2025 NIH Alzheimer's Disease and Related Dementias Research Progress Report:

Advances and Achievements

National Institutes of Health

Contents

Spotlights

Introduction

The Burden of Alzheimer's Disease and Related Dementias

Alzheimer's disease and related dementias are complex brain disorders that slowly destroy cognitive functioning — including thinking, memory, and reasoning skills, among other debilitating symptoms. While dementia is more common in older adults, it is not a normal part of aging. An estimated 7.1 million Americans are currently living with symptoms of Alzheimer's disease, and it is predicted that more than 13.9 million will be living with the disease by 2060. Worldwide, more than 50 million people have dementia, a diagnosis that may include Alzheimer's or a related dementia. While Alzheimer's is the most common dementia diagnosis, related dementias — such as frontotemporal disorders, Lewy body dementia, or vascular contributions to cognitive impairment and dementia — share many cognitive symptoms and brain changes that can make it difficult to distinguish and differentially diagnose. In addition, many individuals often have two or more forms of dementia at the same time. Altogether, dementia is a significant public health challenge that 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, prevention, treatments, and care.

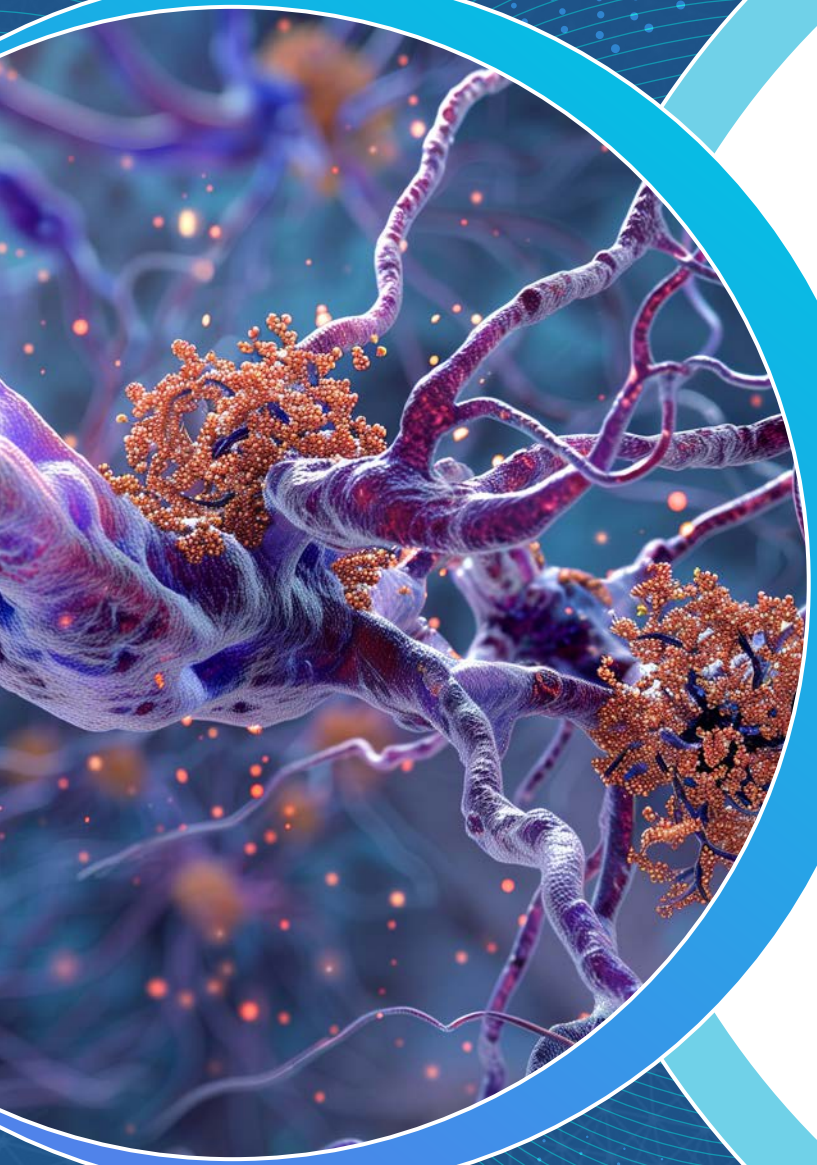
NIH Leads the Nation's Dementia Research Strategy

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. NIH investments also include vital research on understanding the factors that drive risk and resilience to ultimately reduce the prevalence of dementia. 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, spurred a substantial increase in federal dementia research efforts. Since the 2012 release of the first National Plan, NIH has significantly expanded its investments, enabled by increased Congressional appropriations, and broadened its research portfolio in Alzheimer's and related dementias research across the United States and beyond.

As scientists reveal new findings, NIH continues to ensure that the research strategy is guided by the science. In December 2024, the National Academies of Science, Engineering, and Medicine released the report titled, ***Preventing and Treating Dementia: Research Priorities to Accelerate Progress***. This congressionally-mandated study was designed to assess the current state of research on Alzheimer's and related dementias and identify research priorities for treating and preventing these conditions. The report identified existing research areas to bolster and new opportunities to explore. NIH is integrating the report's recommendations into our overarching strategic planning framework for Alzheimer's and related dementias research to inform future advancements.

Recent Advances in Dementia Research

Dementia research has continued to make progress towards developing effective prevention and treatment options that can benefit all Americans. This report features recent science advances and related efforts in areas including drug development and repurposing, behavioral and lifestyle interventions, diagnosis, dementia risk and protective factors, underlying biological pathways, care and caregiving research, career training, and more. Though not exhaustive, the information in this report is an overview of the significant progress researchers have made in the past year towards understanding, treating, and ultimately preventing these devastating diseases. Researchers have identified new therapeutic drug targets along with nonpharmacological interventions. They have also expanded the growing list of genetic factors and molecular pathways involved in these disorders and mapped the progression of dementia in the brain. NIH has expanded dementia research resources, including platforms for data sharing, increased career training opportunities, and research tools to accelerate the development of precision medicine for Alzheimer's and related dementias.



Preventing and Treating Alzheimer's Disease and Related Dementias

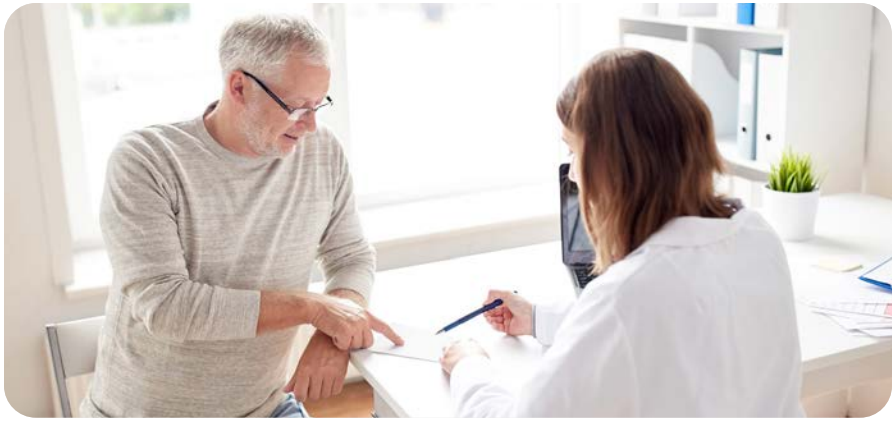
In recent years, there has been significant progress for the treatment of early Alzheimer's, marked by the U.S. Food and Drug Administration's (FDA) approval of the use of specific antibodies against amyloid beta (termed "anti-Aβ" or "anti-amyloid immunotherapies") to slow progression of the disease. While NIH did not fund the clinical trials that led to these approvals, these therapies build on decades of NIH investments in basic and translational research, such as research on the amyloid protein that these drugs target, and amyloid PET imaging — a technology central to the clinical trials because it detects amyloid in the brains of living participants. Although the FDA approvals of these therapies for the treatment of early Alzheimer's represent a significant scientific milestone, further research is needed to develop additional interventions that are effective for treatment and prevention of disease for all who are at risk.

NIH is strategically investing in a precision medicine approach to research, with efforts on numerous therapeutic targets across various biological pathways, to reach the goals of treating and preventing dementia in different populations, with the right intervention at the right stage for each person. A multi-disciplinary research approach is crucial to treating and preventing dementia as earlier research has shown that a single dementia diagnosis may reflect a complex interplay of cellular and functional changes that vary between individuals. Additionally, many individuals who may have been diagnosed with Alzheimer's or a related dementia have multiple different disease pathologies contributing to their symptoms, referred to as mixed dementia, now known to be the most common form of dementia.

To address the complex and varied nature of dementia, NIH has invested heavily in efforts to diversify its clinical and translational dementia research portfolio. As of the end of fiscal year 2024, NIH was funding 495 clinical trials for Alzheimer's and related dementias. This included more than 225 clinical trials testing pharmacological and non-pharmacological interventions to treat or prevent these diseases. Importantly, these ongoing studies are evaluating an increasingly diverse set of potential drug targets and behavior and lifestyle changes.

NIH-Funded Trials of Therapeutic Candidates

NIH is investing in a range of potential therapeutics to treat and prevent dementia. As of the end of fiscal year 2024, NIH was funding 68 clinical trials to test promising drug candidates, including trials on new and repurposed drugs and continued research on FDA-approved anti-amyloid immunotherapies.



New and Repurposed Drugs

NIH investments to develop new treatments for dementia explore a wide range of therapeutic approaches and support multiple stages of drug development research, from basic science to clinical trials.

For example, NIH has funded nearly a decade of research leading to the development of a small molecule drug, called CT1812, that shows promise for treating multiple types of dementia. NIH-funded basic and pre-clinical research has shown that CT1812 may help prevent neurotoxicity associated with dementia by displacing toxic protein aggregates at synapses, the spaces between brain cells that facilitate communication. Interestingly, this molecule can displace two different types of protein aggregates — amyloid beta and alpha-synuclein — each of which is known to contribute to multiple types of dementia. More recently, NIH funded phase 2A clinical trials to evaluate the safety of CT1812 in people with Alzheimer's and Dementia with Lewy Bodies (DLB). Currently, researchers are recruiting participants for an NIH-funded phase 2B study that will evaluate

the efficacy of CT1812 to improve cognitive function in people with early Alzheimer's disease. Notably, treatments, such as CT1812, that may be used for more than one dementia type could hold promise for more patients and their loved ones, particularly due to the growing number of mixed dementia diagnoses. Final determination of the effectiveness of this and other interventions will depend on rigorous and reproducible clinical trials that measure clinically meaningful outcomes.

