

2024 NIH Alzheimer's and Related Dementias Research Progress Report: Advances and Achievements



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Introduction

The Burden of Alzheimer's Disease and Related Dementias

[Alzheimer's disease and related dementias](#) are complex brain disorders that slowly destroy memory and thinking skills, among other debilitating symptoms. While dementia is more common in older adults, it is not a normal part of aging. An estimated 6.9 million Americans are currently [living with Alzheimer's](#). It is likely these numbers will increase as the nation's population ages. Worldwide, more than 50 million people have dementia, a diagnosis that may include Alzheimer's or a related disorder, such as [frontotemporal disorders](#), [Lewy body dementia](#), or [vascular contributions to cognitive impairment and dementia](#). Many individuals may in fact have two or more forms at the same time. This public health challenge takes a tremendous emotional, physical, and financial toll on those living with these diseases and their families and care partners, underscoring the urgent need for effective diagnostics, preventions, treatments, and care.

NIH Leads the Nation's Dementia Research Strategy

The [National Institutes of Health](#) (NIH) drives the nation's research to better understand the complex and varied 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 care partners. This work is carried out across NIH, with the [National Institute on Aging](#) (NIA) and [National Institute of Neurological Disorders and Stroke](#) (NINDS) leading these efforts. The [National Plan to Address Alzheimer's Disease](#), which arose from the [National Alzheimer's Project Act](#) (PDF, 125K), spurred a substantial increase in federal dementia research efforts. Since the 2012 release of the first National Plan, NIH has significantly expanded

its investments in Alzheimer's and related dementias research across the United States and beyond.

Recent Advances in Dementia Research

Alzheimer's and related dementias research has advanced at a remarkable pace over the past several years. This progress helps move us closer to developing effective prevention and treatment options that benefit all Americans. This report features recent science advances and related efforts in areas including drug development, behavioral and lifestyle interventions, cognitive assessments and biomarkers, dementia risk and protective factors, disease mechanisms, care and caregiving research, career training, 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.

Researchers have identified new genetic, behavioral, environmental, and lifestyle risk and protective factors for dementia; advanced research into behavioral and lifestyle interventions to reduce dementia risk; and developed improved diagnostic tools to help determine the cause of a person's dementia symptoms. Researchers have also added to the growing list of genetic factors and molecular pathways involved in these disorders, such as DNA damage, cellular senescence, microbiome changes, and immune dysfunction. NIH has expanded dementia research initiatives and resources, including platforms for data sharing and interdisciplinary collaborations, new research models and methodologies, expanded career training and workforce diversity opportunities, and policies to ensure our clinical trials reflect the breadth of our population.

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Preventing and Treating Alzheimer's Disease and Related Dementias

The Alzheimer's community has seen remarkable progress in the past year, with the first disease-modifying therapy, lecanemab, receiving traditional approval from the U.S. Food and Drug Administration (FDA) for the treatment of early Alzheimer's in July 2023, followed by donanemab receiving traditional approval in July 2024. While NIH did not fund the pivotal phase 3 clinical trials that led to the FDA approvals, NIH funding did enable the essential foundational work for these trials, including research that helped scientists understand the role of amyloid, the protein targeted by these drugs; and develop amyloid PET imaging, a technology central to these trials.



Although the approval of these drugs represents a significant scientific milestone, additional research is needed to understand the impact of these drugs, including addressing amyloid-related imaging abnormalities (ARIA) and other potentially serious concerns observed in some treated individuals. For example, both drugs were approved to treat early Alzheimer's. There remains a need to test these and other drugs at different disease stages and in more diverse populations. NIH is funding additional trials to evaluate lecanemab in treating different stages of Alzheimer's. Some of these trials are using an amyloid blood biomarker test, [PrecivityAD](#) — developed with NIH-funded research and small business support and now available in clinical practice — to aid in recruitment. Recent research indicates that the use of blood tests can [reduce the cost and time needed](#) to enroll individuals in trials. In addition, the use of this simple blood test may help lower barriers to trial participation and has the potential to expand recruitment to broader, more diverse communities. These drugs also may be combined with other therapeutic approaches to treat Alzheimer's. NIH is funding a clinical trial of lecanemab in combination with a second drug candidate to remove tau protein from the brain.

Given the complexity of Alzheimer's, it is unlikely that any one drug or other intervention will successfully treat it in all people living with the disease. While recent progress is encouraging, there remains a need for new drugs, alone and in combination with other drugs and/or non-pharmacologic interventions, to treat and prevent Alzheimer's and related dementias. To that end, in fall 2023, NIH began funding the Alzheimer's Disease Tau Platform Clinical Trial, which will test the ability of two tau-targeting therapies to reduce brain tau levels, either alone or in combination with a drug that reduces amyloid protein, in patients with early Alzheimer's. NIH funds [more than 230 active clinical trials](#) testing new drug candidates and lifestyle interventions to prevent or treat Alzheimer's and related dementias.

NIH-Funded Trials of Drug Candidates

This is an exciting time of significant momentum in dementia drug development. Among the 230+ active NIH-funded clinical trials noted are more than 70 trials of promising drug candidates that target multiple disease processes.

To help save time and cost in developing dementia therapeutics, NIH-funded researchers continue to explore the potential of repurposing existing drugs that are already FDA-approved to treat other diseases and conditions. Through this approach, they have identified several potential candidates to treat Alzheimer's and related dementias. For example, in a small, proof-of-concept clinical trial of cognitively normal individuals, the anti-insomnia drug suvorexant [decreased overall amyloid levels and tau181 phosphorylation](#) for short periods of time. Researchers have now launched a [phase 2 clinical trial](#) to investigate the effects of long-term use of suvorexant on brain amyloid levels.

