A New Era:
Driving Momentum in Alzheimer's and Related Dementias Research

National Institutes of Health

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SPOTLIGHTS: Key Opportunities

Message from NIH Leadership

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On behalf of the National Institutes of Health (NIH), I am pleased to present the NIH Professional Judgment Budget for Alzheimer's Disease and Related Dementias for Fiscal Year (FY) 2025. This document outlines a funding proposal as well as examples of the future research efforts that can be pursued with additional investment in FY 2025. NIH envisions that each of the research initiative examples described within will build upon recent scientific advances and leverage existing research infrastructure, much of which was made possible by generous Congressional support for Alzheimer's and related dementias research.

Although more work is needed, we are closer than ever before to meeting the first goal of the National Plan to Address Alzheimer's Disease: to prevent and effectively treat Alzheimer's and related dementias. These efforts are only possible through meaningful collaboration among the research community, industry, and the broader public. NIH is grateful for the many individuals who have participated in the clinical trials that have helped advance the field to where it is today, and we are committed to leveraging this momentum and delivering even more promising research breakthroughs for people living with dementia and their families.

I am excited and tremendously encouraged about the new era of research on Alzheimer's and related dementias that we have entered, where the outcomes and effects of decades of work are beginning to bear tangible fruit. Perhaps the most notable examples are recent results from Phase 3 clinical trials testing the effects of drugs that target amyloid in the brain, a hallmark of Alzheimer's, in participants in the early stages of the disease. These trials have demonstrated that treatment with these drugs significantly reduces the amount of amyloid burden in an individual's brain and can significantly slow the rate of cognitive decline. These milestone therapeutic advancements mark the beginning of a new era of promise for the field and have reinforced the importance of pursuing amyloid as a strategic therapeutic target.

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Although NIH did not fund these specific trials, NIH research was integral to helping understand the role of amyloid in Alzheimer's. NIH supported basic science investigations led to the discovery of many candidate antibodies that were the basis for these immunotherapies as well as efforts to help translate those findings into potential treatments. Furthermore, NIH contributed to the development of amyloid PET imaging, which was used to select participants for these trials, as well as clinical tools used to measure cognition. NIH also continues to fund multiple clinical trials testing anti-amyloid therapeutics, including three that are testing the drug lecanemab in treating different stages of Alzheimer's.

In addition to interventions designed to clear brain amyloid, NIH is supporting a broad portfolio of trials of drugs aimed at a diverse array of targets, including protein accumulations other than amyloid (e.g., tau), brain inflammation, and more. NIH also funds several non-drug trials for the prevention and treatment of Alzheimer's, including those testing interventions such as cognitive training, diet, and physical activity. Continued clinical research will provide the research community with more evidence about how these interventions, as well as combinations of these approaches, can effectively reduce dementia risk and/or slow cognitive decline across diverse populations, including — importantly — communities who have been historically underrepresented in biomedical research.

Advances in therapeutics have also been accompanied by an enhanced understanding of dementia biomarkers and mechanisms. Research has revealed that these diseases are profoundly complex, and individuals are often living with "mixed" dementia, a condition in which more than one dementia pathology is observed to occur simultaneously in the brain. For example, buildups of amyloid and tau proteins in the brain, generally associated with Alzheimer's disease, often co-occur with blood vessel damage typical of vascular dementia. These findings underscore the importance of applying a personalized medicine approach to treating dementia, where everyone receives the treatment or combination of treatments that is best for them. Essential to precision medicine is a dedication to ensuring clinical research is inclusive so that results of clinical trials are applicable to all populations, especially those most at risk for dementia. NIH remains committed to recruiting and retaining a broad range of clinical trial participants from underrepresented communities and to expanding and diversifying the Alzheimer's and related dementias research workforce. These efforts are key to addressing existing health inequities as we enter a time in which research results are beginning to be translated into clinical practice.

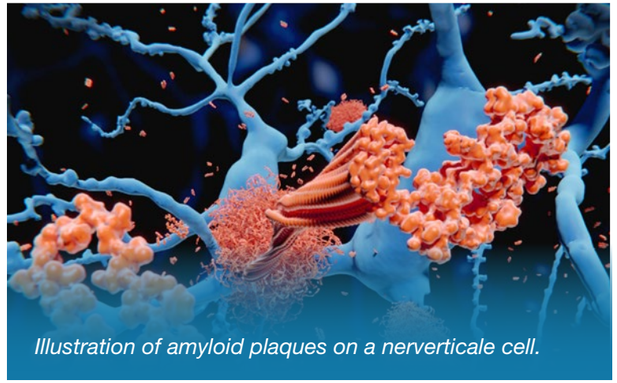


Illustration of amyloid plaques on a nerverticale cell.