The NIH is also investing in clinical research to evaluate approaches for treating less common forms of dementia, such as Progressive Supranuclear Palsy (PSP). PSP is a rare and rapidly progressing neurological disorder with brain changes associated with the tau protein, which has been implicated in other diseases, including Alzheimer's, Parkinson's, and frontotemporal dementia. NIH-funded researchers have identified additional shared characteristics between these diseases, including specific changes to energy production and consumption by cells. Due to such similarities, NIH is investing in efforts to test new treatments originally developed for Alzheimer's and other neurodegenerative diseases to determine if they might be equally or more effective at treating PSP. Notably, researchers recently launched an innovative PSP Platform Trial, which improves the efficiency of clinical research by allowing researchers to test multiple different treatments under the same research protocol. The PSP Platform Trial will test at least three different therapies for PSP, and researchers have committed to sharing data widely with the research community to further accelerate PSP clinical research. This innovative strategy to test treatments could expedite the process to assess potential therapeutics, bringing greater hope for individuals with less common types of dementia.

To further improve efficiencies, NIH is also investing in efforts to understand if drugs used for other diseases could be repurposed to treat dementia. For example, based on findings of abnormal electrical activity in the brains of people with Alzheimer's, multiple studies are evaluating whether drugs used to treat epilepsy may be beneficial in treating Alzheimer's. One recent study tested whether a once-a-day dose of the epilepsy drug levetiracetam was able to halt the progression of mild cognitive impairment. Though levetiracetam did not significantly slow cognitive decline in the overall study population, additional analyses determined that the drug may slow brain atrophy in individuals who do not carry the Alzheimer's risk gene, *APOE4*, while having only a negligible effect for individuals carrying the gene. Though additional studies are needed, these results hold promise for a subpopulation of people with Alzheimer's. This study also demonstrates how some treatments may work for some people and not others, further highlighting the need for a precision medicine approach to treating dementia.

To advance the most promising research for effective therapies, NIH supports robust translational research to pave the way to identify, develop, and deliver better treatments to the millions of Americans impacted by Alzheimer's and related dementias. As of March 2025, at least 25 new drug candidates developed with funding from NIH have advanced to human trials. Of these, 18 are in early stage (phase 1) trials and seven are in mid-to-late stage (phase II and phase III) trials. In 2024, Investigational New Drug (IND) applications were submitted for five drug candidates that were developed based on NIH-funded studies. One of these new drug candidates is a potential treatment for the neuropsychiatric symptoms of Alzheimer's, which often accompany dementia but have been difficult to treat.

NIH Investments Drive Research Progress in Drug Development

NIH's translational research funding initiatives are accelerating the development of new drug candidates by expanding the therapeutic pipeline for Alzheimer's disease and related dementias. For example:

In the past decade, at least 25 new drug candidates developed through NIH translational research programs have advanced into clinical trials.

- These new drug candidates target over a dozen Alzheimer's-related biological processes, including inflammation, metabolic and vascular factors, neurogenesis, synaptic plasticity, APOE-related mechanisms, amyloid and tau biology, neurotransmitters, and growth factors.

In 2024 alone, Investigational New Drug (IND) applications were submitted for five drug candidates developed through the NIH-supported Alzheimer's Drug Development Program (ADDP).

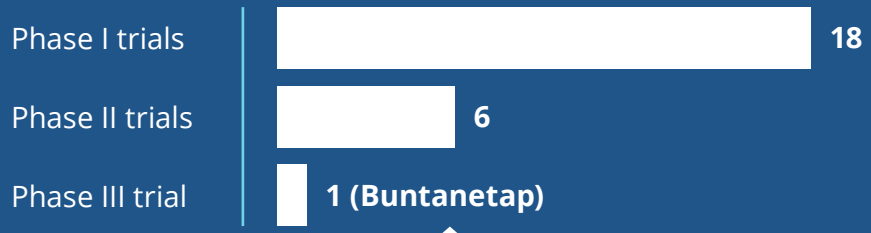
Thirty-eight additional drug candidates are in different stages of preclinical development.

Types of Drug Candidates in Clinical Trials:

Seventeen of these new drug candidates are being developed as medicines that can be taken orally as a pill.

Eight of them are being developed as various types of biologic drugs, such as immunotherapy and gene therapy.

Development Status of Drug Candidates in Clinical Trials:



Buntanetap Development and Testing: A Journey of Public and Private Sector Collaborative Discovery

- Buntanetap (also known as posiphen) is an orally administered drug candidate that inhibits the production of key proteins involved in the pathogenesis of Alzheimer's, Parkinson's, and Lewy body dementia. Buntanetap is being developed as a disease-modifying drug for these diseases by the biotechnology company Annovis.
- Buntanetap was first discovered by NIH scientists.
- Support from NIH's ADDP and small business program funding enabled Annovis to conduct key preclinical studies in animal models necessary for the early- and late-stage human trials.
- Researchers at NIH led the initial phase I trials in humans.
- Annovis is conducting a phase III clinical trial to assess the safety and efficacy of Buntanetap as a disease-modifying treatment for Alzheimer's.

Gene Therapies

As a potential innovative way to prevent or treat dementia, NIH is investing in research on gene therapy, an emerging technology that treats or reverses conditions by correcting problems with DNA.

This research includes the exploration of a gene therapy that increases the amount of a protein associated with reduced dementia risk, APOE2, in individuals with *APOE4*, a genetic variant that confers a higher risk for Alzheimer's. For example, a recent NIH-funded study found that *APOE2* gene therapy in mouse models of dementia with *APOE4* reduced amyloid deposition and improved markers of neuroinflammation and neurodegeneration. These findings on the neuronal changes associated with *APOE2* gene therapy may help inform future clinical trials. As of April 2025, there is a human trial evaluating the effects of an ***APOE2* gene therapy on cognition in individuals with two copies of *APOE4*** and mild cognitive impairment or dementia. While this trial is not NIH-funded, the approach was built upon many years of **NIH-funded pre-clinical studies in mouse models**.

NIH is also investing in research to use gene therapy to target the TDP-43 protein for the treatment of dementia. The dysfunctional form of TDP-43 (termed "TDP-43 loss-of-function" (TDP-LOF) occurs in frontotemporal dementia (FTD) and limbic-predominant age-related TDP-43 encephalopathy (LATE), suggesting that this protein is critical to brain health. However, gene therapy to replace TDP-LOF has unique biological hurdles to overcome. In individuals with TDP-LOF, the dysfunctional TDP-43 is not present in all neurons, and an attempt to treat broadly could worsen the function of otherwise healthy neurons. To address this issue, NIH-funded researchers developed an **innovative method to activate gene therapy only in the specific neurons with dysfunctional TDP-43**. This discovery paves the way for future efforts to precisely induce production of TDP-43 (or other therapeutic genes) in only the neurons that need the fix, which could be applied to the treatment of several types of dementias.

Anti-Amyloid Immunotherapies

In parallel to trials testing a range of potential therapeutic options, NIH also seeks to better understand how to effectively and safely use the current FDA-approved anti-amyloid immunotherapies, i.e., lecanemab and donanemab. Efforts include studying the effects of these drugs at different stages of disease, in different populations, and in combination with other potential treatments.

For example, NIH is funding multiple trials evaluating the ability of these drugs to prevent or delay the onset of Alzheimer's by treating individuals before the onset of clinical symptoms. These studies are a critical next step toward effective treatment for Alzheimer's because the changes in the brain that lead to disease begin years before symptoms arise. The NIH-funded **AHEAD 3-45 Study** is testing the safety and efficacy of lecanemab on individuals with amyloid in their brain, but who have not yet experienced cognitive decline. AHEAD 3-45 completed enrollment in 2024, with more than 20,000 individuals screened with the aid of the **PrecivityAD**, a blood biomarker test developed with NIH investments. Individuals who did not screen into the main trial were still invited to participate in a **longitudinal investigation of biomarker changes over time**.

NIH is also funding studies to evaluate the use of anti-amyloid immunotherapies in populations with heritable forms of Alzheimer's. These studies include a multi-national clinical trial on pre-symptomatic individuals carrying a known causative mutation for Alzheimer's and another study focused on individuals in an extended family in Colombia that carry a form of Alzheimer's caused by a variation in the *presenilin 1* gene, which results in cognitive impairment in nearly all individuals in their 40s. These large-scale studies are major NIH investments to understand if current disease-modifying treatments can prevent disease onset and halt progression, particularly in individuals at high genetic risk.

NIH also invests in clinical trials to test how anti-amyloid immunotherapies work in combination with other possible treatments. In addition to amyloid, several other proteins and mechanisms are also implicated in the disease, and personalized treatments will likely involve a combination of therapeutics. As one example, NIH is funding a clinical trial that will test the ability of two therapies to reduce the levels of tau, another key hallmark of Alzheimer's. These investigational treatments will be evaluated alone and in combination with an approved anti-amyloid therapy.

In addition, NIH funds research aimed at reducing barriers to accessing these FDA-approved treatments, such as investments into the development and testing of diagnostic tools that can be used in primary care settings to support earlier diagnosis, at stages of the disease when treatment may be most effective. This is discussed in further detail in the section titled *Accelerating Development of Tools To Support Dementia Diagnoses and Cognitive Assessment*.

During the clinical trials for anti-amyloid immunotherapies, MRI imaging abnormalities termed "amyloid-related imaging abnormalities" (ARIA) were reported as adverse events. Unfortunately, some patients have experienced severe side effects associated with ARIA, including a leaky blood-brain barrier, edema, brain hemorrhage, and death in rare cases. The cause of ARIA remains a critical question that NIH and the research community are actively working to answer. In September 2023, NIH held a workshop to identify scientific gaps and opportunities in ARIA research. Participants discussed how anti-amyloid antibodies affect the immune system and the potential role of the brain and peripheral immune response in ARIA. Researchers hypothesize that ARIA is caused by the unintended effects of anti-amyloid immunotherapies on the small blood vessels of the brain, which are part of the blood brain barrier.

