetic risk or protective factors for Alzheimer’s. For example, in 2021, researchers found that although genome-wide association studies and family-based studies often identify different sets of Alzheimer’s-related genes, many of these genes [function in the same or similar processes in brain cells](#). This strengthens evidence for the involvement of specific underlying processes in the disease. To understand how these and other gene variants lead to Alzheimer’s, NIA funded six projects in 2021 through the [ADSP Functional Genomics Consortium](#), which will utilize a multipronged team science strategy and large-scale, high-throughput approaches.

Also in 2021, ADSP researchers launched two important initiatives:

- » The [Phenotype Harmonization Consortium](#) is a major effort to combine and organize clinical data from all ADSP studies and share these data with the research community, with the goal of stimulating new drug development. The consortium’s efforts will improve the usability of ADSP data and facilitate research to identify well-targeted therapeutic approaches for Alzheimer’s and related dementias.
- » The [ADSP Follow-Up Study 2.0: The Diverse Population Initiative](#) will expand ADSP data to represent a more diverse population. Current ADSP data are derived mostly from White clinical study participants, and results based



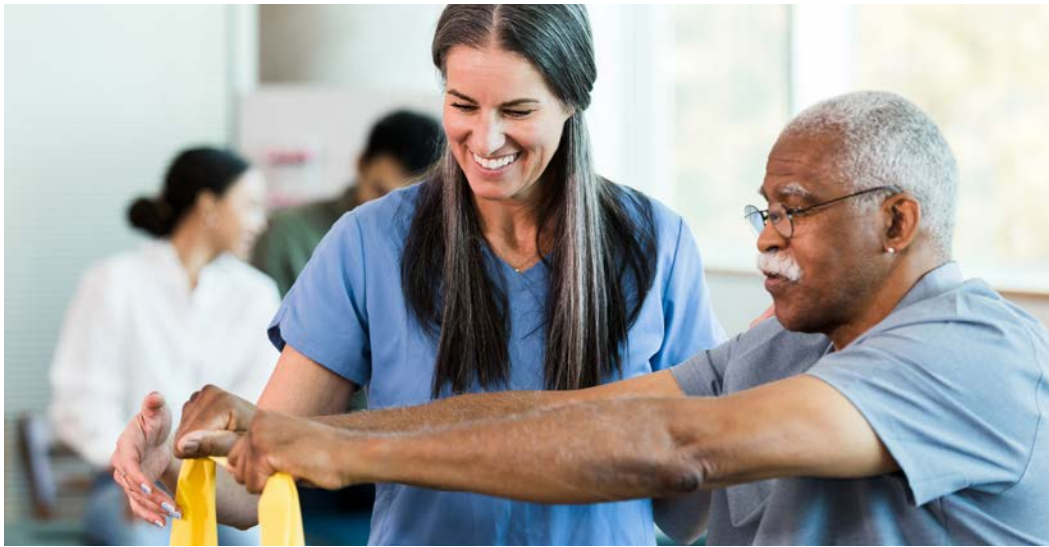
on these data might not be an accurate reflection of the genetic factors linked to Alzheimer’s disease in all populations. The new follow-up study will help researchers identify not only common gene variants but also rare variants that may play an important role in Alzheimer’s and related dementias.

Through NIH population studies, researchers are finding new links to brain changes associated with Alzheimer’s and related dementias.

Dementia-related brain changes can start a decade or more before a person experiences symptoms and may result from a complex interplay among abnormal tau and beta-amyloid proteins and several other factors. Recent results from the following NIH-funded studies shed more light on how brain health in general affects the risk of developing Alzheimer’s:

Dementia-related brain changes can start a decade or more before a person experiences symptoms.

- » People who have Alzheimer’s often have [multiple types of brain lesions](#), and this is more common in people with worse symptoms of dementia. Data from 5,272 individuals from the [National Alzheimer’s Coordinating Center](#) showed that most people with Alzheimer’s have both brain changes that are specific to the disease, such as tau tangles and amyloid plaques in the case of Alzheimer’s, and brain changes more commonly associated with other related dementias.
- » People who have a stroke that is moderate or severe or who have multiple strokes may have a significantly [higher risk of dementia than people who have had a mild stroke](#). According to data from more than 1,000 participants in the NIH-funded [Atherosclerosis Risk in Communities](#) cohort study, people who have two or more moderate or severe strokes are almost seven times more likely to develop dementia when compared with people who have not had a stroke. Having a stroke before age 75 can also significantly



raise the risk of dementia. The findings emphasize the importance of stroke prevention as a means of mitigating dementia risk.

- » People who develop [mental disorders early in life](#) have an increased risk of all types of dementia and of developing dementia at a younger age. These findings, obtained from an analysis of hospitalization records for 1.7 million individuals from New Zealand’s national health system, suggest that effectively treating mental disorders earlier in life may lower the risk of developing dementia.

RESEARCH SPOTLIGHT **NIH funding helps to unravel links between dementia and COVID-19, and other infectious diseases.**

NIH is playing a critical role in [COVID-19](#) response efforts concerning older adults, who are at a much greater risk of severe illness and death from this infectious disease. For example, in 2021, an NIA-funded study based on the electronic health records of about 61.9 million U.S. adults from all 50 states showed that people with any type of dementia have [twice the risk of getting COVID-19](#) when compared with people without dementia. People with dementia are also more likely to have severe or fatal cases of COVID-19, and this risk is even higher for Black people living with dementia.

Also in 2021, NIA hosted a [workshop](#) to update the research community on progress being made through its funded COVID-19 research projects. Presenters described results from early studies in the following areas:

- » The effect of COVID-19 infection on brain health
- » Aging-related risk factors in COVID-19 vulnerability
- » COVID-19 resilience in older adults
- » Dementia care, caregiving, and psychosocial outcomes during the pandemic
- » Efforts to develop therapies for COVID-19
- » Tools and models for coping with a pandemic
- » COVID-19 epidemiology

Current [NIA and NINDS studies](#) are expanding knowledge of how COVID-19 affects brain health in older adults with and without dementia, including the effects of prolonged symptoms of COVID-19, technically called post-acute sequelae of SARS-CoV-2 infection (PASC) and more commonly referred to as “long COVID.”

In 2021, NIH launched the Researching COVID to Enhance Recovery (RECOVER) Initiative, a [patient-centered study of national scale with thousands of diverse participants across the lifespan](#), which will include research into the disease’s effects on cognition, cognitive decline, and dementia.

NIA has also funded a number of research projects on whether viral infections and other microbial pathogens contribute to Alzheimer’s disease. NIA held a [workshop on the infectious etiology](#) of Alzheimer’s in 2021. Additionally, in a study partially funded by NIA, researchers discovered [a link between mononucleosis and Alzheimer’s](#) disease.

NIH-funded population studies analyze genetic risk factors for Alzheimer's.

The NIA [Genetics of Alzheimer's Disease Portfolio](#) supports research to identify genes that raise or lower the risk of Alzheimer's and to understand how these genes influence the processes in cells that lead to the disease. To date, scientists have identified more than 70 genetic regions associated with Alzheimer's.

The *APOE4* gene variant has been found to be one of the most significant genetic risk factors for Alzheimer's; however, the link between *APOE4* and Alzheimer's risk differs between racial and ethnic groups. For example an NIA-supported study published

in 2022 found that the [APOE4 variant is not linked to dementia-related brain changes or cognitive impairment in American Indians](#).

APOE4 is linked with Alzheimer's risk in people of African ancestry, [but not to the same degree as in people of European ancestry](#). A recent study helps explain why this may be the case. It found that people of [European ancestry have higher levels of APOE4 protein in their brains than people of African ancestry](#). The authors think that the region around the *APOE4* gene differs by ancestry and controls how much *APOE* protein is made. These findings and the critical nuances in *APOE4* and disease risk by population group underscore the importance of studying Alzheimer's in diverse populations.

Other recent discoveries from NIH-funded studies include:

» In people of European ancestry, an Alzheimer's [polygenic risk score](#) (an estimate of a person's risk of Alzheimer's based on many known genetic risk factors) gives an accurate estimate of the risk for the disease. However, the risk score, which was made from studies involving mostly people of European ancestry, was not a good predictor in people of African ancestry. This highlights the importance of more diverse population studies in order to determine specific genetic risk factors across racial and ethnic groups and create polygenic risk scores that apply to people of non-European ancestry.

» [Specific regions of DNA](#) may control the levels of proteins linked to neurological disorders in various tissue types. Proteins that are controlled by the same regions of DNA may work together in a biological process to raise or lower a person's risk of dementia.

» A new technique examines how [changes to a gene will affect the 3D structure of proteins](#) made from that gene, which can help scientists identify rare gene variants linked to Alzheimer's. Using the new method, researchers identified new variants of four genes, two of which (*TREM2* and *SORL1*) are known to be linked to the disease. The other two are *CSF1R*, which has been suggested to contribute to Alzheimer's but not confirmed; and *EXOC3L4*, a novel Alzheimer's risk gene. Because changes to a protein's structure can interfere with its function, studying these new gene variants can help researchers understand the roles these genes play in raising the risk of dementia and how to use this information to develop new therapeutic targets.



To date, scientists have identified more than 70 genetic regions associated with Alzheimer's.

Health disparities negatively affect dementia diagnosis and care.

Following specific priorities identified using its [Health Disparities Research Framework](#), NIA has awarded grants to explore the environmental, sociocultural, behavioral, and biological determinants of health disparities related to aging. In 2021, findings from these studies underscored the following:

- » Among people who participate in research studies on Alzheimer’s, Black participants with symptoms of the disease are [less likely to have received a clinical diagnosis of Alzheimer’s](#) than White participants. Additionally, Black participants with Alzheimer’s have more risk factors for the disease and more severe symptoms than White participants. Another study showed that racial disparities in dementia prevalence between Black and White individuals [did not improve from 2000 to 2016](#).
- » [While researchers found that more people living with dementia received a dementia diagnosis from 2006 to 2013](#), the condition is still underdiagnosed in Black and Hispanic individuals, highlighting the need for improved diagnostic methods among racial and ethnic minority populations.