In 2023, results from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) Study, a public-private partnership supported with NIH funding, [were released](#). This phase 3 clinical trial of the drug candidate solanezumab, an anti-amyloid immunotherapy, included more than 1,100 cognitively normal older adults who had brain amyloid. Results indicated that the drug did not slow cognitive decline in cognitively healthy people at risk for Alzheimer's. While overall results of this prevention trial were negative, data and biosamples from the study are being made available to the research community, helping further understanding of Alzheimer's. Importantly, these data have already led to insights related to differences in the presence of Alzheimer's biomarkers among participants from different ethnic and racial groups.

Behavioral and Lifestyle Interventions

While NIH-funded researchers continue to pursue new drugs to prevent and treat dementia, many behavioral and lifestyle interventions also offer promise in reducing dementia risk and improving cognition and memory. Of the more than 230 clinical trials of interventions to treat or prevent dementia that NIH currently funds, nearly 160 are testing a wide range of behavioral and lifestyle interventions, including dietary supplements, cognitive training, and more.

Examples of progress in 2023 include:

- **Hearing aids:** An NIH-funded clinical trial found that hearing aids appeared to [reduce cognitive decline](#) over three years in a group of older adults with specific risk factors for cognitive decline. However, hearing aids did not appear to slow cognitive decline in people without these risk factors. Researchers are now conducting a trial to understand the long-term effects of hearing aid use on brain health.
- **Multivitamins:** An NIH-funded clinical trial found that a daily, broad-spectrum multivitamin modestly [improves memory](#) in older adults when compared to placebo. In addition, a meta-analysis of three trial substudies found that, after two years of daily use, participants taking multivitamins had [better global cognition](#) (a combined measure from 11 separate cognitive tests) compared to placebo.
- **Personalized health coaching:** A recent NIH-funded trial found that [personalized health coaching improved cognition and reduced dementia risk](#) in older adults with at least two modifiable risk factors for dementia (e.g., low physical activity, hypertension, diabetes, smoking). Those in the intervention group were coached in both setting and working toward personalized goals to reduce risk. After two years of personalized coaching, participants experienced

Preventing and Treating Alzheimer’s Disease and Related Dementias

modest improvements in cognition, quality of life, and dementia risk factors when compared to a control group that received health education materials but no coaching. Findings from this study can help inform larger-scale trials of dementia risk reduction interventions.

Behavioral and lifestyle interventions, such as listening to tailored music, also offer promise in reducing the symptoms of dementia, for example:

- **Tailored music listening and sleep:** In a small pilot trial in a racially diverse sample of older adults, researchers found that tailored music listening [slightly increased total sleep duration](#). Scientists are now using information gathered in this trial to inform larger future trials.
- **Tailored music and agitation:** An NIH-funded [trial](#) of nearly 1,000 people living with dementia residing in nursing homes found that individuals who listened to their preferred music had less frequent incidents of verbally agitated behaviors than those in a control group. Music also appeared to increase observed pleasure in trial participants. While more research is needed, music may offer a safer alternative to the use of antipsychotic drugs in nursing home residents living with dementia.

Further, behavioral and lifestyle interventions may be useful in improving important skills in older adults, including those living with cognitive impairment.

- **Remote computerized training:** With NIH small business grant support, the company i-Function [developed remote computerized training](#) (PDF, 395K) that helps older adults, including those with mild cognitive impairment, learn relevant technology skills, e.g., managing medication, navigating telephone menus for ordering prescription refills, and banking via ATMs



and the internet. Further, improvement in these skills lasted beyond the end of training, with greater gains in older adults with mild cognitive impairment.

Enhancing Diversity and Inclusion in Clinical Trials

NIH [remains committed to recruiting and retaining](#) a broad range of clinical trial participants from underrepresented communities that are disproportionately affected by dementia. Clinical research inclusivity is fundamental to ensuring that scientific findings can be generalizable to the entire population.

To enhance researchers’ recruitment materials and outreach activities for clinical trials, NIH officially launched [OutreachPro](#) in September 2023. This online tool enables health care professionals in the community

to easily produce tailored materials and strategies that can be branded locally to increase participant recruitment for clinical studies. OutreachPro currently contains a library of materials in five different languages (English, Spanish, Mandarin, Hindi, and Tagalog) and several different formats (brochures, posters, social media posts, videos, radio scripts, website banners), providing research teams with more than 200 outreach options. Since its official launch, OutreachPro has been used to create nearly 900 tailored materials for clinical study recruitment.

NIH has coupled efforts to promote enhanced study recruitment outreach with stronger monitoring and oversight of ongoing clinical trials. In 2021, NIA launched the [Clinical Research Operations & Management System \(CROMS\)](#) to provide NIA staff and grantees with near real-time tracking, reporting, and management of clinical research enrollment data, study documents, and activities. NIA-funded investigators are required to electronically submit participant enrollment data into CROMS on a monthly basis. NIA can then use these data to proactively identify studies that are at risk of not meeting planned enrollment targets and design corrective action plans to improve trial recruitment. Further, in April 2023, NIA [published a notice](#) of updated policies and procedures for reporting clinical trial enrollment data in CROMS. The notice also outlines potential actions that NIA is able to take for grants that are noncompliant with the required policies and procedures. In addition, NIA implemented a [revised policy](#) for larger grant applications that took effect in January 2024. The revised policy prioritizes applications that include a plan to enroll clinical trial participants, from minoritized populations and other groups experiencing health disparities. These approaches help NIA support advancements in science that appropriately represent the populations affected by dementia, ensure

that research findings are generalizable to a broad range of groups, and maintain the highest level of stewardship of research funding.