As such, NIH is currently investing in research on the adverse brain blood vessel responses to anti-amyloid immunotherapy that result in ARIAs. These projects utilize animal models to investigate whether different anti-amyloid antibodies are more likely to cause ARIA and explore the cellular and molecular events that contribute to the adverse brain blood vessel responses underlying ARIAs. Together, these research efforts and workshop discussions are aimed at better understanding why ARIA occurs and who is at highest risk, to improve patient safety and pave the way for a stronger precision medicine approach.

Behavioral, Lifestyle, and Other Interventions

Multiple lines of research find that several forms of non-pharmacological interventions may also offer promise in reducing dementia risk factors and improving cognition and memory. Results from randomized control trials indicate that interventions with blood pressure control, hearing aids, multivitamins, and personalized health coaching can reduce dementia risk in specific populations, but more research is needed. NIH investments in research continue to explore promising avenues for risk reduction and refine our understanding of which interventions work for which people.

For example, one recent NIH-funded study sought to maximize the potential of tai chi in slowing mild cognitive impairment, which has previously been demonstrated to lead to improvements in global cognition and memory. This recent study compared the effects of traditional tai chi, which consists of physical movement and breathing exercises, to a cognitively enriched form that adds mental puzzles and challenges. The research findings suggest that cognitively enriched tai chi was superior to the standard form in improving global cognition and this outcome was sustained at the 48-week follow-up. If these preliminary results hold up, this enhanced form of tai chi may be an effective, safe, and affordable option for people with mild cognitive impairment (MCI).

NIH researchers are also continuing to build on past scientific discoveries on the link between diet and dementia risk. As one example, NIH-funded investigators found that individuals who consumed a Modified Mediterranean Ketogenic Diet (MMKD), composed of 5–10% carbohydrate, 60–65% fat, and 30% protein, for six weeks had significant changes in both blood and spinal fluid biomarkers associated with Alzheimer's risk. Specifically, individuals following this diet exhibited improvements in several risk factors, including increases in beneficial (high density lipoprotein, or HDL) cholesterol and reductions in body mass index and systemic inflammation. This study is the first exploration of diet-related metabolic changes in spinal fluid and provides evidence of the effects of diet on modifiable risk factors for Alzheimer's.

Additionally, NIH-funded scientists continued to elucidate the long-term effect of blood pressure control on dementia. Building on a 2019 NIH-funded study demonstrating beneficial effect of 3.3 years of intensive blood pressure lowering on preventing MCI over a five-year follow-up, scientists recently found a longer-term effect of intensive blood pressure control on MCI with a continued significant reduction in impairment rates at the seven-year follow-up. This follow-up investigation has refined the field's understanding of what actions an individual can do to reduce their dementia risk.

As dementia is multifaceted and complex, the research community acknowledges that risk reduction strategies are not "one size fits all." NIH is thus investing in research to identify which behavior and lifestyle interventions work for which populations. For example, NIH-funded researchers sought to determine what social factors may influence the effectiveness of cognitive training, which has been shown to delay or slow age-related cognitive decline in older adults. Scientists found that cognitive training conferred a greater degree of protection from dementia for individuals with greater access to education and healthcare. This finding further exemplifies the variable effectiveness of prevention and treatment approaches for different populations and paves the way for a precision medicine approach for individuals with or at risk for dementia.

Accelerating Development of Tools To Support Dementia Diagnoses and Cognitive Assessment

Until the early 2000s, the only definitive way to diagnose Alzheimer's or other forms of dementia was after death when a brain autopsy could be performed. NIH-funded research has helped develop tools that now support diagnoses in living individuals, and currently, NIH-funded researchers are at the forefront of developing newer, less invasive, and less expensive diagnostic tools for Alzheimer's. There remains a critical need, however, to develop more sensitive diagnostics and clinical biomarkers, including those for other forms of dementia. Additional diagnostic tools that can help clinicians identify the type of dementia as well as the earliest disease stages — even before clinical symptoms are evident — are crucial to enabling a precision medicine approach to treating and preventing dementia.

NIH research investments have resulted in the development of new dementia screening approaches and diagnostics, including enhanced biomarkers for Alzheimer's as well as for related dementias, advanced digital diagnostic tools, and brain imaging innovations. Many of these tools are being used in clinical trials to screen participants at early stages of disease and in doctor's offices to confirm diagnosis.

Biomarkers for Alzheimer's Disease

In the past year, blood tests for Alzheimer's have improved significantly, notably due to the incorporation of measurements of a specific phosphorylated form of the tau protein known as p-tau217.

In a study supported in part by NIH, a commercially-available blood test for p-tau217 was found to accurately detect Alzheimer's pathology at all stages of the disease, including before the onset of symptoms. The blood test results outperformed the accuracy of brain imaging and were comparable to results using the current standard test — spinal fluid biomarkers. Notably, the p-tau217 assay was highly accurate in identifying tau pathology in individuals with brain amyloid plaques. This suggests that this assay may help screen participants for anti-amyloid immunotherapies, as these therapies may be less effective in individuals with high levels of tau pathology. Overall, these findings highlight an important role of the p-tau217 blood test as a highly accurate and cost-effective initial assessment tool in the management of cognitive impairment. In individuals with positive p-tau217 blood test results, brain imaging could then be used to determine the location of abnormal tau in the brain to help diagnose the type of dementia, such as Alzheimer's or LATE.

Furthermore, the accuracy of a commercial blood test that was developed, in part, with NIH funding, was improved significantly by combining the detection of p-tau217 with plasma Aβ. The new blood test, PrecivityAD2, is a highly accurate, validated clinical tool to help doctors diagnose pathological Alzheimer's disease in people who are considered at risk for dementia (see the Spotlight on *Improving Diagnostics To Help Primary Care Providers Screen for Dementia*). NIA's small business grants have played a key role in the development of this blood test, which is reshaping how researchers are detecting, and clinicians are diagnosing, dementia. In particular, PrecivityAD2 is being used in clinical trials for anti-amyloid therapies to screen for potential trial participants in early stages of pathological disease who may be at risk of cognitive decline (i.e., individuals who have Alzheimer's pathology without cognitive symptoms).

Looking ahead, NIH remains committed to supporting research that informs the accuracy and precision of diagnostic tests for different populations. For example, NIA is funding CLEAR-AD, a cross-disciplinary, multi-institutional program to identify the next generation of Alzheimer's biomarkers for testing and validation in different populations.

Biomarkers for Related Dementias

NIH is also making great strides in identifying new biomarkers to detect pathologies associated with Alzheimer's related dementias, including FTD, Lewy body dementias (LBD), and vascular contributions to cognitive impairment and dementia (VCID).

According to an NIH-funded study, a new spinal fluid biomarker may someday help detect amyotrophic lateral sclerosis (ALS) and FTD in the early stages. In people with ALS and FTD, a protein called TDP-43 builds up in an abnormal site within cells, causing changes in how genes are read and ultimately generating irregular proteins. Investigators developed a new antibody test that can detect one of these irregular proteins in human blood and spinal fluid samples before symptoms of ALS or FTD appear.

Another protein, alpha-synuclein, builds up in the brain and nerve cells leading to several neurodegenerative disorders, including LBD, Parkinson's disease, and mixed dementias. For example, Lewy body pathology is combined with Alzheimer's disease pathology in approximately 30% of Alzheimer's cases. The results of an NIH-funded study showed that an alpha-synuclein seed amplification assay performed in CSF is highly accurate and 97% specific for detecting Lewy body pathology in individuals with a clinical diagnosis of dementia due to Alzheimer's disease. Notably, individuals positive for alpha-synuclein combined with Alzheimer's had faster cognitive decline than those without alpha-synuclein and presented with earlier symptoms. These important results suggest that this assay may help diagnose mixed dementia involving alpha-synuclein to inform prognosis and treatment plans.

Cerebrovascular disease represents a major factor in cognitive decline in older adults. MarkVCID is an NIH-funded consortium dedicated to validating risk, disease monitoring, and prognostic biomarkers for vascular cognitive impairment and dementia. A study conducted by MarkVCID used brain imaging to validate the association of cerebrovascular reactivity (CVR) — the action of cerebral small vessels dilating in response to inhalation of carbon dioxide — with changes in cognition, proving support for CVR as a biomarker for VCID. These results suggest that CVR measurement may be a useful diagnostic tool for the detection of VCID to inform the treatment and management of cognitive decline.

Advanced Computer Models To Detect Dementia

Artificial intelligence, or AI, may help to spot early warning signs of Alzheimer's disease from electronic health records (EHRs), according to an NIH-funded study. Researchers trained computer programs to recognize data patterns in the EHRs of people with Alzheimer's diagnoses and of healthy controls. When combined with health care utilization data, the programs were approximately 86% accurate in predicting

an Alzheimer's diagnosis seven years before clinical diagnosis and about 90% accurate in predicting a diagnosis one year in advance. The researchers also showed that the AI programs could be used to identify sex-specific risk factors. For example, osteoporosis appeared to be a warning sign for women while chest pain was one for men. This study provides a blueprint for how researchers may use machine learning algorithms and other advanced analytical methods on clinical and biological data to better understand each person's risk for Alzheimer's and inform more personalized risk reduction strategies.

In another NIH-funded study, researchers developed a computer model to detect the possible presence of other forms of dementia in people with Alzheimer's pathology. First, they identified unique imaging signatures for LBD, TDP-43, and Cerebral Amyloid Angiopathy (CAA) — a type of vascular dementia — based on three-dimensional brain scans combined with clinical and autopsy reports from older adults. Next, they combined these signatures with results from cognitive, biomarker, and genetic tests to create a computer model to detect the possible presence of these other forms of dementia in people with Alzheimer's pathology. The model's accuracy was 81% for detecting LBD, 84% for TDP-43, and depending on how it was calculated, 76% to 93% for CAA. Similar to other studies on mixed dementias, the model predicted a high degree of co-pathologies — TDP-43 in 49%, Lewy bodies in 24%, and moderate to severe CAA in 32% of the participants who had Alzheimer's-like levels of amyloid or tau. Moreover, further analysis showed that these other forms of dementia may contribute to the cognitive decline experienced in Alzheimer's, with LBD, TDP-43, and CAA pathology contributing to nearly 25% of decline, and amyloid and tau contributing to 26% and 36% of cognitive decline. This study provides a promising new brain-scan-based method for detecting these co-pathologies that may enable more personalized, precision medicine approaches in treatments, and in clinical trials for Alzheimer's disease and related dementias.