In this study, researchers compared the number of people diagnosed with dementia using three sources of data: cognitive tests, detailed neuropsychological tests, and diagnosis codes from Medicare claims. They found that over the years, the difference in estimated prevalence of dementia from these three data sources has lessened, showing that dementia underdiagnosis is decreasing overall.

- » Compared with older adults living in urban areas, older adults who live in rural communities are [less likely to receive a clinical diagnosis of Alzheimer’s](#) or a related dementia, are often diagnosed at later stages of dementia, and have a shorter survival time after diagnosis. Increased measures to promote dementia screening in rural areas could help address these disparities.
- » People who [do not have easy access to primary care](#) have a higher risk of cognitive impairment. Improving health care access may help lower the risk of cognitive decline and dementia.



Differences between men and women are associated with disparities in dementia risk.

Differences between men and women have been shown to affect Alzheimer’s and other neurological disease outcomes. NIH research is helping to increase our understanding of how the risks of developing these diseases are influenced by both biological and social factors. This research could help advance personalized treatment options and population interventions for both men and women. In 2021, NIH-funded scientists made these discoveries:

- » DNA methylation patterns that are linked to Alzheimer’s are [different in men and women](#). DNA methylation, a process that



involves chemical modification to DNA, helps control how much of a specific protein the body makes and can turn a gene on or off. These findings shed light on the biological factors that play a role in dementia prevalence. The results may help scientists identify new biomarkers and therapeutic targets for dementias.

- » [Access to education may contribute to differences](#) in Alzheimer’s risk between men and women. The difference in dementia risk between women and men is more significant in older age groups, in which women tend to have a lower level of educational achievement than men. In age groups in which women have a similar education level to men, there is a smaller gap in dementia risk.

Managing early cardiovascular, metabolic, and lifestyle risk factors may modify dementia risk.

Results from NIH-funded population studies in 2021 and 2022 continue to provide insights on how taking steps to keep the body healthy may also slow cognitive decline and lower the risk of developing dementia. These findings include:

- » [People who have risk factors for cardiovascular disease](#), such as a high body mass index, high fasting glucose levels, and high blood pressure in early adulthood, have a higher risk of cognitive impairment later in life. Treating these conditions may help preserve brain health.
- » [People who develop type 2 diabetes at a younger age](#) have an increased risk of dementia and are more likely to have the disease at a younger age. People who have diabetes along with cardiovascular diseases such as coronary heart disease, heart failure, or stroke have an even higher risk.
- » Men who have lower levels of bile acids (made when the body breaks down cholesterol) are more likely to have [higher levels of amyloid protein in the brain and a higher risk of dementia](#).
- » Medium to high [physical activity is associated with slower rates of cognitive decline](#), especially in people with high levels of tau in their blood. Tau protein builds up into tangles in the brain in Alzheimer’s, and higher levels of tau are linked to cognitive decline and an increase in memory and thinking problems.
- » [Sleep patterns earlier in life may contribute to later dementia risk](#). People in their 50s and 60s who get six hours of sleep or less are 30% more likely to be diagnosed with dementia than people who get at least seven hours per night. Another study found that about [15% of older adults routinely take medication](#) to improve sleep and that frequent use of sleep medication is linked to a higher risk of dementia.
- » Taking care of oral and eye health may help lower dementia risk. A study found that [older adults with tooth loss](#) have a higher risk of cognitive impairment and dementia. This risk increases with each missing tooth. However, using dentures mitigates this risk. Another study showed that for older adults with cataracts,

STUDY SPOTLIGHT

A large population-based study of women’s health shows links between common cardiovascular conditions and brain health.



New findings from the NIH-funded [Study of Women’s Health Across the Nation \(SWAN\)](#) show that [a woman’s health in midlife](#) can strongly affect her brain and heart health as an older adult. Cardiovascular risk factors such as high blood sugar, diabetes, belly fat, and an unhealthy heart during midlife are linked to a higher risk of cognitive decline. Future

SWAN research will continue to provide insights into normal aging and the risk factors for dementia and other common age-related health conditions in women from diverse communities.

Since the 1990s, SWAN has been collecting data on more than 3,000 women from diverse racial and ethnic groups to understand the links between life experiences in midlife and health and quality of life during aging.

[surgery to remove the cataracts and improve eyesight lowers the risk of developing dementia](#). The study controlled for factors such as health, education, and access to health care. The authors suggest restoring sensory functions such as vision may be useful in reducing dementia risk.

- » A recent study reported that, while high blood pressure in midlife is linked to a higher risk for dementia, [higher blood pressure levels are associated with a lower risk in people 60 to 70 years old](#). However, for those older than 75, both low and high blood pressures are linked to decreased dementia risk — a U-shaped association reported in other studies as well. This research points to a potential need for age-tailored blood pressure management that takes individuals' health context and life expectancy into consideration. These observational study results contradict evidence from randomized controlled trials, including the NIA-supported Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension (SPRINT MIND) study, which suggested that controlling high blood pressure [can reduce dementia risk](#) at all ages studied.

The authors of the recent study speculate that the novel association that they observe may be because their cohorts consist of a broader, older population rather than a specific subgroup of older people with high blood pressure and other cardiovascular risk factors.

Social connections can affect dementia risk.

Understanding how social interactions and educational achievement affect cognitive health in older adults can help inform future evidence-based interventions. Findings from recent NIH-funded studies reveal how these factors are linked to risk of cognitive decline and dementia:

- » Among older adults in male-female marriages, [men who have good-quality marriages](#) have better cognitive health and slower cognitive decline than [men who have poor-quality marriages](#) and marital stress. Men who are widowed during midlife have a greater risk of cognitive impairment as older adults. Neither marital quality nor widowhood was associated with cognitive health in women after accounting for variability in sociodemographic factors and resources. Interventions to improve marital quality or





socially engage midlife widowers might lower the risk of cognitive decline among older men. While these studies focused on marriages between women and men, research is underway to explore the link between cognitive health and marriage or cohabitation in same-sex couples.

- » Another study found that, for individuals who experience [divorce or widowhood during midlife](#), finding a new partner lowers risk of cognitive impairment as older adults.
- » Individuals who have both a large, diverse, and interconnected social network and a small, tight-knit, and intimate group of close family and friends [have a lower risk of dementia](#). People with these types of social networks

have both cognitively enriching and supportive social interactions, which are both associated with better brain health. Adults between 60 and 79 years who feel [lonely three or more days a week have a higher risk of developing dementia](#) within 10 years than those who are lonely less often. The link was especially strong for people with low

genetic risk for dementia. Measuring loneliness, especially in individuals at lower risk for Alzheimer's disease, may be important for early detection of dementia and may help identify individuals who would most benefit from interventions to improve social connections.

Measuring loneliness, especially in individuals at lower risk for Alzheimer's disease, may be important for early detection of dementia.

Personality traits can point to future dementia risk.

In 2021, results from the NIA-led and -funded Baltimore Longitudinal Study of Aging linked certain [personality traits to dementia-related brain changes](#).

Among cognitively normal individuals, people who scored higher on neuroticism (a personality trait often associated with anxiety, self-doubt, and depression) had more amyloid and tau deposits in their brain. Conscientiousness is associated with being self-disciplined, responsible, organized, and focused on achieving goals. People with lower conscientiousness scores also had more amyloid and tau, suggesting that personality traits may help protect against the neuropathology of dementia before symptoms, such as cognitive impairment, occur.



Clinical Study Recruitment Initiatives to Enhance Diversity

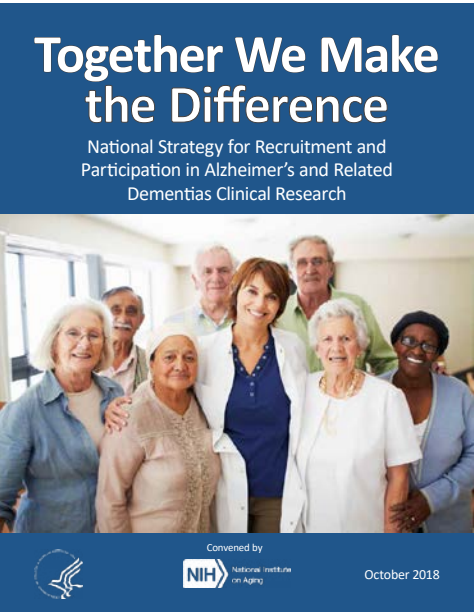
NIH is currently funding more than 400 active Alzheimer's and related dementias prevention, treatment, and caregiving clinical trials. Of these, approximately 200 are testing interventions for effective prevention and treatment of these diseases, and others are testing dementia care and caregiving interventions. To ensure that findings will be relevant for all people, clinical trials must include participants who reflect the diversity of the U.S. population.

NIH continues to invest in initiatives to support the recruitment of participants from various races, ethnicities, genders, ages, and socioeconomic statuses. These investments — including grants for new recruitment approaches, resources for creating culturally sensitive recruitment materials, and innovative tools to monitor outreach and recruitment — are helping scientists and clinicians better reach groups that have been historically underrepresented in biomedical research. In addition, NIH is working to move beyond the confines of large academic medical centers to work more closely and directly with communities on research into Alzheimer’s and related dementias.

NIA’s new online tool can help boost participation in dementia clinical studies.

In 2021, NIA launched [Outreach Pro](#), a tool that helps researchers, clinicians, and local communities increase awareness of and participation in clinical trials involving Alzheimer’s and related dementias. Outreach Pro provides resources to create customized recruitment materials, in multiple languages, for African American/Black, Hispanic/Latino, and Asian American and Pacific Islander potential study participants.

Outreach Pro is an integral part of NIA’s efforts to implement the [National Strategy for Recruitment and Participation in Alzheimer’s and Related Dementias Clinical Research](#).



Its recruitment resources include websites, brochures, fact sheets, social media posts, photos, videos, and motion graphics. These materials incorporate culturally sensitive, nationally tested messages, taglines, concepts, and images that resonate within specific communities.

RESEARCH SPOTLIGHT

NIA study underscores that clinical trial data must be representative of all communities.