Updates on Drug Discovery and Development

Clinical trials for dementia build on years of extensive foundational research to identify key disease mechanisms, screen potential drug candidates, and develop and test the most promising therapeutics. NIH is committed to investing in a strong pipeline of preclinical and translational studies, which may pave the way for forthcoming therapies for clinical application. Importantly, NIH-funded researchers continue to develop, and make openly available, resources to validate new drug targets for the next generation of dementia therapeutics. As one example, NIH-funded scientists recently [developed new chemical tools](#) and strategies to engage a novel genetic target of dementia, which may help set the stage for future therapeutic development. In addition, NIH-funded researchers recently developed a [data portal](#) that enables systematic evaluation of drug candidates for entry into preclinical testing.

NIH funding is also crucial to advancing therapeutic development from its initial stages to proof-of-concept studies and beyond. As one example, aggregation

of an improperly functioning protein, TDP-43, in the brain is implicated in the development of several neurodegenerative conditions, including frontotemporal dementia, amyotrophic lateral sclerosis (ALS), and a recently characterized form of dementia known as limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC). In a small proof-of-concept study in mice, NIH-funded researchers were able to use [injections of a new therapy](#) known as an antisense oligonucleotide to counteract some of the effects of TDP-43 aggregation. While much more research is needed, these findings suggest a possible avenue for future treatment of conditions associated with TDP-43.

These and similar research approaches enhance the drug development pipeline and accelerate efforts to find effective drugs for Alzheimer's and related dementias. In fact, since 2006, NIH has supported the development of 20 new drug candidates for the treatment of dementia that have received FDA permission to enter clinical trials and are currently being evaluated in human trials. These new investigational drugs target a broad range of different biological processes, including inflammation, metabolism, growth factors, and hormones.



Accelerating Development of Tools To Support Dementia Diagnosis and Cognitive Assessment

In addition to the amyloid plaques and tau tangles that characterize Alzheimer's, there are other factors that contribute to Alzheimer's and related dementias, including cerebrovascular disease, aggregations of other proteins, and more. It is often the case that multiple pathologies are present in an individual with dementia. Sensitive, affordable diagnostic techniques and cognitive assessments — validated among diverse populations — help clinicians diagnose the correct condition(s) and understand disease stages, and are therefore crucial to preventing and treating dementia.



Cognitive Assessments

Face-to-face cognitive assessment, in which an individual is assessed by a clinician using a battery of relevant tests, remains the gold standard for detection of cognitive impairment. However, it is important that health care providers can perform a cognitive assessment within an average medical visit, which may only last 15 minutes or less. NIH-funded researchers are developing accurate and highly sensitive tests that can detect potential issues quickly, and in some cases, outside the clinic. For example, an NIH-funded [study](#) demonstrated the feasibility and reliability of measuring individuals' learning curves while repeating the same brief battery of memory tests over seven days. The participants — cognitively normal older adults — completed the tests at home on their own laptops and smartphones. Researchers found that information collected at home was comparable to traditional cognitive measures. Next, the investigators plan to assess the ability of this at-home test to detect mild cognitive impairment or early-stage dementia.

NIH-funded researchers have also [developed a web-based cognitive test](#), available in English and Spanish, that can detect mild cognitive impairment. The test takes under 15 minutes to complete and can be performed without the need for a skilled test administrator. Researchers found that the test was able to distinguish between people with normal cognition and those with mild cognitive impairment. They also found that test scores were associated with the size of brain regions affected in Alzheimer's among persons with mild cognitive impairment, supporting its usefulness as a potential screening test for cognitive decline.

Fluid Biomarkers

Although advances in brain imaging are generating exciting findings, the imaging modalities used in dementia research are often only available at specialized medical centers and can be expensive and often impractical for individuals with cognitive impairment. However, simple blood tests are emerging that can support a diagnosis or risk evaluation in the doctor's office. With support from NIH small business funding, C2N Diagnostics released a second-generation blood test in 2023 that combines measures of amyloid and tau to help physicians make an accurate and timely diagnosis. This test, PrecivityAD2, and the earlier PrecivityAD test, can help lower costs and increase access to diagnostic tools for Alzheimer's.

Other dementia-related tests using blood and plasma may not be far behind. Researchers have found that levels of another form of tau, [p-tau181](#), in blood are associated with cognitive performance and reliably differentiate cognitively impaired and nonimpaired individuals. In addition, higher levels of p-tau181 are associated with more rapid cognitive and functional decline. Baseline plasma levels of p-tau181 and glial fibrillary acidic protein (GFAP), a protein expressed by support cells in the central nervous system, [can predict cognitive decline](#) over the following four years, and GFAP levels [correlate with severity of clinical symptoms](#) in Alzheimer's.

The cerebrospinal fluid (CSF), which bathes the brain and spinal cord, also contains biomarkers that can predict or diagnose neurodegenerative diseases. For example, NIH-funded researchers recently [validated the first tau](#)

[biomarkers in CSF](#). Just a few years ago, changes in tau levels could only be reliably measured via PET scan, a complex and expensive process. The identification of biomarkers for tau in the CSF will make it easier for researchers and clinicians to diagnose Alzheimer's and other dementias and monitor treatment response.

In a separate study, NIH-funded researchers found that changes in levels of a protein called [neuronal pentraxin 2 \(NPTX2\)](#), which supports communication among brain cells, have been shown to predict development of mild cognitive impairment among cognitively normal middle-aged adults. In another study, NIH-funded investigators measured proteins in CSF and identified biomarker profiles [highly specific for Lewy body dementia](#), a disease for which diagnosis is challenging. The investigators have used this information to translate these findings to a biomarker panel that may help accurately identify Lewy body dementia, potentially paving the way for improved diagnostics and clinical trials.