Speech and Dementia Detection

Subtle changes in speech are associated with early signs of Alzheimer's in the brain, according to an NIH-funded study. The researchers analyzed speech patterns of participants responding to a storytelling memory task, along with PET brain scans measuring changes in proteins amyloid and tau. They found that changes in speech patterns, such as speaking more slowly and taking longer and more frequent pauses, are linked to an increase in tau protein and may indicate early signs of Alzheimer's.

Another NIH study used a digital test to analyze speech patterns in asymptomatic individuals who carried a family gene known to increase risk for FTD. Researchers found gradual declines in language ability in carriers of the gene along with shrinkage of brain tissue in areas of the brain associated with language.

Both studies showed that speech changes occurred before cognitive decline, suggesting that speech markers could be used to help health care providers diagnose Alzheimer's or FTD earlier in the disease progression.

Lastly, the Phase 1 first place winner of the NIA PREPARE (Pioneering Research for Early Prediction of Alzheimer's Disease and Related Dementias EUREKA) Challenge identified

and refined a dementia dataset using audio recordings, demographic information, and clinical assessments for further analysis. This dataset will be used to develop and validate an algorithm in the second and third phases of the competition to improve clinical approaches used in identifying individuals at risk for developing dementia.

Brain Imaging

NIH continues to invest in validating new brain imaging techniques to detect brain changes linked to dementia. For example, two innovative, MRI-based brain imaging techniques were found to be promising tools for the detection of LBD:

- Neurite Orientation Dispersion and Density Imaging (NODDI)
- Diffusion-weighted magnetic resonance imaging (dMRI)

In LBD, white matter, or the tissue composed of nerve cell connections which function to transmit information between different parts of the brain, becomes damaged as the disease progresses. An MRI technique called Neurite Orientation Dispersion and Density Imaging (NODDI) can measure the density of brain neurites, which are parts of a nerve cell that help it send and receive signals. Using this method, NIH-funded researchers were able to evaluate white matter injury over time in people with both LBD and Alzheimer's pathologies. They observed widespread changes in white matter regions in LBD, some of which were not attributed to Alzheimer's pathologies but were likely due to abnormal alpha-synuclein. These findings provide new insights into LBD disease progression and suggest that NODDI may be a useful tool to aid the diagnosis and tracking of LBD.

Another study used dMRI, a specialized form of MRI-based imaging that examines free-water in the brain to assess structural changes in the tissue associated with the progression of LBD. Over two years, free-water increased in multiple brain regions in people with LBD, likely due to brain tissue shrinkage due to neurodegeneration, and correlated with changes in cognitive decline. These findings suggest that free-water imaging may be a promising tool to track LBD disease progression.

In 2019, NIH-funded researchers helped characterize LATE, a new classification of dementia with symptoms that are often mistaken for Alzheimer's. In LATE, abnormal clusters of the protein TDP-43 form between neurons and are associated with the deterioration of parts of the brain involved in memory. It is estimated that one third of people over 85 years of age are affected by LATE, and the disease frequently occurs along with Alzheimer's pathology. This overlap in symptoms complicates the ability to diagnose LATE. To address this need, new clinical criteria for the diagnosis for LATE have been proposed. The criteria — developed only five years after the characterization of LATE — were established using data from NIH-funded research, including brain imaging, cognitive assessments, biomarker data, and available pathologic outcomes from autopsies. This set of clinical criteria is a pivotal step forward for the field, serving as an essential guide for differentiating LATE from Alzheimer's and other dementia pathologies, or identifying the existence of co-pathologies, which is critical for accurate participant screening for clinical trial as well as patient diagnosis, prognosis, and treatment.

SPOTLIGHT

Improving Diagnostics To Help Primary Care Providers Screen for Dementia

For individuals experiencing cognitive decline and their families, early detection allows for more rapid access to treatment options and supports to address needs and quality of life. Sadly, according to an NIH-funded study, the detection of early dementia is often missed in primary care settings. NIH investments are improving dementia diagnostics to help primary care doctors screen and detect dementia early.

- NIH has long supported the development of the PrecivityAD blood tests to aid in making an Alzheimer's diagnosis. A recent NIH-funded study compared results of the PrecivityAD2 blood test, with those from either a spinal-fluid test or PET brain imaging scan, and with clinical evaluations. They found that PrecivityAD2 predicted a diagnosis of Alzheimer's with 88% to 92% accuracy. The results support the use of blood biomarker tests — which is much less invasive and less expensive than spinal-fluid and imaging tests — by doctors for dementia diagnosis.
- With NIH funding, researchers developed a culturally-unbiased cognitive test, named 5-Cog, which can be administered in primary care or other everyday care settings in about five minutes when a patient, relative, or care provider have concerns. If the results suggest cognitive decline 5-Cog automatically adds notes in the patient's electronic medical record that include a set of clinical follow-up recommendations for an individual's health care provider. In addition, this simple, rapid test improved access to dementia care by tripling the odds of receiving dementia-related care within 90 days of taking the 5-Cog assessment compared to individuals who did not take the 5-Cog assessment.

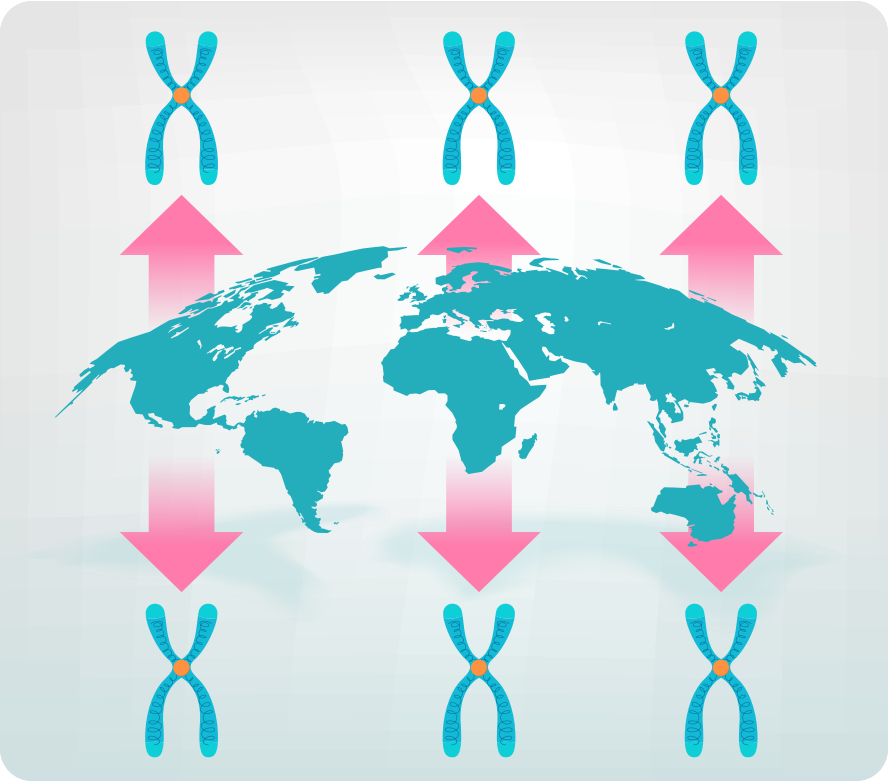
- An NIH-funded study found that people who received an annual wellness visit had a higher rate of first MCI diagnosis (21%) than those who did not. These data suggest that annual wellness visits improve early dementia diagnosis among Medicare beneficiaries, which can lead to more proactive care for these older adults.

Understanding Risk and Protective Factors for Dementia

To bring us closer to developing prevention and treatment options for all, NIH invests in research to improve our understanding of how genetic, environmental, sociocultural, behavioral, and other factors influence risk for Alzheimer's and related dementias. Recent findings are leading to innovative approaches for risk assessment and reduction, as well as identification of new therapeutic targets which hold promise for next-generation, tailored treatments.

Variations in genes — even small changes — can affect the likelihood of a person developing a disease such as Alzheimer's. In most cases, Alzheimer's does not have a single genetic cause. Instead, it can be influenced by multiple genes in combination with lifestyle and environmental factors. Identification of gene variants associated with Alzheimer's and related dementias can help predict a person's dementia risk and can inform actions to reduce that risk, such as lifestyle changes. In addition, as described earlier in this report, innovative gene therapies may be able to block or enhance gene activity to prevent or treat the disease. NIH-funded researchers are at the forefront of the search for gene variants that influence dementia risk to identify biological pathways linked to different dementia-related diseases leading to new diagnostic, prevention, and therapeutic approaches.

One approach that researchers are using to advance personalized medicine and health disparities research is to look at genetic ancestry. Genetic ancestry refers to the global region from which portions of a person's genome descended — African, Asian, American Indian, and European descent. People of the same race and ethnicity may share substantial genetic ancestry, but this is not uniformly the case across the genome. Large genetic research studies can help scientists identify unique factors that are linked to genetic ancestry. NIH-funded researchers are at the forefront of the search for gene variants that influence dementia risk, either risk factors or protective factors, in different populations to identify ways to prevent, diagnose, and treat Alzheimer's in all people.



Genetic Risk Factors for Alzheimer's Disease

While only 1-2% of Alzheimer's cases (often called early-onset Alzheimer's disease) are genetically determined, family studies suggest that genetic factors have an effect in at least 80% of Alzheimer's cases and that multiple genetic variants contribute to a person's chances for developing the more common late-onset form of Alzheimer's disease. For example, one of the strongest Alzheimer's genetic risk factors is a gene variant known as *APOE4*. A study with funding from NIH examined a large number of brain tissue samples and clinical data from

individuals of mainly European ancestry and found that people with two copies of *APOE4*, known as ***APOE4* homozygotes**, have a 60% chance of developing Alzheimer's by age 85. These findings suggest that Alzheimer's in *APOE4* homozygotes may share characteristics with known genetically determined forms of Alzheimer's. More research is needed to understand the impact of having two copies of *APOE4* across populations because existing research indicates that *APOE4* confers different levels of risk across populations of different genetic ancestry.