In 2021, an [NIA-funded study](#) found significant differences in the extent to which sociodemographic, health, and genetic risk factors were linked to cognitive and neuroimaging results for dementia based on the study population. Researchers compared data from two other NIH-funded studies: the clinic-based [Alzheimer’s Disease Neuroimaging Initiative \(ADNI\)](#), whose participants are predominantly White, and the community-based [Atherosclerosis Risk in Communities \(ARIC\)](#) study, which includes Black and White participants. The findings reinforce that the results identified in a single population cannot be assumed to represent the population as a whole and that studies that include participants from diverse backgrounds are critical to establishing a holistic understanding of population and individual-level health outcomes.

In 2021, NIA began working with all researchers conducting NIA-funded clinical trials to enter enrollment data into CROMS each month.



An NIA repository provides a wealth of additional resources for clinical trial recruitment.

NIA's [Alzheimer's & Dementia Outreach, Recruitment, and Engagement Resources \(ADORE\)](#) is a repository of additional resources for engagement, recruitment, and retention of clinical trial participants. Researchers can search for materials by keyword, explore by tag, or review a wide range of topics to find materials that work best for their study. The repository houses materials to help researchers plan their recruitment strategies and engage specific populations. ADORE also enables researchers to share their recruitment resources, helping to amplify the impact of successful recruitment and retention tools. In 2021, this tool was accessed nearly 30,000 times.

Monitoring clinical trial enrollment will help address challenges.

NIA's [Clinical Research Operations & Management System \(CROMS\)](#) offers real-time tracking, reporting, and management of clinical trial enrollment data, study documents, and study activities. In July 2021, NIA began working with all researchers conducting NIA-funded clinical trials to enter enrollment data into CROMS each month. The ability to closely monitor participant enrollment data enables NIA staff to help researchers address enrollment challenges promptly and work toward improving the enrollment of underrepresented communities in dementia clinical trials. To date, every NIA-funded trial as of July 2022 has an entry record in CROMS.

NIH leads new recruitment strategies to encourage clinical trial participation.

In 2022, NIA released a [Request for Information \(RFI\)](#) to learn more about using community-based research networks to promote the inclusion of underrepresented

populations in clinical research. The goal is to extend beyond traditional academic and medical research centers partly by working with community-based clinicians, primary care centers, assisted living facilities, and other organizations to reach people who could participate in studies focused on Alzheimer's and related dementias. The majority of the RFI responses were supportive of the need for consistent, sustainable, and authentic community engagement, including community-based research networks, to increase diversity in clinical trial participants and to overcome some of the systemic and persistent challenges, such as lack of trust and resources, research logistic challenges, and communication issues. With NIH funding, the networks could play a significant role in developing interventions that improve the lives of all people living with dementia, their caregivers, and their communities.



Dementia Care and Caregiver Support Studies

Alzheimer's disease and related dementias place a huge burden on families, caregivers, and society. With NIH funding, researchers continue to make progress in better understanding the impact of these diseases, addressing emerging support needs for people living with dementia and their care partners, and improving equity in health care access for people living with these diseases.

A significant majority of older adults with dementia and other health conditions still engage in meaningful activities.

In 2021, a national survey of [older adults not living in nursing homes](#) found that many older adults engage in meaningful activities despite having dementia, depression, or a disability. The survey showed that 74% of participants with dementia regularly engage in meaningful activities, compared with 84% of participants without dementia. Fifty-six percent of participants with a disability, 68% of those with depression, and 35% with dementia, a disability, and depression reported engaging in meaningful activities. Encouraging people who have dementia to engage in activities they enjoy, such as reading, socializing with others, or engaging in physical activity such as walking may help improve their quality of life.

Emerging care delivery models may help promote health equity.

Over the past year, NIH-funded study findings have shed light on health disparities in dementia care and helped foster concrete measures to promote health equity.

» [Accountable Care Organizations \(ACOs\)](#) are groups of doctors, hospitals, and other health care providers who come together voluntarily to give coordinated high-quality care to the Medicare patients they serve. Policies that make ACO-affiliated hospitals available to more people may increase health equity in dementia care. Hospitals with ACO affiliations have [fewer preventable hospitalizations for people with dementia](#), but Black individuals with Alzheimer's are less likely to receive care at such facilities than White individuals.

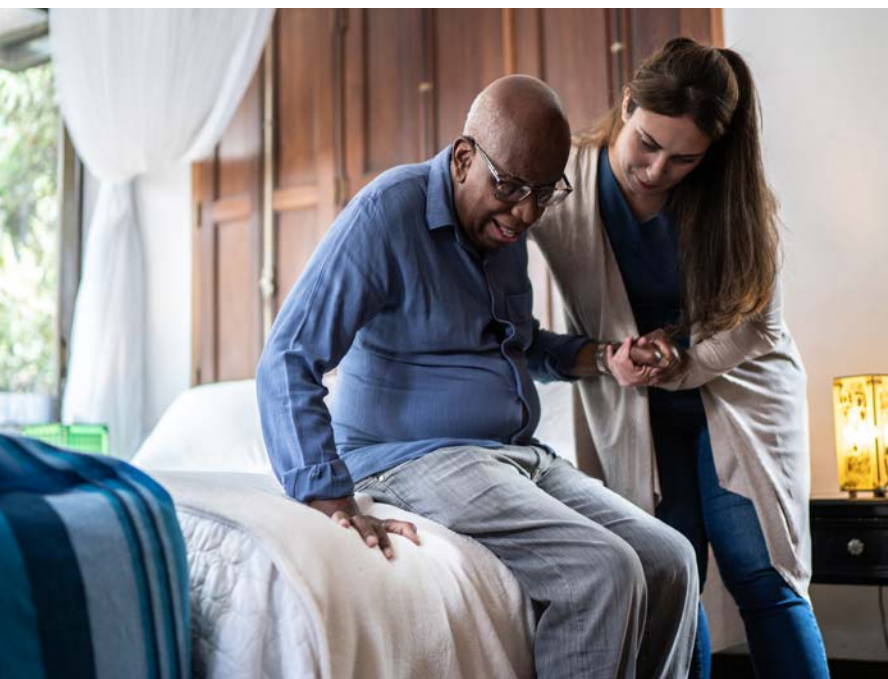
A national survey showed that

74%

of participants with dementia regularly engage in meaningful activities.



» Improving access to ACO-affiliated hospitals in rural areas could help decrease preventable emergency department visits for dementia patients. Hospitals affiliated with ACOs have a [lower likelihood of preventable emergency department visits](#) than those without an ACO affiliation, whether urban or rural. Because rural areas frequently lack specialists who treat cognitive impairment, people with dementia living in rural areas generally make more visits to an emergency department than those living in urban areas. ACO models of care coordination may help reduce this rural/urban disparity.



» There is an ongoing effort to provide long-term services and support for older adults in home- and community-based settings instead of in nursing homes. However, the number of [Black and Hispanic older adults receiving nursing home care has increased](#) over the past 11 years, while the number of White older adults in nursing homes has declined. The authors suggest that state Medicaid programs could help fill gaps in funding to enable more non-White older adults to receive long-term care at home.

These studies suggest that innovative care delivery and payment models can improve care quality and prevent avoidable health care utilization among high-need, high-cost, and diverse populations with Alzheimer's and related dementias.

State Medicaid programs could [help fill gaps in funding to enable more non-White older adults to receive long-term care at home.](#)

RESEARCH SPOTLIGHT

For people living with dementia, having a family member available to help reduces the need for paid care.



People with worsening dementia increasingly have trouble caring for themselves and need the support of one or more caregivers. A 2021 NIA-funded study found that women, Black

individuals, and people with lower incomes are [more likely to have adult children as unpaid caregivers](#) than men, White individuals, and those with higher incomes. Having an adult child lowers the likelihood of a person receiving care in a nursing home.

Men, White individuals, and those with higher incomes, on the other hand, are more likely to have a spouse available for unpaid care. The study provided national estimates of the availability of family caregivers that may help experts predict on a large scale whether people with dementia will need paid care. These findings could help determine policies for developing an equitable national caregiving system that considers both paid and unpaid care for people with dementia.

RESEARCH SPOTLIGHT

For older adults living with dementia, multiple prescription medications may increase health risks.

In 2021, results from an NIA-funded study showed that nearly 14% of older adults with dementia who do not live in nursing homes are prescribed [three or more medications affecting the central nervous system](#), including the brain. Taking a combination of such drugs can increase the risk of falling, breathing issues, and heart problems, and can also affect thinking and memory. A separate NIA-funded study of Midwest nursing home residents with dementia identified [small but statistically significant increases in antidepressant and opioid prescriptions](#) issued during the COVID-19 pandemic.

In both of these cases, better understanding how these medications are used, their effects, and associated risks could help health care providers and dementia patients make safer, more informed care decisions.

Difficulty managing medications may be an early predictor of dementia.

An NIH-funded 2021 study found that having trouble managing medications may be a risk factor for developing dementia. The researchers compared data from people diagnosed with Alzheimer's or a related dementia with data from those who were not. They found that those who were eventually diagnosed with Alzheimer's were [four times more likely to have had trouble managing their medications](#) one to two years prior. The findings suggest that older adults who struggle with this daily task might need a detailed cognitive screening even in the absence of other dementia symptoms. This approach is especially important for racial and ethnic minorities, who are at higher risk of not receiving a clinical diagnosis of dementia.

The COVID-19 pandemic has had a considerable impact on dementia patients and their caregivers.

The COVID-19 pandemic put enormous economic, social, and psychological strains on the health care system and society at large. In the past year, these NIH-funded

studies revealed ways in which the early stages of the pandemic affected people living with dementia and their caregivers:

- » Soon after the pandemic started, people with cognitive impairment who were over age 60 and lived alone experienced [significant distress, including fear, confusion, loneliness, and yearning for former social activities](#).
- » In Virginia, almost 50% of caregivers for people with dementia living in rural areas [felt exhausted and overwhelmed](#) within two weeks of the state's stay-at-home order going into effect. These caregivers also expressed concerns about reductions in the availability of care aides and support from family and friends due to COVID-19.

These studies indicate that dementia patients and their caregivers would likely benefit from having expanded access to home care aides and mental health services, especially during times of increased infectious disease risk and uncertainty.





Research Enterprise

NIH maintains momentum in Alzheimer's disease and related dementias discoveries through a broad range of strategies and policies aimed at continued advancement of the research enterprise. The agency invests in highly collaborative and innovative research approaches, including resources for sharing data and other knowledge, and in leveraging the broad and varied strengths of scientists from diverse backgrounds and areas of expertise.