Digital Tools

Researchers are increasingly using emerging “big data” methods to identify individuals at risk of dementia and even detecting undiagnosed dementia in real-world populations. For example, the [eRADAR tool](#), which analyzes routinely collected data from electronic health records to detect undiagnosed dementia, was recently validated in separate populations and across racial and ethnic groups. Once individuals with potential undiagnosed dementia are identified, they can be referred for further assessment and, potentially, enrollment in a clinical trial.

Emerging and Future Biomarkers

Researchers continue to identify and develop next-generation biomarkers that may be less invasive and less expensive than those currently available to researchers and clinicians. The expanding field of brain imaging biomarkers — that is, changes in the architecture of the brain as well as the shapes of proteins visualized using state-of-the-art techniques — has opened doors to new and more accurate diagnoses. It has also enabled researchers to learn more about the brain and about potential risk factors or markers for cognitive decline. For example, researchers found that [cognitively healthy people with less myelin](#), the fatty tissue that protects nerve cells, experience more rapid cognitive decline over time. Further research is needed to clarify the relationship between myelin integrity and cognition.

Researchers are also working to facilitate biomarkers beyond brain imaging. For example, beta-amyloid, a protein found in the brains of individuals with Alzheimer's, can also be detected easily and noninvasively in the retina. Recent studies of postmortem tissue showed that [levels of amyloid in the retina](#) were higher in people with Alzheimer's than in people with mild cognitive impairment, suggesting that a simple eye test could be used both to detect and track progression of Alzheimer's. In another study, NIH-funded investigators found that a [PET scan of the heart](#) may help identify people who will go on to develop Parkinson's disease or Lewy body dementia among at-risk individuals by revealing low levels of norepinephrine, a hormone that is depleted in these diseases.

Biomarkers in plasma, the liquid component of blood, are also being explored for utility in distinguishing Alzheimer's from LATE-NC, which is clinically similar to Alzheimer's and often overlaps with both Alzheimer's

and Lewy body pathology. For example, research has shown that [plasma levels of the protein TDP-43](#), which is implicated in LATE-NC, are associated with the condition's characteristic structural changes in the brain. [Blood-based measurement of TDP-43](#) accumulation in tiny particles known as extracellular vesicles, particularly those derived from specific types of brain cells, also shows promise as a diagnostic tool for LATE-NC.

TDP-43 is also being explored as a biomarker for other forms of neurodegenerative diseases. For example, using donated brain tissue, researchers identified a [unique form of amyloid filament formed by TDP-43](#) in a specific type of frontotemporal dementia. These findings

could help guide the development of diagnostic and therapeutic compounds for disorders associated with TDP-43 accumulation.

Furthermore, research has revealed that TDP-43 dysfunction is common in Alzheimer's and is associated with greater disease severity. NIH-funded investigators are currently exploring the role of [cryptic RNAs](#) — snippets of genetic material that can interfere with a cell's function — in Alzheimer's. Researchers have found that the same cryptic RNAs that indicate TDP-43 dysfunction in ALS and frontotemporal lobar degeneration are present in Alzheimer's with TDP-43 dysfunction, suggesting potential diagnostic and therapeutic targets and hinting at a common mechanism among these disorders.

Spotlight

NIH PREPARE (EUREKA) Challenge

Existing cognitive tests are not always sensitive enough to identify subtle signs of cognitive decline at the earliest stages of the disease course when treatment may be most effective. Moreover, the predictive power of current tests can vary among population groups, which may result in less effective screening and diagnosis of dementia in groups that have been historically underrepresented in research.

To address this need and spur the development of solutions to improve early prediction of dementia symptoms among diverse populations, NIH launched the [Pioneering Research for Early Prediction of Alzheimer's Disease & Related Dementias EUREKA](#)

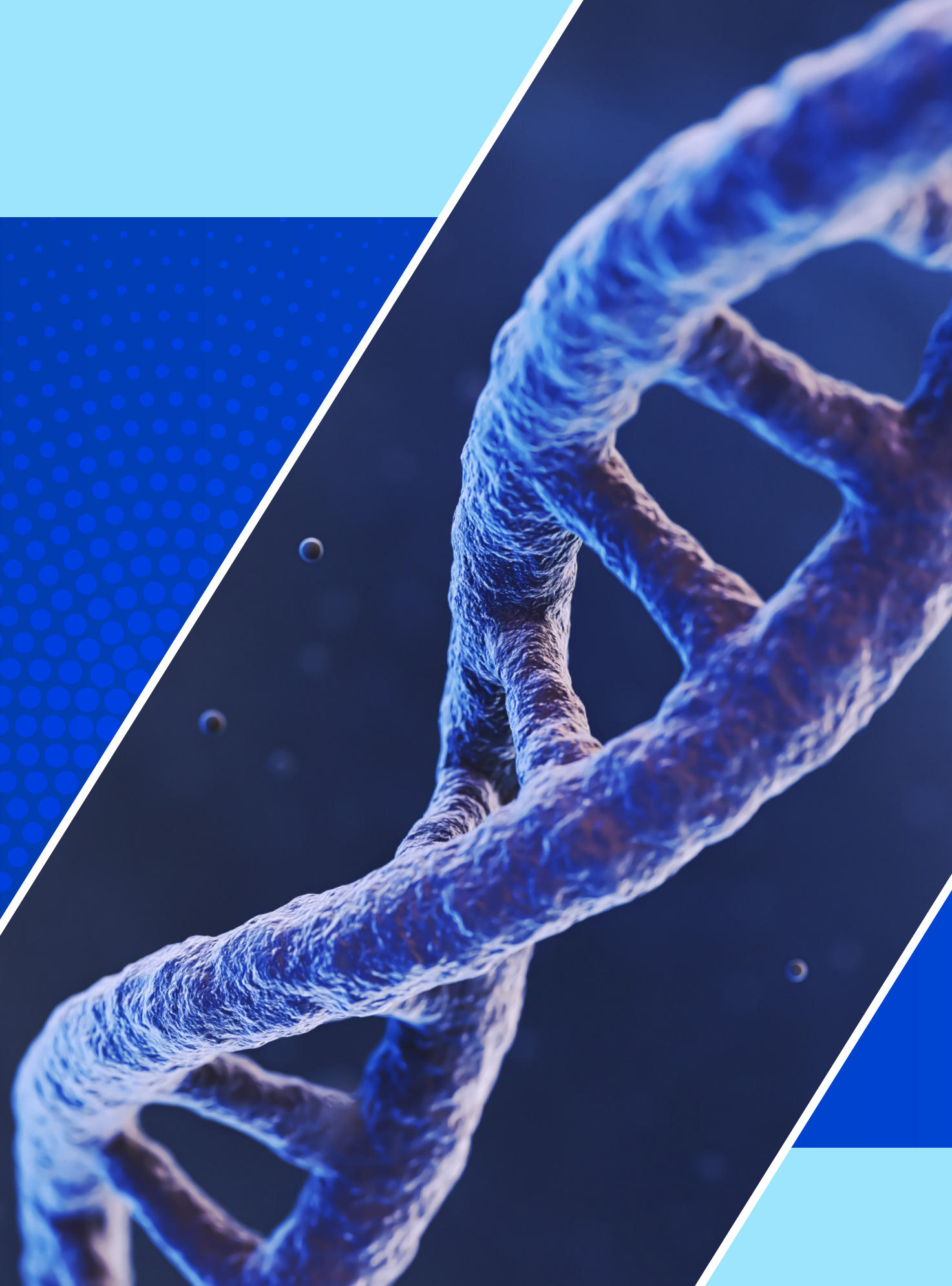
[\(PREPARE\) Challenge](#) in fall 2023. This challenge, which consists of three phases, is intended to stimulate creativity and innovation through the award of substantial cash prizes.