In a separate NIH-funded study, researchers analyzed genetic information from multigenerational families that self-identified as African American. These families have a history of Alzheimer's but no known genetic variants for early-onset Alzheimer's. Data revealed that several families had a genetic hotspot of interest on chromosome 5. Within this region, investigators identified **rare gene variants associated with late-onset Alzheimer's in people with African ancestry**. These findings, along with other NIH-funded research showing that Black **individuals with African ancestry and Alzheimer's have lower levels of amyloid compared to non-Hispanic Whites**, elevate the importance of identifying new biomarkers for people of different ancestries to help develop a successful precision medicine approach for Alzheimer's.

Protective Gene Variants

Investigators in other studies have identified gene variants that may delay cognitive impairment in individuals who are otherwise genetically predisposed to developing Alzheimer's. In one study, researchers found that having a single copy of the protective gene variant ***APOE3-Christchurch (APOE3Ch)*** was associated with delayed onset of cognitive impairment among members of an extended family with a very high prevalence of Alzheimer's. In a second study, investigators found that certain forms of the ***fibronectin 1*** gene may protect against Alzheimer's in people with one copy of *APOE4*.

A longitudinal study funded by NIH identified **nine genetic variants** that may have helped a man with a family history of Alzheimer's avoid dementia for at least two decades longer than expected. While many members of his family had a *PSEN2* genetic variant linked to early-onset Alzheimer's and developed Alzheimer's around age 50, the researchers found that this individual, at age 61, had full cognitive function, and based on memory tests, remained normal for over ten years. Notably, this man had brain amyloid plaques similar to a person with Alzheimer's but lacked the abnormal tau clusters in brain regions associated with the disease. Genetic analysis confirmed that this individual had the same *PSEN2* genetic variant as his relatives — along with nine genetic variants that his family members lacked. Six of these variants had not previously been associated with Alzheimer's but are known to be involved in neuroinflammation and protein folding. While more research is needed to narrow down the list of candidate variants, it is likely that resilience to Alzheimer's is likely influenced by a combination of genetic, environmental, and biological factors. As researchers clarify the interplay of these factors in determining who does and doesn't develop Alzheimer's, this will help reveal the underlying disease mechanisms at play and identify potential new pathways for prevention and treatment.

Psychological, Social, Behavioral, and Environmental Factors

NIH also invests in research to further explore the role of psychological, social, behavioral, and environmental factors on dementia risk and resilience. Recent studies have provided important insights, including further evidence that healthy lifestyles, such as not smoking, being physically active, limiting alcohol, eating a healthy diet, and participating in cognitively stimulating activities may be linked to better cognitive function in older adults and may also mediate risk among those at an otherwise increased risk for dementia. For example, investigators have found that an unfavorable social environment, such as economic instability, low education, lack of access to high quality health care, poor neighborhood safety, or low social support, is linked to an increased risk of dementia, but that healthy lifestyles can provide some protection.

In another study, researchers analyzed data from an NIH-funded long-term study of aging and dementia which tracked participants' lifestyle habits and scored them based on five factors: diet, physical activity, cognitively stimulating activities, alcohol intake, and smoking history. Higher scores indicating healthier lifestyles were associated with better cognitive functioning — even among those with dementia-related brain changes (e.g., amyloid beta, tau tangles, and vascular damage). In a separate NIH study, smoking was the lifestyle factor most closely linked to cognitive decline in middle-aged and older adults, based on an analysis of the associations between different lifestyle factors and decline in memory and verbal fluency in older adults from 14 European countries over 10 years.

Other individual elements of a healthy lifestyle may independently influence cognition, as well. For example, NIH-funded investigators found that higher adherence to the MIND diet, which is rich in nutrients important for brain health, including green leafy vegetables, berries, beans, nuts, and one or more weekly servings of fish, was associated with a slower pace of biological aging and a lower risk of dementia. In another study, adherence to a MIND-style diet was associated with slower rates of cognitive decline, with effects being stronger in women than in men and in Black older adults than in White older adults. Conversely, food insecurity in older adulthood has been associated with increased dementia risk and more rapid memory decline.

Social factors have also been shown to influence cognition. In the largest meta-analysis to date on the association between loneliness and dementia, investigators confirmed associations between loneliness and Alzheimer's, vascular dementia, and non-dementia cognitive impairment. For example, an NIH-funded study found that individuals with dispositions that are neurotic

or often experience anxiety, fear, anger, and guilt are more likely to be diagnosed with dementia than individuals who tend to be more conscientious, extraverted, or regularly experience feelings such as joy, interest, and alertness. The results support the idea that certain personality traits may be risk factors for dementia and may help identify individuals at higher risk and inform behavioral interventions to help reduce risk.

Other NIH research has linked education to a lower risk of dementia. For example, an NIH study found that higher educational attainment is associated with lower dementia risk in five countries (United States, England, Mexico, China, and India), suggesting that efforts to improve education in high- and middle-income countries may yield cognitive health benefits in the future. Another study found that higher levels of adolescent cognitive ability, including greater educational attainment, is associated with a lower risk of cognitive impairment and dementia in older adulthood. Together, these studies on the association of education and dementia risk underscore the influence of early-life factors on long-term cognitive health.

Finally, both physical and emotional stressors may increase dementia risk. For example, NIH-funded researchers have found that racial discrimination during middle age predicts higher levels of blood biomarkers for neurodegeneration a decade later, and that chronic psychological stress is associated with the appearance of brain biomarkers of Alzheimer's in cognitively normal midlife individuals — but the specific biomarkers vary by sex and menopausal status in women. In regard to physical stressors, an international team led by NIH intramural investigators found that influenza, viral, respiratory, and skin infections were associated with increased long-term dementia risk. The team also identified molecular mediators by which infections may contribute to neurodegeneration.

Collectively, as NIH-funded research uncovers the many aspects of a person's life that can affect their risk of developing dementia — from education to diet — we move closer to finding new solutions to reduce these risks and potentially prevent dementia in the future.

Sex Differences and Dementia Risk

Roughly two-thirds of individuals diagnosed with Alzheimer's in the United States are female, and women's longer average life span does not fully explain this disparity. NIH supports research to characterize, understand, and where possible, address sex-based differences in dementia risk.

For example, amyloid plaques typically appear in the brain years before the onset of clinical symptoms, but research suggests sex differences in the disease trajectory. An NIA intramural collaborative study found that while women are at higher risk than men to develop dementia, once amyloid pathology appears in the brain, men experience steeper increases in blood and brain biomarkers than women. At the same time, men had steeper declines in brain volume and cognitive performance than women. However, other recent research has shown that while both men's and women's memory networks have compensatory mechanisms that are triggered as Alzheimer's pathology spreads through the brain, these mechanisms may be less effective in women. These findings may help explain the accelerated trajectory of cognitive decline in women and may provide new treatment targets to reduce Alzheimer's risk in women. Whether men or

women show more rapid decline has varied across studies, and age is one factor receiving additional attention as a modifier influencing the direction of sex differences.

Researchers have also identified marked sex differences for individuals living with LBD, such that women are more likely than men to have Lewy body pathology combined with Alzheimer's pathology. NIH researchers sequenced the X-chromosome — a chromosome involved in sex determination — to identify sex-specific genetic risk factors in women with LBD. They found that MAP3K15, one component of the MAPK pathway, is specifically associated with LBD in women. The MAPK pathway regulates cellular activities such as cell growth, cell survival and programmed cell death and is linked with the risk of developing Alzheimer's and Parkinson's disease. The findings suggest a potential role of Alzheimer's-related genetic risk for women with LBD and highlights the importance of considering sex differences, especially for differential diagnoses and mixed dementia. A better understanding of the differences in the processes that contribute to sex differences in dementia risk help inform personalized approaches to reduce dementia risk and improve treatments to bridge the gap between men and women living with Alzheimer's and related dementias.

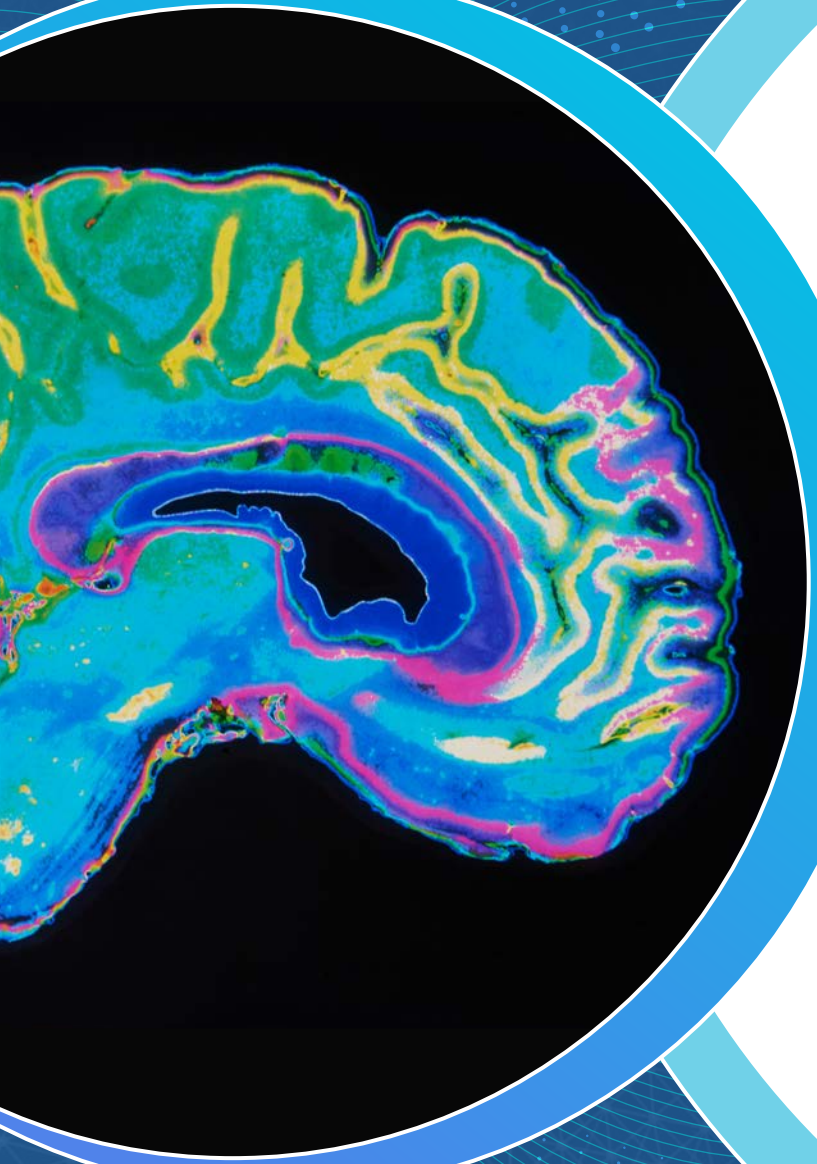
SPOTLIGHT

Social Determinants of Health and the Exposome

Understanding and measuring the interaction of different exposures across the lifespan, and the cumulative effect of these exposures — such as lifestyle, social, and environmental risks — on health outcomes is crucial to advance the science of dementia risk, resilience, and disparities to inform approaches to reduce dementia risk.