New research models help scientists better understand dementias.

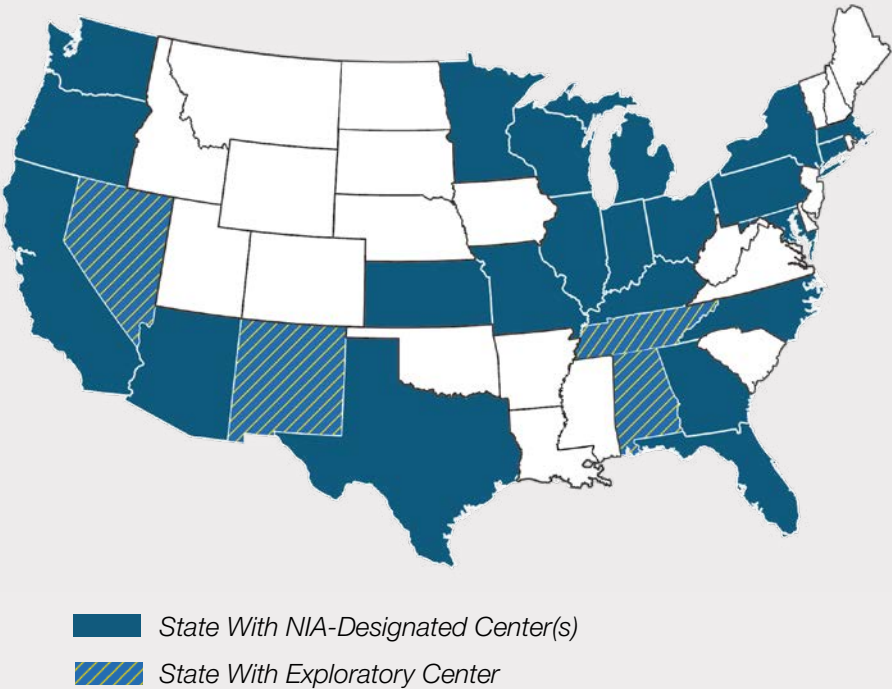
NIH-funded science continues to make significant strides in creating and improving upon research models for studying dementia. For example:

- » Using an innovative technology that enables scientists to turn skin cells back into stem cells and further into neurons, scientists have been able to develop “mini-brain” research models for studying frontotemporal dementia (FTD). Through this approach, scientists have discovered the sequence of damaging events that causes brain cells to die in people who have FTD. The new model was developed from the voluntarily donated cells of people who had a gene variant that raises the risk of developing FTD.
- » Innovative “disease-in-a-dish” models for Alzheimer’s enable scientists to study the biology of dementias in ways that more closely represent the disorder in the human brain. These models were created from cells voluntarily donated by research study participants who either had Alzheimer’s or no signs of the disease. The use of these technologies can help us more accurately model Alzheimer’s and other dementias in isolated human cells and tissues before potential treatments or therapies are ready for testing in living humans.

PROGRAM SPOTLIGHT

NIA’s Alzheimer’s Disease Research Centers broaden and advance dementia research nationwide.

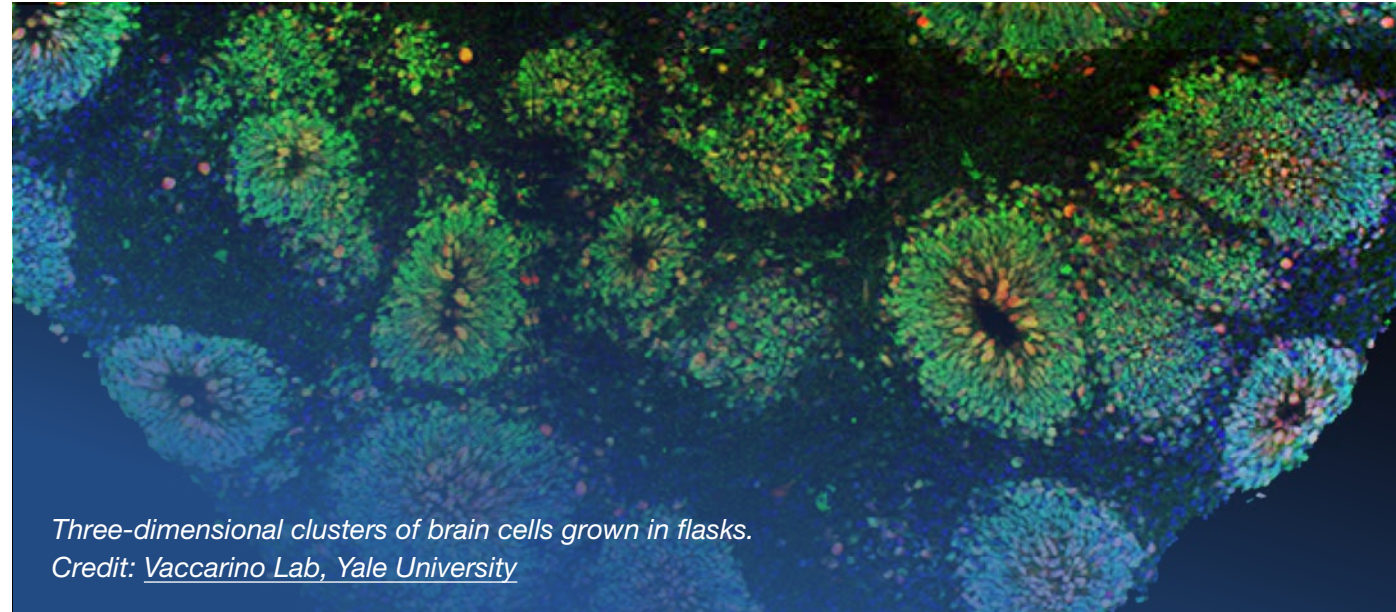
NIA-funded [Alzheimer’s Disease Research Centers \(ADRCs\)](#) are a cornerstone of Alzheimer’s and related dementias research in the United States. In the more than 30 years since the ADRC program was initiated, it has [expanded](#) to 33 centers covering diverse urban and rural population centers across the U.S.



ADRCs have been at the forefront of several major advancements in Alzheimer’s and related dementias research, including playing a major role in developing a biological framework for Alzheimer’s that defined the disease signatures for researchers and clinicians. ADRC investigators also played a critical role in identifying and describing the Alzheimer’s-like LATE disorder (limbic-predominant age-related TDP-43 encephalopathy), the pathology of which has been found to be responsible for many of the cases of dementia previously assumed to be Alzheimer’s.

ADRC scientists openly share data, biological samples, and other significant research resources to support patients and their caregivers. Clinical research conducted through the ADRCs helps broaden research and education opportunities for underrepresented communities, including African Americans, Native Americans, and people who live in rural areas.

- » A new approach to [making patient-derived neurons](#) grows donated skin cells from people with Alzheimer's in the laboratory and converts them directly into neurons. These new brain cells (called induced neurons) can help researchers study Alzheimer's in living cells.
- » A new [rhesus macaque model of Alzheimer's](#) could be more useful than existing animal models in finding treatments for the disease. By introducing an abnormal form of the human tau protein into the brains of macaques, researchers induced biological changes that mirror the changes seen in people who have Alzheimer's.
- » [A new mouse model](#) that produces a form of the human beta-amyloid protein is now available. These mice show age-related changes in gene expression and later develop cognitive impairment, as seen in people with the disease. The model will help scientists explore genetic, environmental, and behavioral aspects of Alzheimer's, as well as test drug candidates prior to clinical trials.



Three-dimensional clusters of brain cells grown in flasks.
Credit: [Vaccarino Lab, Yale University](#)

Data sharing is key to advancing dementia research.

NIH champions transparency and accessibility in research and continues to modernize and expand its data sharing tools, resources, and policies. Through its continued support of the [AD Knowledge Portal](#), NIH facilitates resource sharing among scientists worldwide with the goal of accelerating and diversifying Alzheimer's and related dementias drug discovery. The portal houses data and analysis tools assembled through the NIA Alzheimer's Disease Translational Research Program, and hosts the:

- » [Accelerating Medicines Partnership® Program for Alzheimer's Disease \(AMP® AD\)](#), a public-private partnership focused on accelerating the development of new diagnostic and treatment options.
- » [Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease \(MODEL-AD\) Consortium](#), through which scientists are developing new animal models for Alzheimer's based on human data.
- » [TaRget Enablement to Accelerate Therapy Development for AD \(TREAT-AD\) Consortium](#), focused on speeding up and diversifying the Alzheimer's and related dementias drug development pipeline.



- » [Agora](#) portal, which provides researchers with access to data on whether a specific gene is linked to Alzheimer's and related dementias. Researchers can also access information on more than 600 potential drug targets for these diseases.

As of May 2022, the AD Knowledge Portal houses data from eight NIA-supported programs, which have a total of 57 individual projects contributed by 430 researchers from 82 research institutions. The data from the portal are being widely used by global researchers from academia and industry, and have led to [numerous new findings](#) on Alzheimer's and related dementias and on brain aging in general. One example is how certain types of [blood lipids play a role in influencing Alzheimer's risk](#). Findings from these and other studies have been published in more than [1,400 articles](#), demonstrating the portal's role as a vital resource for advancing discoveries.

NIH standardizes sample and data collection to drive collaborative dementia research.

Consistency in sample and data collection is vital for the continued success of collaborative dementia research. In 2021, NIH [funded](#) new research to establish and use uniform participant selection and data collection methods across multiple sites, including:

- » The [Study to Uncover Pathways to Exceptional Cognitive Resilience in Aging \(SUPERAgging\)](#), which establishes networks of researchers to collect data on older adults with superior cognitive performance.
- » The [Resilience/Resistance to Alzheimer's Disease in Centenarians and Offspring \(RADCO\)](#) study, which examines the genetic factors that protect people from developing symptoms of dementia even at advanced ages.

PROGRAM SPOTLIGHT

Biobanking provides crucial resources to dementia researchers.