Phase 1 of the challenge, which ran from September 2023 to January 2024, emphasized identifying datasets to support early prediction of dementia, especially in historically underrepresented groups. Phases 2 and 3, slated to begin in September 2024 and March 2025, respectively, will foster approaches to develop and use ethical and inclusive algorithms to support early prediction of dementia. Challenge winners are expected to share widely their findings, learnings, and approaches to enable impactful real-world translation.



Understanding Risk and Protective Factors for Dementia

NIH-funded research has uncovered many new factors that influence the risk for dementia, including genetic, environmental, sociocultural, behavioral, and other factors. Understanding how these factors affect dementia risk is leading to new strategies for risk assessment and reduction as well as identification of new therapeutic targets.



Identification of Genetic Risk and Protective Factors

In 2010, we knew of just 10 genetic areas associated with Alzheimer’s. Today, thanks in large part to the work of NIH-funded researchers, we know of at least 80 genetic areas associated with this disease. The identification of genetic risk and protective factors is important to enable better risk assessment and find new therapeutic targets.

Protective gene variants

Scientists are uncovering rare forms of genes that may help protect against Alzheimer’s, including a variant of the *RELN* gene called [RELN-COLBOS](#) and a variant of the *APOE* gene (a gene known to be associated with Alzheimer’s risk) called [APOE3ch](#). In a recent study in mice, researchers found that [APOE3ch enhances the activity of immune cells called microglia](#), leading to reduced tau tangle formation in the brain. Understanding how these rare variants promote dementia resilience opens new avenues for developing treatments. For example, [APOE3ch-inspired antibodies](#) are already being developed as a potential Alzheimer’s therapeutic.

Genetic factors for Alzheimer’s-related dementias

Scientists are also uncovering genetic risk factors for Alzheimer’s-related dementias. By combining cutting-edge computer algorithms with machine learning, NIH researchers identified [large genetic changes](#), known as structural variants, that contribute to dementia risk in Lewy body dementia and frontotemporal dementia, paving the way for new research in this area. To accelerate the pace of discovery, the analysis code and data are now available to the scientific community, along with an interactive app to explore the presence of structural variants in genes of interest.

Exploring genetic factors in diverse populations

To help identify new pathways for therapeutic approaches and prevention, researchers must be sure to include representatives from diverse populations. For example, the identification of the [RELN-COLBOS](#) and [APOE3ch](#) protective variants would not have been possible without inclusion of international populations — in this case, the participation of a large extended family in Colombia with more than 6,000 members, including more than 1,200 individuals who carry a specific gene variant that causes them to develop Alzheimer’s in their 40s. Likewise, the *APOE* variant [APOE ε3\[R145C\]](#) was identified as an Alzheimer’s risk variant in adults of African ancestry and indicates a potential new biomarker for genetic risk assessment in this population. In addition, studies of closely related “genetic founder” groups can help to clarify the genetic basis for Alzheimer’s. For example, NIH-funded researchers were able to identify [potential genetic risk factors for Alzheimer’s](#) in people of Ashkenazi Jewish descent.

NIH also funds Alzheimer’s research focused on individuals with Down syndrome, who have an elevated risk of developing the disease. For example, NIH-funded

researchers found that [Alzheimer’s progression in Down syndrome](#) appears similar to other genetic, early-onset forms of the disease, suggesting common disease mechanisms. This indicates that individuals with Down syndrome may benefit from participating in a broad range of studies of Alzheimer’s therapies meant to prevent and treat dementia.

An Association Between Sensory Loss and Dementia

Recent research studies have highlighted associations between sensory impairment and cognitive decline and dementia. For example, one NIH-funded study found that [having a good sense of smell is associated with slower loss of brain volume and cognitive decline](#) in older adults. Another found an [association between vision impairment and dementia](#). Further, protein deposits in the retina are linked with retinal abnormalities. As noted earlier in this report, these same protein deposits may serve as a noninvasive way to detect Alzheimer’s. These findings suggest that monitoring sensory changes and addressing loss may help detect and prevent dementia. For example, NIH-funded researchers estimate that as many as 100,000 U.S. dementia cases could potentially have been prevented with improved eye care.