To foster collaboration and accelerate life course research on the social, behavioral, psychological, and economic exposures that shape Alzheimer's and related dementias outcomes, NIA established an innovative Exposome Coordinating Center in August 2024. Through interdisciplinary collaboration and with input from the research community on priority data needs, the Center will serve as a centralized hub for accessing, harmonizing, and linking environmental data and individual exposure data for NIH-funded research projects across six areas: climate, physical environment, policy, community services, social environment, and life experiences.

Complementing this Center, NIH has also established a robust, cross-disciplinary consortium that uses a precision environmental health approach to stimulate research on the body's response to a wide range of environmental toxicants, including air pollution, heavy metals, and microplastics, and how these factors contribute to dementia and disease risk and progression in humans.



Identifying Biological Pathways and Brain Changes That Contribute to Dementia

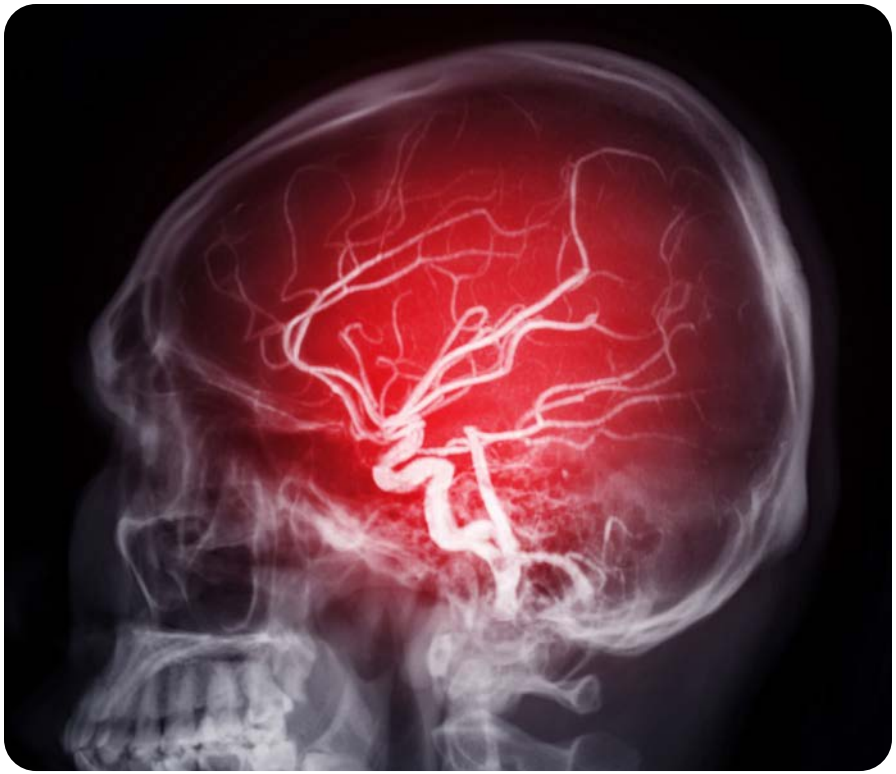
Healthy brain function depends on the operation of biological pathways that consist of intricate, interwoven series of molecular, cellular, and systemic processes. With investments from NIH, researchers are uncovering diverse pathways involved in the progression and risk of developing dementia. Such discoveries are undoubtedly advancing the field's understanding of disease progression and bringing us closer to developing precision prevention and treatment approaches.

Changes to the Brain Vasculature

One area of active research is the investigation of strong links among vascular disease in the brain, cardiac disease, and cognitive decline leading to dementia. This area of research is referred to as "vascular contributions to cognitive impairment and dementia," or VCID. Importantly, several NIH-supported research studies have uncovered biological pathways associated with dementia that involve the brain's blood vessels, including post-stroke cognitive decline. Additionally, a significant side effect associated with FDA-approved anti-amyloid immunotherapies are brain hemorrhages, or bleeding due to damaged vessels. Recent research in human cells and in mice demonstrated that small clumps of amyloid beta trigger molecular pathways that lead to reduced energy production and death in cells that compose arterial walls in the brain. Separately, an NIH-supported research team using a high-resolution imaging technique found that changes in blood flow precede changes in blood vessel structure and co-occur with early stages of Alzheimer's pathology in brains of young mice that model genetic forms of Alzheimer's. These findings provide important new insights about the biological processes involved in vascular health and may inform future research on treatments for Alzheimer's and related dementias, including vascular contributions to cognitive impairment and dementia.

Changes in Brain Metabolism

NIH-funded scientists are examining how disruptions in brain metabolism, or energy production in the brain, may lead to cellular energy depletion and thereby affect cognitive decline. As a key example, experiments in mouse models of Alzheimer's



and in cells generated from humans with or without Alzheimer's, NIH-funded researchers found that abnormal forms of amyloid beta and tau increase the activity of a protein, called IDO1, that regulates energy production of astrocytes — a type of cell that supports neurons. In turn, this overactivation of IDO1 reduces the astrocytes' capacity to produce and provide energy to neurons. Interestingly, the team observed that reducing IDO1 activity reverses biological dysfunction triggered by amyloid beta and tau. These findings suggest that targeting IDO1 may provide a therapeutic strategy for Alzheimer's, and potentially a range of other neurodegenerative conditions that differ in their hallmarks but share metabolic disruption as a common feature.

Role of Specific Proteins in Disease Pathways

Other NIH-supported research strives to identify the specific proteins and roles in disease processes associated with dementia. In several cases, researchers are gaining deeper insight into proteins and pathways previously implicated in disease progression. For example, NIH-supported research demonstrated that components of a molecular pathway involving the APOE receptor 2, which binds to APOE — a key protein implicated in dementia — accumulates in brains of individuals with mild cognitive impairment or sporadic Alzheimer's disease. Additionally, in a study focused on TDP-43, another protein implicated in multiple forms of dementia, researchers analyzed a large set of brain autopsies and found that TDP-43's cellular location and function in brain cells start to become compromised at approximately 50 years of age, about a decade before TDP-43 begins to form disease-characteristic deposits.

Additionally, NIH-funded investigators sought to interrogate the role of amyloid beta, a classic hallmark of Alzheimer's, in a specific heritable form of Alzheimer's involving mutations in the *PSEN1* gene. These researchers found that Alzheimer's mouse models with mutations in the *PSEN1* gene showed similar signs of dying brain cells with or without the gene that encodes amyloid beta. This finding suggests that neurodegeneration in *PSEN1*-associated dementia is not driven by amyloid beta, adding to a body of work suggesting that *PSEN1* genetic variants may cause dementia in humans through loss of the protein's essential function, rather than effects on amyloid. The study may have implications for treatment, as it suggests that removing amyloid is unlikely to be effective for treating patients with dementia caused by *PSEN1* gene variants.

In addition to studies to further understand the roles of known molecular players, NIH continues to invest in studies that uncover new proteins involved in disease. For example, an NIH-supported study identified for the first time that abnormal assemblies of the protein TAF15 may provide a molecular signature of disease in brains of a subset of individuals with FTD. While the role of TAF15 filaments in disease remains to be studied, the discovery of this protein's relevance could provide the basis for follow-up work to develop tools to diagnose a subset of FTD. In another study funded by the NIH, researchers discovered that the proteins ANX11 and TDP-43 aggregate together in a subtype of FTD. These molecular players identified in subtypes of FTD could pave the way for new therapeutic targets and a precision medicine approach to dementia.

Advanced Assays To Identify Biological Pathways Involved in Dementia

In service of these and future findings, NIH invests in the development and application of innovative techniques to identify the biological pathways that underlie dementia, as well as to determine the extent to which these pathways are shared between diseases. For example, an NIH-supported study compared gene-related molecular changes that occur in brains of deceased individuals whose tissue showed biological signatures of Alzheimer's or LBD. In a core finding of this work, Alzheimer's and LBD appear to share common pathways that are broadly associated with brain inflammation, while each also involves distinct inflammatory processes that are specific

to the disease. Separate work funded by NIH utilized large-scale measurements of protein abundance to demonstrate that Alzheimer's and LBD are associated with both distinct and overlapping changes in "networks" of related proteins. Such insights into the common and unique characteristics of each type of dementia will inform research into mixed dementias and reshape how researchers and clinicians approach the field.

In a technical tour de force, an NIH-supported study analyzed over 1 million cells from brains of nearly 50 deceased individuals with and without Alzheimer's disease to identify associations between Alzheimer's and changes in specific cell types, brain regions, and biological pathways. The researchers diagnosed Alzheimer's in these individuals based on the presence and location of amyloid beta and tau aggregates. This study provided evidence that a special population of neurons expressing the protein Reelin were particularly depleted in Alzheimer's. By implicating the Reelin protein in brain cell loss, the study parallels a previous finding that a Reelin genetic variant conferred resilience to disease progression in an individual with a heritable form of Alzheimer's. Altogether, these two findings build upon each other to implicate Reelin as important in neuronal survival and could be a target to bolster resilience against dementia.