The [National Centralized Repository for Alzheimer's Disease and Related Dementias \(NCRAD\)](#) is one of the largest biorepositories in the field and an [NIA-supported resource](#) that enables scientists to access data and more than 1 million biological samples for dementia research. Currently, NCRAD includes samples from more than 92,000 participants and 45 NIA-funded studies. NCRAD supports state-of-the-art genome and genotyping arrays for samples in several new studies. It provides researchers with materials, protocols, and training to standardize sample collection.

PROGRAM SPOTLIGHT



A new NIH intramural dementia research center is accelerating a broad range of scientific discovery.

CARD supports the largest-ever genome engineering project for human induced pluripotent stem cells.

NIH established the [Center for Alzheimer's and Related Dementias \(CARD\)](#) in 2020 to initiate, accelerate, and support research to improve the prevention and treatment of dementias. In 2021, CARD researchers announced a [strategy to study more than 100 genetic variants linked to dementias](#). Led by NIA and NINDS, CARD brings together researchers from NIH and other government agencies, academia, and industry, with an emphasis on innovation and collaboration across various fields of dementia research. In 2022, CARD laboratories were relocated to the new Roy Blunt Center for Alzheimer's Disease and Related Dementias Research building on the NIH main campus in Bethesda, Maryland.

CARD supports the largest-ever genome engineering project for human induced pluripotent stem cells (iPSCs), known as the



Newly launched intramural Roy Blunt Center for Alzheimer's Disease and Related Dementias Research Building.

iPSC Neurodegenerative Disease Initiative, or the iNDI project. Recently the iNDI project launched a new online portal for scientists to access a [catalog of neurodegenerative disease human iPSC lines](#). The portal is a powerful research catalyst and contains more than 100 variants associated with Alzheimer's and related dementias across 73 genes.

PROGRAM SPOTLIGHT

Training and early career development programs spark a sustained interest in dementia research.

NIH is dedicated to developing the biomedical research workforce through [training and career development opportunities](#) for students, early career scientists, and clinician-researchers. In FY 2021 and 2022, NIA directly supported nearly 800 trainees pursuing Alzheimer's disease research, many with funds targeted to increase workforce diversity. An [NIA analysis of 2015-2018 data](#) found that 29% of Alzheimer's and related dementias grant awardees were new investigators, and 38% were new to the field of Alzheimer's research, indicating the field is growing.

» NIA's [Summer Trainee in Aging Research Program](#) and NINDS' [Summer Internship Program](#), both part of the broader [NIH Summer Internship Program in Biomedical Research](#), offer unique opportunities



for high school, college, graduate, and medical students to obtain [hands-on experience in scientific research](#).

» The [Butler-Williams Scholars Program](#) provides opportunities for junior faculty and researchers new to the field of aging to gain insights into aging research. This long-standing annual event includes lectures, seminars, and small group discussions on aging research design and studies on aging in ethnic and racial minority populations.

NIA's small business funding bolsters Alzheimer's and related dementias research.

Through its [Small Business Research Program](#), NIA provides grants to small businesses for the development of new ways to prevent, detect, or treat Alzheimer's and related dementias. These funds support innovative early-stage research and development for products, interventions, tools, and technology that can be made commercially available.

In 2021, NIA published a [paper highlighting the impact of its small business funding](#).

To date, NIA has invested \$280 million and issued more than 600 grants to support more than 230 small businesses. Companies receiving these grants have developed, among many other accomplishments, medical alert systems that detect falls, blood tests to help diagnose Alzheimer's, and a promising Alzheimer's drug that is currently undergoing clinical trials.

NIH initiatives help strengthen the dementia research workforce.

NIH recognizes that a [vibrant, diverse workforce](#) of scientists and clinicians plays a vital role in advancing dementia research. Through its [Scientific Workforce Diversity Programs](#), NIA provides [training opportunities](#) for researchers from all racial, ethnic, and cultural backgrounds, both within NIH and beyond. In 2021, NIA and NINDS, along with other NIH Institutes and Centers, issued a [funding opportunity](#) to support researchers who want to re-enter the biomedical research workforce after life events have placed their research careers on hold.

Also in 2021, NINDS issued 15 supplements to existing grants to support new and talented independent researchers from diverse backgrounds conducting Alzheimer's and related dementias research. NINDS also published a funding announcement to support [Institutional AD/ADRD Research Training Program awards](#) to enhance the depth and breadth of training across the spectrum of dementia research.

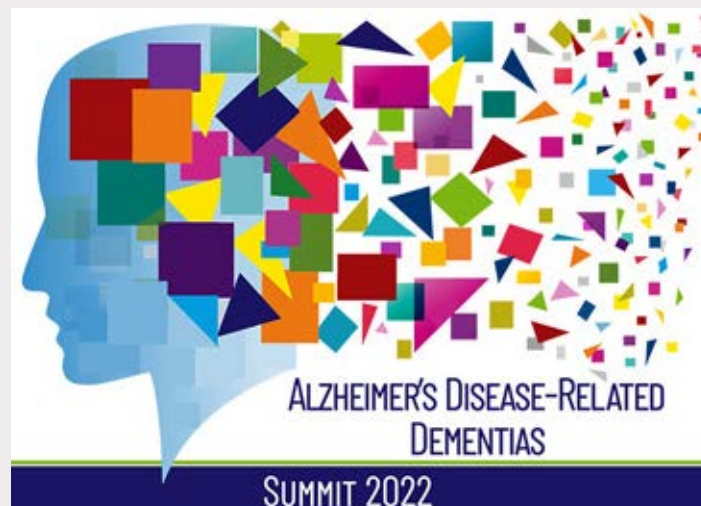
EVENT SPOTLIGHT **NIH's annual Alzheimer's and related dementias research summits map dementia research initiatives.**

To advance the national strategy for dementia research, NIH gathers input through annual research summits. Hosted by NIA and NINDS, the summits provide a platform for experts in the field to present and discuss the most meritorious ideas and advancements in Alzheimer's and related dementias research. Through the summits, NIH solicits input from the broader scientific community, people living with dementia and their care partners, members of the advocacy community, and policymakers. Summit outcomes help inform the National Plan annual updates and new or revised Research Implementation Milestones.

The [2021 NIA Alzheimer's Research Summit](#) was held virtually April 19-22. Presenters showcased advances in dementia research, identifying gaps and opportunities including those relevant to precision medicine. Precision medicine is an approach that considers the genetics, environment, and lifestyle of a person to determine the intervention that could work

best for that individual. Participants also discussed the need for expanded dementia research resources and diversity in clinical trials and encouraged collaboration among researchers to accelerate the pace of new discoveries. A [draft summary](#) outlining the gaps and opportunities identified at this summit is now available on the NIA website.

Presenters showcased **advances in dementia research**, identifying gaps and opportunities including those relevant to precision medicine.



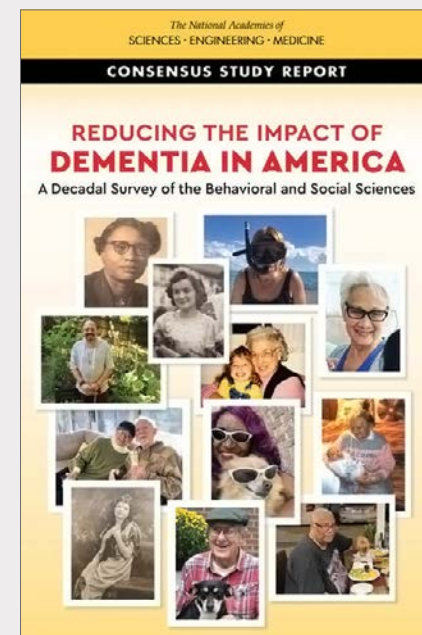
The [2022 NINDS Alzheimer's Disease-Related Dementias Summit](#) was held virtually March 22-23. This summit addressed research priorities for [Alzheimer's disease-related dementias](#). Researchers presented insights into the biological mechanisms that cause these types of dementias as well as dementias with mixed pathologies, new biomarkers

to facilitate early diagnosis, promising new treatments for these diseases, and the impact of COVID-19 on dementia risk and outcomes. Speakers also discussed broader concepts in biomedical research, including health equity and diversifying the dementia research workforce. The summit report, which includes 52 new and refined Research Implementation Milestones, is available on the NINDS website.

The 2023 National Research Summit on Care, Services, and Supports for Persons Living with Dementia and Their Care Partners/Caregivers will be held virtually on March 20-22, 2023. A follow-on to the 2020 summit, this upcoming event will

bring together individuals with a variety of backgrounds to identify evidence-based programs, strategies, approaches, and other research that can be used to improve the care, services, and supports of persons with dementia and their caregivers.

Beyond the annual research summits, NIH also gathers community input by hosting smaller workshops and scientific gatherings and through participation in workshops and conferences organized by other institutions across the United States and globally.



Additionally, reports commissioned by NIA from the National Academies of Science, Engineering, and Medicine (NASEM) have proven extremely valuable in identifying aging and Alzheimer's research gaps and informing future directions. Relevant NASEM projects have included a [review of the evidence on interventions to prevent cognitive decline and dementia](#) and an [analysis of the evidence on dementia care and caregiving interventions](#), as well as [a decadal survey \(conducted every 10 years\) focusing on developing a research agenda in the behavioral and social sciences](#).



Real-World Applications

A crucial step in the research process is ensuring that proven interventions move as efficiently as possible into real-world practices to ultimately improve public health. NIH funds and conducts research in this area and also leads robust communications and outreach programs to ensure that Alzheimer's and related dementias research discoveries are widely shared with the broader scientific community and the public.

PROGRAM SPOTLIGHT

An NIH-funded consortium accelerates science advances into practice.



In 2017, NINDS, in collaboration with NIA, established the [Consortium for Detecting Cognitive Impairment, Including Dementia \(DetectCID\)](#) to develop, validate, and implement effective screening tools to help primary care providers diagnose cognitive impairment and dementia.

In 2022, researchers from DetectCID [published their insights on successful translational research](#), emphasizing the following points:

- » The importance of engaging primary care teams in research
- » The need to empower primary care teams to effectively diagnose cognitive disorders and provide ongoing care and support
- » The need to integrate newly developed screening tests with electronic health records
- » The importance of ensuring that detection approaches address the needs of diverse populations

With DetectCID now in its second phase, consortium research teams are validating their diagnostic tools in a larger number of research participants and aim to recruit at least 50% of participants from racial and ethnic minority groups.