Spotlight

Molecular Subtypes of Cognitive Impairment

Cognitive impairment, which may consist of memory or thinking problems and typically precedes dementia, is itself a complex condition with multiple

underlying causes. Scientists continue to make key advances in understanding this condition. NIH-funded researchers recently identified additional [molecular subtypes](#) of cognitive impairment, which may help better inform how cognitive impairment is diagnosed and lead to novel treatments in the future.

In addition, as also referenced in an earlier part of this report, researchers recently found that hearing aids may slow cognitive decline in some people experiencing hearing loss and who have certain risk factors for dementia.

Identifying Psychological, Social, Behavioral, and Environmental Factors

Many aspects of a person’s life can affect their risk of developing dementia, including factors ranging from education, job complexity, and social status to [where someone lives](#) and more. NIH-funded researchers are discovering how these factors, collectively called the “exposome,” affect dementia.

NIH-funded studies have identified several factors associated with an increased risk of dementia, including but not limited to:

- [Exposure to air pollution](#), including pollution associated with agriculture and open fires. This suggests that interventions that reduce air pollution may decrease the lifelong risk of developing dementia.
- Living in [lower income neighborhoods with less green space](#). This finding could inform interventions targeting disadvantaged neighborhoods.
- [Sedentary behavior](#). This supports the idea that more time spent not moving — such as sitting while watching TV, working on a computer, or driving — may be a risk factor for dementia.

Other factors were associated with a lower risk of cognitive decline, including:

- A [higher measure of purpose in life](#), which may promote resilience against brain changes and better cognitive function.

- [Holding positive attitudes toward aging](#), which may aid in recovery from mild cognitive impairment. Older adults with “positive age beliefs” were 30% more likely to recover from mild cognitive impairment, and displayed faster recovery, than those with “negative age beliefs.”

Compared with White Americans, Hispanic Americans are about 1.5 times more likely to develop dementia, and Black Americans are about twice as likely. NIH-funded research has focused on identifying the factors that contribute to disparities in dementia rates.

- [Socioeconomic status and discrimination](#) were linked to self-reported cognitive decline in a study of African American women.
- Increased [vascular health issues \(e.g., diabetes, heart disease\) and barriers to health care](#) were identified as factors contributing to increased dementia risk for Black and Hispanic Americans.

Spotlight

Blood Pressure and Dementia Risk

High blood pressure is an established risk factor for dementia. In 2019, the NIH-funded [SPRINT MIND trial](#) showed that intensive blood pressure control (i.e., a systolic blood pressure target of less than 120 mmHg) reduced the risk of mild cognitive impairment, a well-established precursor to dementia, and slowed accumulation of white matter lesions, a risk factor for dementia.

Results from SPRINT MIND have informed the ongoing NIH [Mind Your Risks](#) public health campaign, which aims to help people — particularly Black men ages 28-45, who are at increased risk for midlife high blood pressure and late-life dementia — learn about the importance of taking charge of their health to prevent stroke and dementia. The

campaign encourages medical, behavioral, and lifestyle modifications such as taking appropriate medications, healthy eating, exercising, quitting smoking, and talking to a health care provider to help develop a blood pressure management plan.

In addition, NIH-funded researchers have developed a [low-cost, universal attachment](#) for use with a smartphone to measure blood pressure from their fingertips. The “BPClip” is designed for at-home access to blood pressure monitoring, especially for people who find it difficult to access health care services. While more research is needed before the BPClip becomes available, this early pilot study demonstrates the potential of smartphone-based blood pressure devices, which could help improve the accessibility of long-term blood pressure monitoring.



Exploring How the Hallmarks of Aging Contribute To Dementia

Researchers recognize a set of “hallmarks of aging” as important molecular, cellular, and systemic contributors to aging and age-related diseases, including Alzheimer’s. Understanding the hallmarks of aging, and how they interact across the lifespan and in response to stressors and other factors, is critical to better understanding of the causes and progression of these diseases and informing further research, including identifying potential targets to inform preclinical efforts.



Understanding Hallmarks in Disease Pathways

NIH-funded research has advanced our understanding of the roles of these hallmarks in disease pathways that play critical roles in dementia-related neurodegeneration, identifying new pathways for further exploration.

Senescence

Cellular senescence is a process in which cells lose normal function, including the ability to divide and replicate, but continue to release molecules that may damage neighboring cells. Senescence has been implicated in Alzheimer's, with one NIH-funded study finding that [more neurons have markers of senescence in brains with Alzheimer's](#) compared to brains without the disease.

Genomic instability

An NIH-funded study showed that the [accumulation of DNA damage](#) in neurons leads to changes in how the genome is arranged and impacts genes related to connections between neurons, which could contribute to neurodegeneration in Alzheimer's.

Changes in gene expression

NIH-funded researchers explored the differences in gene activity between brains with and without Alzheimer's. Using brain samples from people with Alzheimer's, the researchers found [altered activity in genes involved in various functions](#), including clearance of beta-amyloid, a hallmark of Alzheimer's, and immune function, among others. They were able to link some of these changes to Alzheimer's-associated genetic variants such as *APOE4*, indicating potential therapeutic targets.

Dysfunction of mitochondria

Mitochondria produce most of the energy that cells use to function. However, mitochondrial function declines with aging. NIH-funded researchers found that [lower mitochondrial function in human skeletal muscle](#) increases the risk of mild cognitive impairment and dementia and can also increase brain amyloid and blood proteins associated with brain inflammation. The findings suggest that age-related mitochondrial dysfunction may contribute to the development of Alzheimer's and that strategies to improve mitochondrial function in muscle may be beneficial for brain health.