New Insights into the Progression of Alzheimer's Disease and Related Dementias

NIH-funded research continues to elucidate hidden complexities in the progression of dementia. Through an extensive analysis of molecular changes in a brain region associated with the transition to advanced Alzheimer's disease, researchers funded by the NIH BRAIN Initiative determined that Alzheimer's affects the region in two distinct stages: an initial stage in which disease hallmarks accumulate gradually, and a second stage in which more severe hallmarks develop rapidly.

Scientists are also identifying new associations between the progression of brain changes traditionally linked to distinct forms of dementia. For example, NIH-funded researchers studying when and where protein deposits tend to appear in brains of individuals with LBD not only identified multiple spatial patterns of disease progression, but also that these patterns tend to co-occur with Alzheimer's disease-associated brain changes at different rates.

These two detailed studies provide snapshots into how Alzheimer's and LBD progress, but the full potential value of this work is yet to be realized, as these studies will serve as reference atlases for further investigations.

SPOTLIGHT

APOE and Immune System Interaction in Dementia

The *APOE* gene is well-recognized as playing a critical role in Alzheimer's and related dementias, with the variant *APOE4* serving as a significant risk factor for Alzheimer's. One active area of robust research is to understand the mechanism by which the APOE protein, encoded by the *APOE* gene, can affect the functioning of immune cells and influence disease onset and progression.

Recently, NIH-funded scientists determined that ***APOE4*** promotes lipid buildup in immune cells found in the brain, called microglia. Stopping this buildup reduces tau pathology and neuroinflammation in mouse models of Alzheimer's. Additionally, when a group of NIH-funded researchers blocked the APOE protein from binding to a protein receptor called LILRB4 located on the surface of microglia, they observed a reduction in amyloid beta plaques and Alzheimer's-associated risk-taking behavior in mouse models of dementia. Their findings suggest that a therapeutic that targets this interaction could potentially allow microglia to better clear amyloid beta plaques and ameliorate symptoms associated with Alzheimer's. Furthermore, NIH-funded researchers have started to uncover how a rare variant of *APOE*, called *APOE3ch*, confers resilience to Alzheimer's (i.e., protects against the disease) by studying mouse models with the variant. Mice with the *APOE3ch* variant appear to have enhanced microglial activity and reduced tau tangle formation, providing further support for the idea that microglia may play an important role in dementia disease processes. Understanding how rare variants promote dementia resilience opens new avenues for developing treatments.

Recent scientific advances also provide evidence for interaction between *APOE* and the peripheral immune system that operates primarily outside of the brain. For example, an NIH-funded study found that peripheral immune cells in the blood of individuals with Alzheimer's are epigenetically altered — meaning the immune cell's DNA is changed in a way that affects gene expression without altering the DNA sequence of the cell — and that some of these changes are dependent on which *APOE* gene variants the individuals possess.

In another study, NIH intramural researchers identified proteins associated with cognitive resilience — meaning they did not develop cognitive impairment — in women who carry the *APOE4* risk gene for Alzheimer's. Two of the proteins are known to be involved in immune system signaling (PTX3, NCR1). Importantly, this set of proteins was unique to women with the *APOE4* gene and is largely unique from proteins associated with cognitive resilience in women with the protective risk gene, *APOE3*. These findings suggest that specific immune responses may play a role in preserving normal cognition in women despite an elevated genetic risk for Alzheimer's. Collectively, these results suggest that immune dysfunction in dementia is associated with *APOE* and the protein for which it codes, and more work is needed to understand how to target the immune system to halt or slow the onset and progression of dementia.

Advancing Care and Caregiving Research

While progress in treating and preventing dementia continues, there is also a critical need to provide comprehensive care for those currently living with dementia and to provide their care partners with information and support. NIH funds a wide range of care and caregiver research, from understanding the economic impact of dementia care to improving care at home and in long-term care facilities, to help address the complex needs of individuals living with dementia and provide evidence-based support for them and their caregivers.

Predictive Care Models

Caregivers, families, and those living with dementia often grapple with the question of if, or when, to move a person with dementia to a long-term care facility, like a nursing home. Using large data samples from NIH-funded research resources, researchers have developed computational models to help predict the need for nursing care among older adults living with dementia. The models used a combination of dementia-predicting details such as age, general health, the ability to perform activities of daily living, driving status, and history of falls. In addition to the current standard process of self-reported information as well as information typically provided by a caregiver or family member, the predictive models may provide additional information to help caregivers as they discuss future care plans and may alert clinicians to patterns that could inform changes in care recommendations.

Dementia Care Quality

Many factors influence care quality for nursing home residents with dementia. One NIH-funded study analyzed the relationship between staffing and health outcomes in nursing homes with different percentages of residents with dementia. While increasing nursing staff had positive effects on outcomes, there were notable outcome differences between nursing homes with high and low populations of residents with dementia, regardless of the staffing level. For example, in nursing homes with larger numbers of dementia patients, there was greater use of medications to manage behavioral and psychological symptoms of dementia, and a greater decline in activities of daily living among residents. However, these same homes had better outcomes in terms of fewer pressure sores and fewer emergency room visits, when compared to nursing homes with fewer dementia residents. These findings suggest that increased staffing may only be part of improving care for nursing home residents and point to the need to examine additional areas for improvement, including staff training and retention and facility design.

Dementia Care Costs and Decision-Making

Dementia care is expensive, and NIH research has revealed significant differences in costs between different groups of individuals. For example, an NIH study analyzing sixteen years of Medicare claims found that dementia care expenditures were higher for Black and Hispanic people than White beneficiaries. Another NIH study examined racial and ethnic disparities in the monetary value of informal caregiving for people with dementia — which is unpaid, ongoing assistance provided by individuals, typically family members or friends — and found that informal caregiving is valued at an annual replacement cost of $44,656 for Hispanics, $37,508 for Blacks, and $25,121 for Whites.

Crucial care decisions arise when a person living with dementia is facing potential admission to a long-term acute care hospital (LTCH) — a facility specializing in treating seriously ill patients who are often transferred from an intensive care unit and typically stay three to four weeks. An NIH-funded study found that within 2.5 years of admission to a LTCH, 80% of adults over age 50 either died or had poor long-term cognitive and/or physical outcomes after prolonged hospitalization. People living with dementia or other significant impairment had the poorest

outcomes. These results underscore an urgent need for more discussions about palliative care and care goals for people living with dementia.

Increasingly, people living with dementia prefer home- and community-based services (HCBS) such as home health care, respite care, and adult day care programs that will allow them to live longer in the community, instead of prematurely entering a nursing home or an assisted living residence. However, gaps persist in understanding the cost, quality, and accessibility by communities that are medically underserved. To address this crucial but complex need, NIH is funding collaborative research centers.

One example is the Community Care Network for Dementia (CaN-D) which is designed to foster knowledge-sharing, develop valuable data tools on structure, process, and outcome measures of dementia HCBS, and to grow the care research community. Another is the State Alzheimer's Support Center (StARS) which is building a national data infrastructure to enable states and communities to better understand the effect of dementia care services on care transitions and inform research on dementia care services within and across states. These centers are generating data to help address gaps in access to, quality of, and costs of dementia HCBS.

Lucidity and Dementia

Lucid episodes are characterized by periods of mental clarity in individuals with dementia who are assumed to have lost coherent cognitive capacity. As lucid episodes are commonly reported by care providers and family caregivers, there is a need to characterize these episodes to improve understanding of the neurobiology of dementia and a more nuanced concept of the minds of people living with dementia.

NIH-funded researchers conducted interviews with 30 family caregivers of individuals with severe dementia and found that 25 described a total of 34 lucid episodes, revealing that brief bouts of lucidity are common. The family members often called the lucid episodes — ranging from seconds to almost 45 minutes — a small, positive "blip" in an otherwise negative downward journey with their loved one. For many caregivers, the lucid episodes affected their day-to-day approaches to care and suggests that clinicians should ask caregivers if they have witnessed such events to help inform ongoing care efforts.

Another study identified four types of lucid episodes based on information collected from family caregivers of individuals living with dementia, including proximity to death, cognitive status, duration, communication quality, and circumstances prior to lucid episodes. The most common type of lucid episode occurred among individuals with dementia who were not at the end of their life, and during family visits. These findings suggest that lucid episodes can be precipitated by external stimuli. While research on lucidity is challenging when families are managing the many aspects of caring for a loved one with dementia, additional research is important to confirm these types of lucid episodes and the factors influencing their occurrence.