Accomplishments of the Last Decade

With increased investment in Alzheimer's and related dementias research, NIH has been able to spearhead incredible progress over the last decade. Accomplishments include:

- Advancing our understanding of the risk factors, genetics, and mechanisms of dementia
- Diversifying and de-risking the therapeutic pipeline for disease-modifying drugs
- Accelerating drug repurposing and combination therapy development
- Developing tools to detect, diagnose, and monitor dementia
- Advancing clinical research on lifestyle interventions
- Increasing our understanding of how social and environmental factors affect dementia risk and disparities
- Expanding research on dementia care and care partner supports

Accompanying the release of this prospective Professional Judgment Budget, NIH has also released a Progress Report on Alzheimer's Disease and Related Dementias Research. This year's report provides a summary of pivotal dementia research advances from the last 10 years, including a more in-depth review of the accomplishments highlighted above.

A Roadmap for the Future

We have entered a new era for dementia research, in which evidence now indicates that removing amyloid in the brain of individuals with Alzheimer's disease can modestly slow cognitive decline. In July 2023, the anti-amyloid antibody lecanemab-irmb (brand name Leqembi) received approval from the Food and Drug Administration (FDA) based on a demonstrated effect in slowing cognitive decline. It is the first traditional (full) approval of a treatment that affects the underlying disease process of Alzheimer's, instead of only treating the symptoms of the disease. In addition, biomarker research has also accelerated, and the field has now developed less invasive and less expensive diagnostic tools with the potential for broad scalability. These advances aid researchers in diagnosing disease earlier, tracking disease progression, selecting a diverse range of participants for clinical trials, and measuring response to potential treatments. We must continue to sustain this hard-won pace toward reaching the goal of finding effective treatments for all by prioritizing promising basic, translational, and clinical research on dementia.

The FY 2025 Professional Judgment Budget for Alzheimer's Disease and Related Dementias presents examples of research opportunities that could be pursued with additional investments to ensure that we preserve this critical momentum in dementia research. Within this narrative, we describe the additional resources needed to pursue examples of promising new research opportunities that can help accelerate progress toward the goals of the National Plan.

Investment priorities are organized along six research areas:

- Epidemiology/ Population Studies
- Translational Research and Clinical Interventions
- Disease Mechanisms
- Dementia Care and Impact of Disease
- Diagnosis, Assessment, and Disease Monitoring
- Research Resources

Among the research opportunities described across these six areas, we feature as Spotlights three bold endeavors that NIH seeks to accomplish with increased Alzheimer's and related dementias research investment in FY 2025. Furthermore, we emphasize cross-cutting research efforts focused on international studies, findings from which benefit the entire dementia research enterprise. Such work will bring us all closer to being able to effectively treat and prevent Alzheimer's and related dementias and have a real impact on individuals and families affected by these diseases.

Professional Judgment Budget: FY 2025

Annual Budget Estimate

This budget proposal outlines the additional funding needed in FY 2025 to advance NIH-supported research toward achieving the goals outlined by the National Plan. The professional budget estimate includes $318 million in additional resources for new research, with the overall resources needed totaling $4.07 billion. The projected cost of resources needed in FY 2025 for new research is $504 million. This estimate is reduced by $186 million in funding from completed projects that will be available for new research initiatives. As a result, the additional resources needed for new research in the FY 2025 budget is $318 million.

Impact

Alzheimer's and related dementias take a tremendous emotional, physical, and financial toll on the individuals living with these diseases, their loved ones, and society. NIH is focused on turning new discoveries into health to meet the needs of the estimated 6.7 million Americans currently living with Alzheimer's as well as individuals living with other forms of dementia, such as Lewy body dementia, frontotemporal dementia, and vascular cognitive impairment/dementia. NIH has made remarkable progress in our understanding of these diseases and has revolutionized how they are diagnosed in clinics around the country. The first wave of disease-modifying therapeutic interventions for dementia is emerging, and clinical trials for potential next-generation therapeutics — aimed at a range of novel disease targets — are underway. In addition, researchers now know that intensive blood pressure control can reduce the risk for mild cognitive impairment, often a precursor to dementia. This progress would not have been possible without sustained federal funding in dementia research. With increased investment, NIH will leverage this tremendous progress to bring the research field even closer to effectively preventing, detecting, and treating these challenging and complex disorders.