Microbiome changes

NIH-funded researchers found that [changes in the human gut microbiome precede Alzheimer's cognitive decline](#). Study participants with preclinical Alzheimer's had markedly different communities of gut bacteria than those without preclinical Alzheimer's. The team also found that these microbiome changes were correlated with amyloid and tau levels in the brain. Researchers are now conducting a follow-up study to better understand whether the differences observed in the gut microbiome are a cause or consequence of the brain changes seen in Alzheimer's.

Spotlight

The Role of Immune Dysfunction in Alzheimer's and Related Dementias

Research suggests that dysfunction of the immune system plays an important role in the development of Alzheimer's and related dementias, including the buildup of amyloid plaques and tau tangles in the brain. NIH funds research to better understand how immune system dysfunction may be involved in the disease processes and identify new disease pathways for further studies to discover potential therapeutic targets.

- Researchers compared brain tissues from people with and without Alzheimer's and found [changes in the activity of many genes with known links to the disease](#) in the prefrontal cortex of the brain.

These changes most often occurred in microglia, immune cells that engulf and clear waste, including beta-amyloid.

- Another study showed that [more microglia enter an inflammatory state](#) in the Alzheimer's brain compared to a healthy human brain. The findings suggest a role for microglia and inflammation in the development of Alzheimer's.
- A study in a mouse model of high blood pressure suggests that immune cells around and within the brain [become abnormally activated](#) under conditions that mimic a common form of high blood pressure. This activation leads to impaired brain function. These findings underscore the importance of managing high blood pressure to reduce the risk of cognitive impairment.

Advancing Care and Caregiving Research

While significant advances in treating and preventing Alzheimer's and related dementias have been made recently, there continues to be a critical need to provide comprehensive care for those currently living with dementia as well as increase supports for their care partners. NIH currently funds a broad portfolio of care and caregiver research, from developing new research tools and measures to understanding the economic impact of dementia to supporting more than 220 trials of care and caregiving interventions.



In March 2023, NIH held the [2023 Dementia Care and Caregiving Research Summit](#), one of three rotating summits (including one on Alzheimer's and another on Alzheimer's-related dementias). The goal of the event was to review research progress, highlight innovative and promising research, and identify unmet needs with input from the broader research community, persons living with dementia and their care partners, providers of health care and supports to persons living with dementia, and other stakeholders. Informed by the 2023 summit, NIH established [eight new research implementation milestones](#) to help guide future research activities in dementia care and caregiving.

In addition to the summit, the views and perspectives of persons living with dementia and their care partners are gathered via other forums to inform NIH research activities. For example, the NIH-funded [IMbedded Pragmatic Alzheimer's disease and Alzheimer's-Related Dementias Clinical Trials \(IMPACT\) Collaboratory](#) works to build the nation's capacity to conduct pragmatic trials; that is, clinical trials of nondrug interventions where people already live and work, including in skilled nursing facilities ("nursing homes"). In 2021, the IMPACT Collaboratory established the [Lived Experience Panel](#), comprised of people living with cognitive symptoms or caring for persons living with dementia. This panel helps inform research priorities and identify challenges that are important to the broader community of people living with dementia and their care partners. The panel [issued a report](#) (PDF, 530K) in 2023 outlining key issues in health equity for dementia care and research. This report is already being used to inform the design of upcoming pragmatic trials. Further, NIH hosted the ADRD Research Roundtable in 2023, which brought together nonprofit leaders, persons with lived experience, and NIH staff to discuss gaps and opportunities in Alzheimer's-related dementias research.



Moreover, quality care depends on several factors, including the training and expertise of care providers. NIH continues to fund research exploring the impact of training initiatives for care providers, including health care workers. For example, a small study of nurse care managers found that providing these important care providers with telephone-based dementia care training [improved several aspects of care](#). Compared to those without such training, trained nurse care managers were more likely to engage in a range of positive care behaviors. For example, trained managers engaged in more conversations with family caregivers about safety, including identifying backup caregivers; initiated more conversations about advanced care planning; engaged in more discussions regarding family caregiver well-being; and increased their identification of behavioral symptoms (e.g., depression, agitation), which can enable subsequent management of these symptoms.

Researchers also found that, for persons living with dementia residing in skilled nursing facilities, certain characteristics of these nursing facilities [may affect quality of care](#). More specifically, nursing homes where more than 90% of residents have dementia seem to provide better dementia care than nursing homes with a lower proportion of residents with the condition. For example, facilities where 90% or more of residents have dementia had significantly higher-skilled nursing hours per resident than nursing homes with lower percentages. In addition, hospitalization and emergency department admissions for residents with dementia dropped rapidly as the proportion of these residents increased. These findings suggest that different standards may be appropriate for supporting care for nursing home residents with dementia and may have important implications for staffing at skilled nursing facilities.

NIH continues to support research to better understand the factors affecting the dementia care workforce and staffing levels. In 2023, NIH funded the [National Dementia Workforce Study](#), which will help generate new insights into the nature and training of the professional dementia care workforce and connect this information to objective measures of care delivered to persons living with dementia. This effort will complement the activities of the [Advancing Workforce Analysis and Research for Dementia](#) (AWARD) Network, launched in 2022. This network aims to advance research on the dementia direct care workforce — including geriatricians, social workers, home care aides, and nursing assistants, among others — to inform evidence-based policy and practice decisions.

Research Enterprise

NIH has long supported and built key research and clinical infrastructure to advance Alzheimer's and related dementias research around the nation. These critical investments in robust research infrastructure continue to pay dividends and make new research possible. For example, the more than 30 Alzheimer's Disease Research Centers (ADRCs) work to translate research advances into improved diagnosis and care for people living with Alzheimer's.