NIH funds studies to promote the widespread use of evidence-based interventions.

In 2022, NIH announced a [funding opportunity](#) to support research studies, including clinical trials, that examine the barriers to effective translational research and dissemination of evidence-based interventions. This includes NIA-supported studies on Alzheimer's and related dementias. The funded research will also offer solutions to ensure that all — including underrepresented communities — have the same level of access to therapies and other treatment approaches.

The NIH Stage Model helps structure behavioral intervention research.

Many behavioral interventions that are tested in studies, even those that seem to be very effective, are never disseminated. This is because of a combination of factors, including challenges in moving from research to community settings, additional research needed into why and how the intervention works, and an increased focus on scalability in the initial intervention design. The [NIH Stage Model](#) is a framework designed to address this issue, defining the research activities that

may be crucial for development of effective and scalable behavioral interventions as they progress through different stages of research. The model outlines six stages of intervention development research addressing basic research relevant to the intervention; intervention creation, adaptation, and pilot testing (including the creation, adaptation, and pilot testing of any necessary procedures to train people in how to deliver the intervention correctly); traditional efficacy testing in controlled research and community settings; efficacy testing with real-world providers; effectiveness testing under natural, real-world conditions; and the development of strategies to promote widespread implementation and dissemination.

In 2021, NIA announced funding opportunities, rooted in the NIH Stage Model, to support [research](#) and [clinical trials](#) for dementia care and ways to ensure that effective interventions can be used widely in the community or in health systems. Studies funded under this opportunity are helping to create and test interventions that address the care needs and promote the well-being of people living with Alzheimer's and related dementias, and their caregivers.

NIH delivers evidence-based health information on Alzheimer's and related dementias.

NIH directly supports dissemination initiatives to provide science-based dementia information that is understandable and actionable. NIA's [Alzheimer's and related Dementias Education and Referral Center](#) reached people with current, comprehensive, and evidence-based health information on Alzheimer's and related dementias in both [English](#) and [Spanish](#). NIA also regularly publishes [research highlights](#), which are plain language summaries of research funded or conducted by the institute. Likewise, NINDS provides [health information](#) for the public and summaries of important [science advances](#).

In 2022, NIA hosted a virtual [workshop to discuss opportunities and strategies](#) to leverage social networks to disseminate interventions. Workshop attendees focused on methods to encourage behavioral change to promote healthy aging, prevent or slow down the symptoms of Alzheimer's and related dementias, and provide support for caregivers.

The IMPACT Collaboratory offers growing support for real-world dementia care innovators.

One of the biggest challenges to helping people living with Alzheimer's and their care partners is identifying and delivering effective innovations in real-world situations and health care settings. The IMbedded Pragmatic Alzheimer's Clinical Trials (IMPACT) Collaboratory, a fast-evolving NIA-funded program, supports embedded pragmatic (real-world) clinical trials to catalyze improvements in dementia care. NIA leveraged the network to study this vulnerable population during the COVID-19 pandemic. [One study](#) found that nursing home residents with moderate or severe cognitive impairment who had COVID-19 were [twice as likely to die](#) as those with no or mild cognitive impairment. Another study tested an [intervention to increase COVID-19 vaccination](#) among nursing home residents and staff.

PROGRAM SPOTLIGHT

A NINDS initiative raises awareness of dementia risk factors.



First launched in 2015, the NINDS [Mind Your Risks®](#) campaign is designed to educate the public on the importance of controlling blood pressure, especially during midlife, to help lower the risk of stroke and dementia later in life. The campaign encourages behavior and lifestyle modifications such as healthy eating, exercising, quitting smoking, and talking to a health care provider to help develop a blood pressure management plan.

In 2021, NINDS relaunched the Mind Your Risks® campaign to focus on Black men ages 28 to 45, who have a greater risk of high blood pressure. The campaign's updated website includes engaging social media content, downloadable flyers, an educational [video](#), a discussion guide for medical appointments, and information for health care professionals. Moving forward, NINDS aims to strengthen its partnerships with community organizations and other federal and nonfederal stakeholders through this campaign to boost the impact of the messaging.

Looking Forward

Over the past year, NIH has conducted and funded remarkable Alzheimer's and related dementias research that is bringing us closer to effective prevention, diagnostics, treatments, and improved care for the people living with these conditions, along with better support for care partners.

This momentum continues. Discoveries with real-world applications are on the near horizon, and in the not-too-distant future, we expect to see:

- » Improved, less invasive diagnostic tests — including blood tests for Alzheimer's and related dementias — that will facilitate Alzheimer's and related dementias screening years before symptoms appear.
- » Advances in health equity that will enable us to better understand the unique causes, risk factors, and efficacy of interventions for Alzheimer's and related dementias in different populations.
- » Further collaborations between NIH and the private sector to accelerate the development of new FDA-approved treatment options that, combined with early diagnosis, will prevent or slow the development of symptoms.

- » Advances in precision medicine — delivering to people the right medicine in the right place at the right time — which will play a major role in treatment and prevention of Alzheimer's and related dementias.
- » Discovery of more factors that contribute to dementia, such as inflammation or changes in our microbiome, the microbes that live in and on our bodies.
- » New research that further explores the impact of behavior and lifestyle changes, such as controlling high blood pressure and exercising regularly, to help lower the risk or delay symptoms of Alzheimer's and related dementias.

With continued federal support and collaboration among dementia researchers, clinicians, people living with dementia, and their care partners and families, the future holds hope and promise.



Appendix: References and Citations

Introduction references:

2022 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2022;18(4):700-789. doi:10.1002/alz.12638.

Yuan J, et al. [Severity distribution of Alzheimer's disease dementia and mild cognitive impairment in the Framingham Heart Study](#). *Journal of Alzheimer's Disease*. 2021;79(2):807-817. doi:10.3233/JAD-200786.

Drug Development references:

Avgerinos KI, et al. [Effects of monoclonal antibodies against amyloid- \$\beta\$ on clinical and biomarker outcomes and adverse event risks: A systematic review and meta-analysis of Phase 3 RCTs in Alzheimer's disease](#). *Ageing Research Reviews*. 2021;68:101339. doi:10.1016/j.arr.2021.101339.

Bolaender A, et al. [Chemical tools for epichaperome-mediated interactome dysfunctions of the central nervous system](#). *Nature Communications*. 2021;12(1):4669. doi:10.1038/s41467-021-24821-2.

Desai RJ, et al. [Comparative risk of Alzheimer's disease and related dementia among Medicare beneficiaries with rheumatoid arthritis treated with targeted disease modifying antirheumatic agents](#). *JAMA Network Open*. 2022;5(4):e226567. doi:10.1001/jamanetworkopen.2022.6567.

Fredericks C. [Methylphenidate for apathy in Alzheimer disease—Why should we care?](#) *JAMA Neurology*. 2021;78(11):1311-1313. doi:10.1001/jamaneurol.2021.2942.

Ghazarian A, et al. [National Institute on Aging seed funding enables Alzheimer's disease startups to reach key value inflection points](#). *Alzheimer's & Dementia*. 2022;18(2):348-359. doi:10.1002/alz.12392.

Hsueh SC, et al. [N-adamantyl phthalimidine: A new thalidomide-like drug that lacks cereblon binding and mitigates neuronal and synaptic loss, neuroinflammation, and behavioral deficits in traumatic brain injury and LPS challenge](#). *ACS Pharmacology and Translational Science*. 2021;4(2):980-1000. doi:10.1021/acspsci.1c00042.

Izzo NJ, et al. [Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification](#). *Alzheimer's & Dementia*. 2021;17(8):1365-1382. doi: 10.1002/alz.12302

Lecca D, et al. [Role of chronic neuroinflammation in neuroplasticity and cognitive function: A hypothesis](#). *Alzheimer's & Dementia*. 2022. doi:10.1002/alz.12610. Online ahead of print.

Mintzer J, et al. [Effect of methylphenidate on apathy in patients with Alzheimer disease: The ADMET 2 randomized clinical trial](#). *JAMA Neurology*. 2021;78(11):1324-1332. doi:10.1001/jamaneurol.2021.3356.

Petrushina I, et al. [Characterization and preclinical evaluation of the cGMP-grade DNA-based vaccine AV-1959D to enter the first-in-human clinical trials](#). *Neurobiology of Disease*. 2020;139:104823. doi:10.1016/j.nbd.2020.104823.

Rafii MS, et al. [Safety, tolerability, and immunogenicity of the ACI-24 vaccine in adults with down syndrome: A Phase 1b randomized clinical trial](#). *JAMA Neurology*. 2022;79(6):565-574. doi:10.1001/jamaneurol.2022.0983.

Roberts J, et al. [A brain proteomic signature of incipient Alzheimer's disease in young APOE e4 carriers identifies novel drug targets](#). *Science Advances*. 2021;7(46):eabi8178. doi:10.1126/sciadv.abi8178.

Salloway S, et al. [A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease](#). *Nature Medicine*. 2021;27(7):1187-1196. doi:10.1038/s41591-021-01369-8.

Taubes A, et al. [Experimental and real-world evidence supporting the computational repurposing of bumetanide for APOE4-related Alzheimer's disease](#). *Nature Aging*. 2021;1:932-937. doi:10.1038/s43587-021-00122-7.

Biomarker Research references:

Bock JR, et al. [Application of digital cognitive biomarkers for Alzheimer's disease: identifying cognitive process changes and impending cognitive decline](#). *Journal of Prevention of Alzheimer's Disease*. 2021;8(2):123-126. doi:10.14283/jpad.2020.63.

Brickman AM, et al. [Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study](#). *Alzheimer's & Dementia*. 2021;17(8):1353-1364. doi: 10.1002/alz.12301.

Fagan AM, et al. [Comparison of CSF biomarkers in Down syndrome and autosomal dominant Alzheimer's disease: a cross-sectional study](#). *Lancet Neurology*. 2021;20(8):615-626. doi: org/10.1016/S1474-4422(21)00139-3.

Gendron TF, et al. [Comprehensive cross-sectional and longitudinal analyses of plasma neurofilament light across FTD spectrum disorders](#). *Cell Reports Medicine*. 2022;3(4):100607. doi: 10.1016/j.xcrm.2022.100607.