An estimated

6.7M

Americans are currently living with Alzheimer's disease

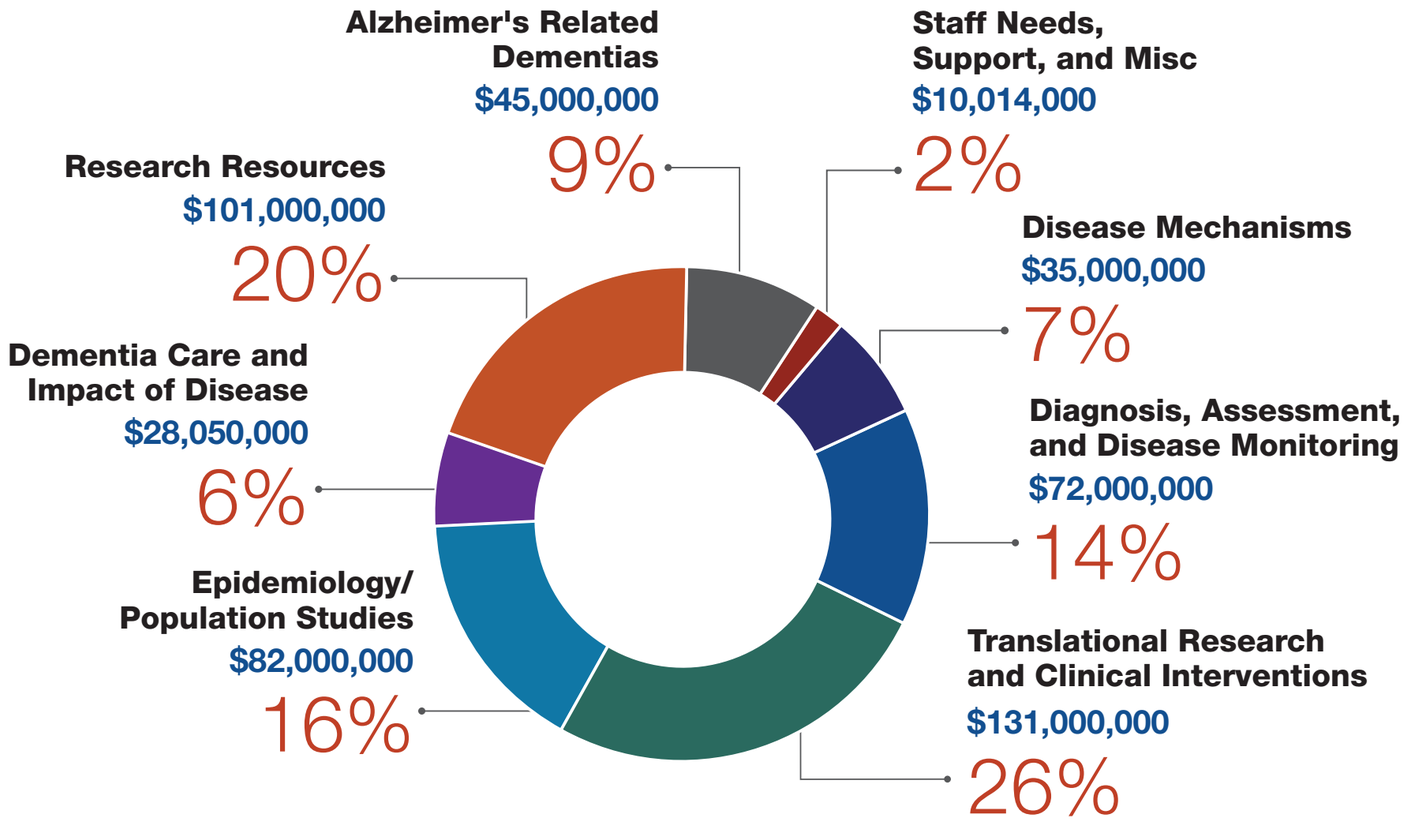
FY 2025 AD/ADRD Professional Judgment Budget

PROFESSIONAL JUDGMENT BUDGET FY 2025 ADDITIONAL RESOURCES NEEDED	*Amount*
Epidemiology/Population Studies	$82,000,000
Disease Mechanisms	$35,000,000
Diagnosis, Assessment, and Disease Monitoring	$72,000,000
Translational Research and Clinical Interventions	$131,000,000
Dementia Care and Impact of Disease	$28,050,000
Research Resources	$101,000,000
Alzheimer's Disease-Related Dementias	$45,000,000
Staffing Needs and Administrative Support	$10,014,000
Total Costs for New AD/ADRD Research	**$504,064,000**
Less: Funding from completed projects that will be available for new AD/ADRD research	**($186,000,000)**
Additional FY 2025 Resources Needed for New AD/ADRD Research	**$318,064,000**