In 2023, NIH funded a new consortium that will leverage the ADRCs to standardize PET and MRI imaging protocols. This will help researchers better understand Alzheimer's and related dementias, including mixed dementias (dementia with more than one underlying cause), in living people. As another example, IMPACT Collaboratory researchers published a [national database of older adult COVID-19 vaccine data](#) in October 2023 that can be used by scientists to understand vaccine effectiveness in older adults, including those with dementia. In addition, the IMPACT Collaboratory has spurred the development of the [Long-Term Care Data Cooperative](#). This provider-led effort assembles electronic health record data across multiple long-term care providers to generate real-world evidence on different treatments and care practices for nursing home residents. Already the largest and most comprehensive health records database of its kind, the Data Cooperative has continued to grow, with more than 2,700 nursing facilities from over 230 companies currently participating, representing more than 500,000 residents. This data infrastructure will enable monitoring for future public health emergencies and improve assessment of the impact of treatment and policy changes.

In early 2022, the NIH [Center for Alzheimer's and Related Dementias](#) (CARD) opened its doors on the NIH campus. CARD is meant to accelerate efforts to understand, prevent, and treat Alzheimer's and related dementias. CARD researchers have already made significant headway in producing and sharing invaluable resources with the broader scientific community, with several new recent advances:

- CARD scientists identified and made available a [collection of stem cells](#) that can be used to study the gene variants behind Alzheimer's and other neurodegenerative disorders. The cells will help scientists worldwide study how these variants damage the nervous system in a uniform genetic background.

- CARD researchers have [established a stem cell repository](#) containing stem cells from both healthy individuals and those diagnosed with Alzheimer's. The full repository will include 200 stem cell lines, with a balanced gender mix that captures a broad range of diverse ancestries (e.g., European, Black and African American, Asian, Native American, and Latino/Hispanic backgrounds). Cell lines are already being made available to the research community and may help researchers find new biomarkers of Alzheimer's progression and understand how the disease affects different types of brain cells.
- CARD researchers have also made new tools and resources available to scientists. As one example, genome sequencing is a powerful research method used to discover genetic variations in human populations. However, some portions of the human genome can be very difficult to sequence appropriately. To address this issue, CARD's genetic experts [developed and published a new protocol](#) to sequence challenging regions of the human genome. These methods will be used by the research community to learn more about the Alzheimer's genome and identify new and rare genetic variants. This protocol may also have broad applications beyond dementia research that can help investigators researching the genomes of other conditions. Further, CARD researchers developed and used a new machine learning tool to uncover similarities in key genetic risk variants across different neurodegenerative diseases, which can help advance our understanding of these conditions. The researchers have not only made this powerful tool available to the research community but have also developed an interactive website to help scientists further explore research findings.

In addition to establishing key research and dissemination infrastructure, NIH funds several important efforts to support and develop a well-trained and inclusive workforce engaged in this research and capable of making use of NIH-funded infrastructure. (See page 20 for more.)



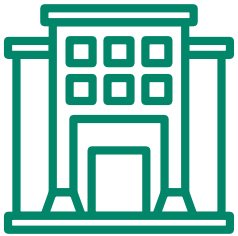
Growing the Scientific and Clinical Research Workforce

NIH programs encompass a broad range of workforce development initiatives across the spectrum of career opportunities, from academia to clinical research to entrepreneurship and beyond. Examples include but are not limited to:



Programs for Undergraduate Students

One of NIA’s signature programs is the Advancing Diversity in Aging Research (ADAR) program, which aims to increase the number of undergraduate students, including those from underrepresented backgrounds, who pursue advanced degrees and research careers in aging-related areas, including Alzheimer’s and related dementias. More than 450 student participants took part in ADAR in 2023.



Programs for Graduate Students and Early-Career Individuals

NIH funds several programs for predoctoral and postdoctoral scholars in dementia research. As one example, NIH’s Research and Entrepreneurial Development Immersion (REDI) program helps better prepare biomedical researchers for the full spectrum of modern career options beyond tenure-track faculty positions. More than 120 early-career researchers benefited from this and similar programs in 2023.



Programs for Early-Career Scientists

In 2023, NIH funded 10 Resource Centers for Minority Aging Research (RCMARs). These centers emphasize development of early-career scientists from diverse backgrounds in behavioral and social science research fields, including those in dementia-related priority areas.



Programs for Research Professionals

Jointly funded by NIH and the Alzheimer’s Association, the [Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD \(IMPACT-AD\)](#) aims to expand and diversify the dementia clinical trials workforce.

More than 150 participants, including early-stage investigators and those new to dementia trials, have completed this comprehensive training program in conducting clinical trials for Alzheimer’s and related dementias, including 43 in the 2023 cohort.



Programs for Entrepreneurs

The [NIA Start-Up Challenge and Accelerator](#) fosters a more inclusive workforce by encouraging a diverse group of researchers and entrepreneurs with bold new ideas for aging research.

Participants receive strategic resources and mentorship provided through an accelerator program and compete for cash prizes. In 2023, NIA awarded five prizes to help accelerate new technologies in aging research.

Looking Forward

NIH continues to make significant progress in addressing Alzheimer's and related dementias, thanks to sustained investments over the past several years. The achievements made in 2023 build on earlier advances and help sustain momentum in NIH's efforts to prevent and treat dementia and enhance care for those living with the disease and their care partners. NIH continues to be profoundly grateful to all the researchers, study participants, care partners, and others whose hard work and dedication made these discoveries possible.

The accomplishments described here provide an expanding base of knowledge that will be the foundation for future research. NIH will continue to explore new opportunities to advance dementia research and bring us closer to living in a world where Alzheimer's and related dementias do not take the enormous tolls that they take today.



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