Hu Y, et al. [Assessment of a Plasma amyloid probability score to estimate amyloid positron emission tomography findings among adults with cognitive impairment](#). *JAMA Network Open*. 2022;5(4):e228392. doi:10.1001/jamanetworkopen.2022.8392.

Jacobs HIL, et al. [In vivo and neuropathology data support locus coeruleus integrity as indicator of Alzheimer's disease pathology and cognitive decline](#). *Science Translational Medicine*. 2021;13(612):eabj2511. doi: 10.1126/scitranslmed.abj2511.

Kaesler SA, et al. [A neuronal blood marker is associated with mortality in old age](#). *Nature Aging*. 2021;1:218-225. doi:10.1038/s43587-021-00028-4.

Li Y, et al. [Validation of plasma amyloid- \$\beta\$ 42/40 for detecting Alzheimer disease amyloid plaques](#). *Neurology*. 2022;98(7):e688-e699. doi: 10.1212/WNL.00000000000013211.

Lu H, et al. [MarkVCID cerebral small vessel consortium: II. Neuroimaging protocols](#). *Alzheimer's & Dementia*. 2021;17(4):716-725. doi:10.1002/alz.12216.

Mecca AP, et al. [Synaptic density and cognitive performance in Alzheimer's disease: A PET imaging study with \[11 C\] UCB-J](#). *Alzheimer's & Dementia*. 2022. Epub Feb 17. doi: 10.1002/alz.12582.

Oblak AL, et al. [Comprehensive evaluation of the 5XFAD mouse model for preclinical testing applications: a MODEL-AD study](#). *Frontiers in Aging Neuroscience*. 2021;13:713726. doi: org/10.3389/fnagi.2021.713726.

Thijssen EH, et al. [Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study](#). *Lancet Neurology*. 2021;20(9):739-752. doi: 10.1016/S1474-4422(21)00214-3.

Veitch DP, et al. [Using the Alzheimer's Disease Neuroimaging Initiative to improve early detection, diagnosis, and treatment of Alzheimer's disease](#). *Alzheimer's & Dementia*. 2022;18(4):824-857. doi:10.1002/alz.12422

Wilcock D, et al. [MarkVCID cerebral small vessel consortium: I. Enrollment, clinical, fluid protocols](#). *Alzheimer's & Dementia*. 2021;17(4):704-715. doi:10.1002/alz.12215.

Disease Mechanisms references:

Agrawal S, et al. [Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change and microvascular pathologies in community-dwelling older persons](#). *Brain Pathology*. 2021;31(3):e12939. doi: 10.1111/bpa.12939.

Bourdenx M, et al. [Chaperone-mediated autophagy prevents collapse of the neuronal metastable proteome](#). *Cell*. 2021;184(10):2696-2714. e25. doi:10.1016/j.cell.2021.03.048.

Brown A-L, et al. [TDP-43 loss and ALS-risk SNPs drive mis-splicing and depletion of UNC13A](#). *Nature*. 2022;603(7899):131-137. doi: 10.1038/s41586-022-04436-3.

Da Mesquita S, et al. [Meningeal lymphatics affect microglia responses and anti-Aβ immunotherapy](#). *Nature*. 2021;593(7858):255-260. doi: 10.1038/s41586-021-03489-0.

De Miguel Z, et al. [Exercise plasma boosts memory and dampens brain inflammation via clusterin](#). *Nature*. 2021;600(7889):494-499. doi:10.1038/s41586-021-04183-x.

Gate D, et al. [CD4\(+\) T cells contribute to neurodegeneration in Lewy body dementia](#). *Science*. 2021;374(6569):868-874. doi: 10.1126/science.abf7266.

Islam MR, et al. [Exercise hormone irisin is a critical regulator of cognitive function](#). *Nature Metabolism*. *Nature Metabolism*. 2021;3(8):1058-1070. doi: 10.1038/s42255-021-00438-z.

Kim K, et al. [Therapeutic B-cell depletion reverses progression of Alzheimer's disease](#). *Nature Communications*. 2021;12(1):2185. doi: 10.1038/s41467-021-22479-4.

Ma XR, et al. [TDP-43 represses cryptic exon inclusion in the FTD-ALS gene UNC13A](#). *Nature*. 2022;603(7899):124-130. doi: 10.1038/s41586-022-04424-7.

Minhas PS, et al. [Restoring metabolism of myeloid cells reverses cognitive decline in ageing](#). *Nature*. 2021;590(7844):122-128. doi: 10.1038/s41586-020-03160-0.

Oliveira MM, et al. [Correction of eIF2-dependent defects in brain protein synthesis, synaptic plasticity, and memory in mouse models of Alzheimer's disease](#). *Science Signaling*. 2021;14(668):eabc5429. doi: 10.1126/scisignal.abc5429.

Reid DA, et al. [Incorporation of a nucleoside analog maps genome repair sites in postmitotic human neurons](#). *Science*. 2021;372(6537):91-94. doi: 10.1126/science.abb9032.

Rustenhoven J, et al. [Functional characterization of the dural sinuses as a neuroimmune interface](#). *Cell*. 2021;184(4):1000-1016.e27. doi: 10.1016/j.cell.2020.12.040.

Shi Y, et al. [Structure-based classification of tauopathies](#). *Nature*. 2021;598(7880):359-363. doi: 10.1038/s41586-021-03911-7.

Wang C, et al. [Selective removal of astrocytic APOE4 strongly protects against tau-mediated neurodegeneration and decreases synaptic phagocytosis by microglia](#). *Neuron*. 2021;109(10):1657-1674.e7. doi: 10.1016/j.neuron.2021.03.024.

Xie M, et al. [TREM2 interacts with TDP-43 and mediates microglial neuroprotection against TDP-43-related neurodegeneration](#). *Nature Neuroscience*. 2022;25(1):26-38. doi: 10.1038/s41593-021-00975-6.

Xiong J, et al. [FSH blockade improves cognition in mice with Alzheimer's disease](#). *Nature*. 2022;603(7901):470-476. doi: 10.1038/s41586-022-04463-0.

Zalocusky KA, et al. [Neuronal ApoE upregulates MHC-I expression to drive selective neurodegeneration in Alzheimer's disease](#). *Nature Neuroscience*. 2021;24(6):786-798. doi: 10.1038/s41593-021-00851-3.

Lifestyle, Behavior, and Cognitive Training Intervention Research references:

National Academies of Sciences, Engineering, and Medicine. [Reducing the Impact of Dementia in America: A Decadal Survey of the Behavioral and Social Sciences](#). Washington, DC: The National Academies Press. 2021; doi:10.17226/26175.

Rebok GW, et al. [Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults](#). *Journal of the American Geriatrics Society*. 2014;62(1):16-24. doi:10.1111/jgs.12607.

Population Studies and Health Disparities references:

Bakulski KM, et al. [Cumulative genetic risk and APOE ε4 are independently associated with dementia status in a multiethnic, population-based cohort](#). *Neurology Genetics*. 2021;7(2):e576. doi: 10.1212/NXG.0000000000000576.

Barbiellini Amidei C, et al. [Association between age at diabetes onset and subsequent risk of dementia](#). *JAMA*. 2021;325(16):1640-1649. doi: 10.1001/jama.2021.4001.

Barinas-Mitchell E, et al. [Cardiovascular disease risk factor burden during the menopause transition and late midlife subclinical vascular disease: Does race/ethnicity matter?](#) *Journal of the American Heart Association*. 2020;9(4):e013876. doi: 10.1161/JAHA.119.013876.

Bloomberg M, et al. [Sex differences and the role of education in cognitive ageing: analysis of two UK-based prospective cohort studies](#). *Lancet Public Health*. 2021;6(2):e106-e115. doi: 10.1016/S2468-2667(20)30258-9.

Brown SL, et al. [Midlife Marital Dissolution and the Onset of Cognitive Impairment](#). *The Gerontologist*. 2021; 61(7), 1085–1094. doi:10.1093/geront/gnaa193.

Davis EJ, et al. [Sex-specific association of the X chromosome with cognitive change and tau pathology in aging and Alzheimer disease](#). *JAMA Neurology*. 2021;78(10):e212806. doi: 10.1001/jamaneurol.2021.2806.

Derby CA, et al. [Cardiovascular risk and midlife cognitive decline in the Study of Women's Health Across the Nation](#). *Alzheimer's & Dementia*. 2021;17(8):1342-1352. doi:10.1002/alz.12300.