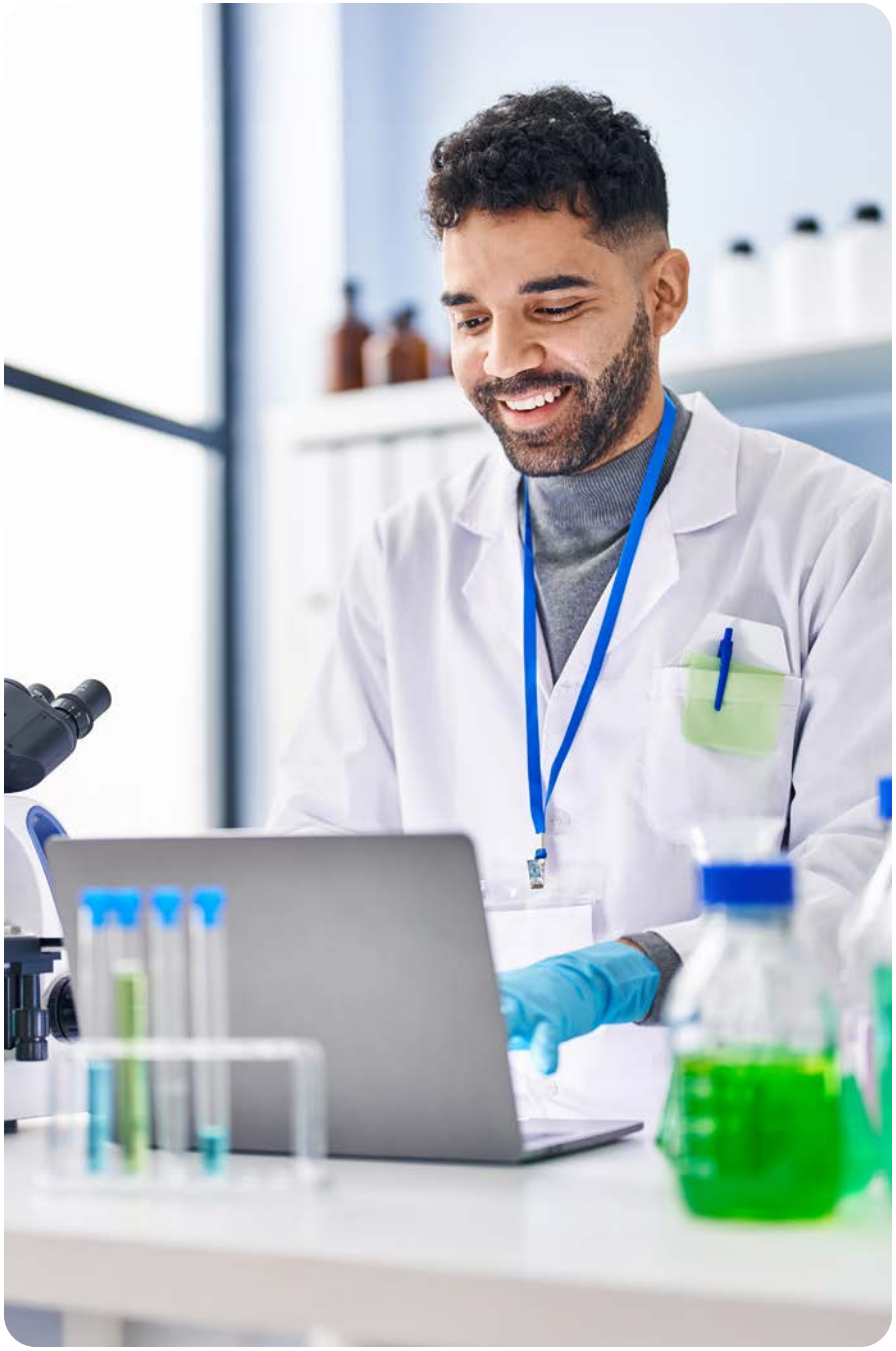
Research Enterprise

The growing prevalence of dementia underscores the compelling need to provide nimble systems to support data sharing and develop innovative research resources and technologies to accelerate scientific discoveries. Building on existing advances in science and medicine, NIH remains committed to bolstering the Alzheimer's and related dementias research enterprise through a multifaceted approach to conduct and support research, build robust research infrastructure, and foster collaborations across a wide spectrum of scientific fields.

Stimulating and Accelerating Alzheimer's and Related Dementias Research at NIH

The NIH's Center for Alzheimer's and Related Dementias (CARD) is a collaborative, intramural research initiative between NIA and NINDS. Through CARD, NIH researchers work across scientific domains and disease boundaries to bridge basic, preclinical, and clinical research to initiate, stimulate, accelerate, and support research that will lead to the development of improved treatments and move towards prevention of Alzheimer's and related dementias.

In addition, CARD builds innovative technologies and resources, such as different brain cell lines with genetic variations associated with Alzheimer's, to support researchers around the world. In 2025, NIH started construction for the CARD Clinical Center on the Bethesda campus, with official opening expected in 2027. The addition of this new clinical facility will position CARD to conduct collaborative research across the entire research pipeline, to accelerate the development of improved treatments and prevention of dementia.



CARD Research Resources and Tools

Recent advances from CARD demonstrate its contributions to strengthening the research enterprise through training, research collaborations, resource sharing, and tools development.

Resource Sharing and Collaborations

CARD is helping to accelerate the pace of research innovations globally by making cell lines and data available to researchers around the world through two key projects involving stem cells, called induced pluripotent stem cells (iPSCs), that are derived from blood or skin cells from study participants:

The iPSC Neurodegenerative Disease Initiative (iNDI) project developed individual stem cell lines for over 135 genetic variants across 73 genes associated with Alzheimer's and related dementias. In phase two, these cell lines are being made into different brain cell types, including neurons, to find new biomarkers of disease progression and examine how disease affects different types of brain cells. Close to 500 lines are available through Jackson Laboratories, and more than 700 labs across 30 countries have purchased lines.

The iPSCs to Study Diversity in Alzheimer's Disease and related dementias (iDA) project has developed stem cell lines from 200 research participants. These cell lines represent nearly all APOE genotypes and capture wide ancestral background, a critical step to understanding why APOE related risk for Alzheimer's disease varies greatly between ancestral groups.

Training

CARD, in collaboration with UMBC, has established a two-year Master of Professional Studies in Data Science Fellowship program which provides a unique pathway to a career in biomedical data science. There are currently 10 fellows enrolled in CARD's Master of Professional Studies in Data Science Fellowship Program.

Tools

Current tools available to the scientific community include:

OmicSynth is an open resource to accelerate the identification of evidence-based, therapeutic targets for neurodegenerative disease. The framework includes a user-friendly web platform to identify genetic targets for drug discovery and repurposing.

GenoTools is a customizable tool to analyze and manage genotype datasets to streamline populations genetics research by integrating ancestry information, quality control, and genome-wide association study results to support novel discoveries in neurodegenerative diseases in diverse populations.

ProtPipe is an open-source tool to visualize and automate dataset analysis to identify proteins and cellular pathways involved in neurodegenerative disease. This tool helps researchers improve the understanding of these diseases to aid the discovery of biomarkers and potential therapeutic targets.

Data Sharing

A valuable aspect of advancing scientific research is the capacity to share data, which allows researchers to leverage resources, accelerate innovation and scientific discoveries, improve efficiency, strengthen collaborations, and inform decision-making. NIH continues to invest in the development of infrastructure to support and expand data sharing.

For example, CARD provides multiple open-access data repositories, such as CRISPRbrain, to provide searchable data on the functions and pathways associated with various genes, variants, and regions in a variety of human cell types. These resources enable researchers to explore, visualize, and compare this data to ask new questions in dementia research.

NIH also recognizes the importance of sharing data, including from trials that may not have met primary endpoints. For example, the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study was a multi-site trial that tested whether the drug solanezumab could slow cognitive decline in the earliest stages of Alzheimer's. While no beneficial treatment effects were observed with solanezumab compared to placebo, the scientific community can now download and explore the A4 trial data and biosamples. Using these data, researchers can learn about the disease process and the molecular and mechanistic determinants of responsiveness to treatment. Analyses of A4 screening data and biosamples have already provided new insights on disease biology, Alzheimer's biomarkers in ancestrally diverse individuals, and sex differences in cognitive performance and neuroimaging biomarkers.

Another example of an NIH-funded data sharing resource is the Dementia DataHub, which identifies Medicare recipients diagnosed with dementia by geographic location. The system enables the analysis of Centers for Medicare & Medicaid Services (CMS) administrative healthcare data and provides publicly accessible information on diagnosed dementia across the United States.

Additionally, in November 2024, NIH launched the Down Syndrome Cohort Development Program (DS-CDP) to enhance understanding of Down syndrome and related health conditions, including Alzheimer's, by tracking individuals with Down syndrome from infancy to adulthood. This initiative will leverage an existing data coordinating center, making it easier for scientists and the Down syndrome community to work together.

Furthermore, the NIH research community is excited about how artificial intelligence (AI) and its related field of machine learning (ML) can expand tools and models using large, open-access datasets to accelerate research in Alzheimer's disease and related dementias. For example, CARD collaborators created FAIRkit, a tool that uses AI to automate labor-intensive aspects of data discovery, such as data harmonization — a process of integrating and transforming data from various sources and formats into a single, unified dataset. Through a large consortium effort led by CARD, FAIRkit is being extended to catalogue and connect all public research data on Alzheimer's disease. Another project is CARD.AI, an advanced AI tool developed to answer questions related to biomedical research and neurodegenerative disorders. By leveraging AI and ML, these tools and others are helping to amplify data sharing activities and analysis to inform new research hypotheses and find new solutions to diagnose, treat, and ultimately prevent Alzheimer's and related dementias.

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 High School, Undergraduate, and Postbaccalaureate Students and Science Teachers

Two of NIH's signature programs are the Expanding Research in Alzheimer's and Related Dementias research education programs. The first program is for high school students, undergraduate students, and science teachers, while the second program focuses on postbaccalaureate students. Four new programs were funded in 2024.

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 Alzheimer's and Related Dementias (IMPACT-AD) aims to expand 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 the Next Generation of Scientists in Alzheimer's and Related Dementias Research

NIH supports programs for early career scientists, as well as established investigators that are new to the field, conducting projects that improve the prevention, diagnosis, treatment, or care for individuals with Alzheimer's disease and related dementias.

One such program is the Small Research Grant Program for the Next Generation of Researchers in Alzheimer's and Related Dementia Research which encourages the next generation of researchers to pursue research and academic careers in dementia research and stimulates established researchers who have not had a major award in dementia research to perform pilot studies to develop new, innovative research programs that leverage their existing expertise. Over 30 of these projects were funded in 2024.

Another example is NIH's Research and Entrepreneurial Development Immersion program to help better prepare biomedical researchers for the full spectrum of modern career options beyond tenure-track faculty positions. More than 150 early-career researchers benefited from this and similar programs in 2024.

Looking Forward

NIH-funded research on Alzheimer's and related dementias holds immense promise, exemplified by the significant scientific progress made over the last year and driven by sustained and increased investments in the research. NIH has continued to advance our understanding of the risk and protective factors, underlying biology, and potential avenues for treatment and care. The achievements described in this report are the result of decades of investments which have supported the broad work across the pipeline, from basic to translational to clinical research. NIH is grateful to the researchers, study participants, care partners, and others who were essential to achieving this progress. Looking forward, NIH remains committed to exploring new research opportunities and sustaining our current promising efforts to bring us closer to preventing and treating dementia for all people.

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