- Desai P, et al. [Longitudinal association of total tau concentrations and physical activity with cognitive decline in a population sample](#). *JAMA Network Open*. 2021;4(8):e2120398. doi: 10.1001/jamanetworkopen.2021.20398.
- Godrich D, et al. [Neuropathological lesions and their contribution to dementia and cognitive impairment in a heterogeneous clinical population](#). *Alzheimer's & Dementia*. 2022;10.1002/alz.12516. doi: 10.1002/alz.12516.
- Greendale GA, et al. [Longitudinal assessment of physical activity and cognitive outcomes among women at midlife](#). *JAMA Network Open*. 2021;4(3):e213227. doi: 10.1001/jamanetworkopen.2021.3227.
- Griswold AJ, et al. [Increased APOE ε4 expression is associated with the difference in Alzheimer's disease risk from diverse ancestral backgrounds](#). *Alzheimer's & Dementia*. 2021;17(7):1179-1188. doi: 10.1002/alz.12287.
- Jin B, et al. [An association test of the spatial distribution of rare missense variants within protein structures identify Alzheimer's disease-related patterns](#). *Genome Research*. 2022;32(4):778-790. doi: 10.1101/gr.276069.121.
- Koton S, et al. [Association of Ischemic Stroke Incidence, Severity, and Recurrence With Dementia in the Atherosclerosis Risk in Communities Cohort Study](#). *JAMA Neurology*. 2022;79(3):271-280. doi: 10.1001/jamaneurol.2021.5080.
- Lee CS, et al. [Association between cataract extraction and development of dementia](#). *JAMA Internal Medicine*. 2022;182(2):134-141. doi: 10.1001/jamainternmed.2021.6990.
- Lennon JC, et al. [Black and white individuals differ in dementia prevalence, risk factors, and symptomatic presentation](#). *Alzheimer's and Dementia*. 2021;10.1002/alz.12509. doi: 10.1002/alz.12509.
- Liu H, et al. [A national longitudinal study of marital quality and cognitive decline among older men and women](#). *Social Science & Medicine*. 2021;282:114151. doi: 10.1016/j.socscimed.2021.114151.
- Mullins MA, et al. [Access to primary care and cognitive impairment: results from a national community study of aging Americans](#). *BMC Geriatrics*. 2021;21(1):580. doi: 10.1186/s12877-021-02545-8.
- Perry BL, et al. [Why the cognitive "fountain of youth" may be upstream: Pathways to dementia risk and resilience through social connectedness](#). *Alzheimer's & Dementia*. 2022;18(5):934-941. doi: 10.1002/alz.12443.
- Power MC, et al. [Trends in Relative Incidence and Prevalence of Dementia Across Non-Hispanic Black and White Individuals in the United States, 2000-2016](#). *JAMA Neurology*. 2021;78(3):275-284. doi: 10.1001/jamaneurol.2020.4471.
- Qi X, et al. [Dose-response meta-analysis on tooth loss with the risk of cognitive impairment and dementia](#). *Journal of the American Medical Directors Association*. 2021;22(10):2039-2045. doi: 10.1016/j.jamda.2021.05.009.
- Rahman M, et al. [Rural-urban differences in diagnostic incidence and prevalence of Alzheimer's disease and related dementias](#). *Alzheimer's & Dementia*. 2021;17(7):1213-1230. doi: 10.1002/alz.12285.
- Richmond-Rakerd LS, et al. [Longitudinal Associations of Mental Disorders With Dementia: 30-Year Analysis of 1.7 Million New Zealand Citizens](#). *JAMA Psychiatry*. 2022;79(4):333-340. doi: 10.1001/jamapsychiatry.2021.4377.
- Robbins R, et al. [Sleep medication use and incident dementia in a nationally representative sample of older adults in the US](#). *Sleep Medicine*. 2021;79:183-189. doi: 10.1016/j.sleep.2020.11.004.
- Sabia S, et al. [Association of sleep duration in middle and old age with incidence of dementia](#). *Nature Communications*. 2021;12(1):1-10. doi: 10.1038/s41467-021-22354-2.
- Salinas J, et al. [Association of Loneliness With 10-Year Dementia Risk and Early Markers of Vulnerability for Neurocognitive Decline](#). *Neurology*. 2022;98(13):e1337-e1348. doi:10.1212/WNL.0000000000200039.
- Samagardny S, et al. [Arterial stiffness accelerates within 1 year of the final menstrual period: The SWAN Heart Study](#). *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2020 Apr;40(4):1001-1008. doi: 10.1161/ATVBAHA.119.313622.
- Suchy-Dicey A, et al. [APOE genotype, hippocampus, and cognitive markers of Alzheimer's disease in American Indians: Data from the Strong Heart Study](#). *Alzheimer's & Dementia*. 2022;10.1002/alz.12573. doi: 10.1002/alz.12573.
- Terracciano A, et al. [Personality associations with amyloid and tau: Results from the Baltimore Longitudinal Study of Aging and meta-analysis](#). *Biological Psychiatry*. 2022;91(4):359-369. doi: 10.1016/j.biopsych.2021.08.021.
- Torres JM, et al. [Adult child socio-economic status disadvantage and cognitive decline among older parents in Mexico](#). *Social Science & Medicine*. 2021;279:113910. doi: 10.1016/j.socscimed.2021.113910.
- van Dalen JW, et al. [Association of systolic blood pressure with dementia risk and the role of age, U-shaped associations, and mortality](#). *JAMA Internal Medicine*. 2022;182(2):142-152. doi: 10.1001/jamainternmed.2021.7009.
- Varma VR, et al. [Bile acid synthesis, modulation, and dementia: A metabolomic, transcriptomic, and pharmacoepidemiologic study](#). *PLOS Medicine*. 2021;18(5):e1003615. doi: 10.1371/journal.pmed.1003615.
- 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;17(8):1297-1306. doi: 10.1002/alz.12296.
- Xue D, et al. [Large-scale sequencing studies expand the known genetic architecture of Alzheimer's disease](#). *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2021;13(1):e12255. doi: 10.1002/dad2.12255.
- Yaffe K, et al. [Cardiovascular Risk Factors Across the Life Course and Cognitive Decline: A Pooled Cohort Study](#). *Neurology*. 2021;96(17):e2212-e2219. doi: 10.1212/WNL.0000000000011747.
- Yang C, et al. [Genomic atlas of the proteome from brain, CSF and plasma prioritizes proteins implicated in neurological disorders](#). *Nature Neuroscience*. 2021;24(9):1302-1312. doi: 10.1038/s41593-021-00886-6.
- Zhang L, et al. [Sex-specific DNA methylation differences in Alzheimer's disease pathology](#). *Acta Neuropathologica Communications*. 2021;9(1):77. doi: 10.1186/s40478-021-01177-8.
- Zhu Y, et al. [Sex, race, and age differences in prevalence of dementia in Medicare claims and survey data](#). *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2021;76(3):596-606. doi: 10.1093/geronb/gbaa083.

Clinical Study Recruitment Initiatives to Enhance Diversity references:

Gianattasio KZ, et al. [Generalizability of findings from a clinical sample to a community-based sample: A comparison of ADNI and ARIC](#). *Alzheimer's & Dementia*. 2021;17(8):1265-1276. doi:10.1002/alz.12293.

Massett HA, et al. [Outreach Pro: The National Institute on Aging's \(NIA\) online tool for AD/ADRD clinical studies recruitment and engagement of diverse and underserved populations](#). *Alzheimer's & Dementia*. 2021;17(S10):e053157. doi:10.1002/alz.053157.

Dementia Care and Caregiver Support Studies references:

Barthold D, et al. [Difficulty with taking medications is associated with future diagnosis of Alzheimer's disease and related dementias](#). *Journal of General Internal Medicine*. 2021;36(4):863-868. doi: 10.1007/s11606-020-06279-y.

Chen J, et al. [Disparities in preventable hospitalization among patients with Alzheimer diseases](#). *American Journal of Preventive Medicine*. 2021;60(5):595-604. doi: 10.1016/j.amepre.2020.12.014. Epub 2021 Apr 6. PMID: 33832801; PMCID: PMC8068589.

Choi H, et al. [Family care availability and implications for informal and formal care used by adults with dementia in the US](#). *Health Affairs (Millwood)*. 2021;40(9):1359-1367. doi: 10.1377/hlthaff.2021.00280.

Gerlach LB, et al. [Changes in medication use among long-stay residents with dementia in Michigan during the pandemic](#). *Journal of the American Geriatrics Society*. 2021;69(7):1743-1745. doi: 10.1111/jgs.17161.

Maust DT, et al. [Prevalence of central nervous system-active polypharmacy among older adults with dementia in the US](#). *JAMA*. 2021;325(10):952-961. doi: 10.1001/jama.2021.1195.

Oh A, et al. [Engagement in meaningful activities among older adults with disability, dementia, and depression](#). *JAMA Internal Medicine*. 2021;181(4):560-562. doi:10.1001/jamainternmed.2020.7492.

Portacolone E, et al. [The effects of the COVID-19 pandemic on the lived experience of diverse older adults living alone with cognitive impairment](#). *Gerontologist*. 2021;61(2):251-261. doi: 10.1093/geront/gnaa201.

Savla J, et al. [Dementia caregiving during the "stay-at-home" phase of COVID-19 pandemic](#). *The Journals of Gerontology: Series B*. 2021;76(4):e241-e245.

Travers JL, et al. [Demographic characteristics driving disparities in receipt of long-term services and supports in the community setting](#). *Medical Care*. 2021;59(6):537-542. doi: 10.1097/MLR.0000000000001544.

Wang N, et al. [Accountable care hospitals and preventable emergency department visits for rural dementia patients](#). *Journal of the American Geriatric Society*. 2021;69(1):185-190. doi: 10.1111/jgs.16858.

Research Enterprise references:

Baglietto-Vargas D, et al. [Generation of a humanized A \$\beta\$ expressing mouse demonstrating aspects of Alzheimer's disease-like pathology](#). *Nature Communications*. 2021;12(1):2421. doi: 10.1038/s41467-021-22624-z.

Beckman D, et al. [A novel tau-based rhesus monkey model of Alzheimer's pathogenesis](#). *Alzheimer's & Dementia*. 2021;17(6):933-945. doi: 10.1002/alz.12318.

Bowles KR, et al. [ELAVL4, splicing, and glutamatergic dysfunction precede neuron loss in MAPT mutation cerebral organoids](#). *Cell*. 2021;184(17):4547-4563. doi: 10.1016/j.cell.2021.07.003.

Chen X, et al. [Modeling sporadic Alzheimer's disease in human brain organoids under serum exposure](#). *Advanced Science*. 2021;8(18):e2101462. doi: 10.1002/advs.202101462.

Ghazarian AL, et al. [National Institute on Aging seed funding enables Alzheimer's disease startups to reach key value inflection points](#). *Alzheimer's & Dementia*. 2022;18(2):348-359. doi: 10.1002/alz.12392.

Lagomarsino VN, et al. [Stem cell-derived neurons reflect features of protein networks, neuropathology, and cognitive outcome of their aged human donors](#). *Neuron*. 2021;109(21):3402-3420.e9. doi: 10.1016/j.neuron.2021.08.003.

Mertens J, et al. [Age-dependent instability of mature neuronal fate in induced neurons from Alzheimer's patients](#). *Cell Stem Cell*. 2021;28(9):1533-1548.e6. doi: 10.1016/j.stem.2021.04.004.

Ramos DM, 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.

Real World Application references:

Bernstein Sideman A, et al. [Lessons from Detecting Cognitive Impairment Including Dementia \(DetectCID\) in primary care](#). *Journal of Alzheimer's Disease*. 2022;86(2):655-665. doi:10.3233/JAD-215106.

Onken L. [Implementation science at the National Institute on Aging: the principles of it](#). *Public Policy & Aging Report*. 2022;32(1):39-41. doi:10.1093/ppar/prab034.