PROFESSIONAL JUDGMENT BUDGET FY 2025 TOTAL RESOURCES NEEDED	*Amount*
Baseline Estimate (based on FY 2023 enacted dollars) for AD/ADRD Research Spending	$3,749,000,000
Additional FY 2025 Resources Needed for New AD/ADRD Research	$318,064,000
Total FY 2025 Resources Needed for AD/ADRD Research	**$4,067,064,000**

In FY 2025, the projected cost of resources needed for new and evolving research to meet the research goals of the National Plan to Address Alzheimer's Disease is $504 million. The estimate is reduced by $186 million in funding from completed projects that will be available for new research initiatives. As a result, the additional resources needed for new research in the FY 2025 budget are $318 million.

Distribution of FY 2025 Total Projected Costs Across Research Areas



In FY 2025, the projected cost of resources needed for new and evolving research to meet the research goals of the National Plan to Address Alzheimer's Disease is $504 million. The estimate is reduced by $186 million in funding from completed projects that will be available for new research initiatives. As a result, the additional resources needed for new research in the FY 2025 budget are $318 million.

Total Projected Costs:

$504,064,000

Less: Funding from completed projects

$186,000,000

Additional Resources Needed for New Research:

$318,064,000

Epidemiology/ Population Studies

With increased investment, NIH anticipates funding additional analyses on complex exposome datasets to advance the field's understanding of the role of diverse external factors on dementia risk and resilience.

State of the Science

A person is exposed to many environmental factors over the course of their life, from toxins and pollutants in the air and water to social dynamics and relationships. The sum of these lifetime exposures to external factors is called the exposome. The scientific study of the exposome is still in its infancy, but scientists are already building an increasingly compelling dataset that indicates that these exposures can have a direct effect on human health, including contributing to the complexities and disparities associated with Alzheimer's and related dementias.

To spark new advances in scientific understanding of the exposome and its role in the onset and progression of dementia, NIH released a series of funding initiatives in 2022 and 2023. These funding opportunities have begun to stimulate research on the role of gene-environment interactions in brain aging at the population level as well as in experimental models of dementia. NIH is also working to establish a Research Coordinating Center, a centralized hub for accessing, harmonizing, linking, and sharing data on social, environmental, and lifestyle exposures from NIH-funded cohort studies, including projects studying individuals living with dementia or groups at heightened dementia risk. This center will be charged with fostering collaborations and generating resources aimed at accelerating research on how exposures — including factors contributing to the broad environmental context as well as individual-level exposures — may shape dementia outcomes and inequities. Research findings stemming from these new projects are expected to contribute to the development of a precision environmental health approach to dementia treatment and risk prevention.

These new initiatives will help establish a critical foundation for exposome and dementia research. Importantly, they will generate an abundance of data that could reveal new insights into the

impact of environmental exposures on brain health and aging. Yet the scale and complexity of these environmental data, including the variation in numbers and types of exposures, and the computing and processing power needed to identify and analyze data from dementia cohorts, presents challenges for the research community. To extract relevant insights from exposure data, researchers must be equipped with the right tools and methods to conduct appropriate analyses to characterize an individual's environmental exposures and estimate the impact on cognitive outcomes. Accordingly, there is an urgent need to employ new technologies to develop advanced tools to study the exposome's role in dementia.

Future Directions

With additional investment, NIH plans to fund more efforts to curate and harmonize currently disparate datasets containing information about environmental and social exposures. NIH also aims to support the development of novel tools and methods to integrate and analyze human and nonhuman data generated from the exposome initiatives described above and other existing dementia cohorts. This may include research that harnesses powerful artificial intelligence and machine learning (AI/ML) approaches to identify patterns and relationships across environmental datasets. These efforts will help outline and describe the contribution of environmental factors to the underlying causes of dementia and health inequities and aid researchers in developing more personalized dementia prevention and treatment strategies.

SPOTLIGHT:
Key Opportunity

Viral Exposure and Dementia Risk

Severe viral or bacterial infections can have a number of long-term health effects, such as memory problems or muscle weakness, and many people infected by viruses, like the virus that causes COVID-19, report cognitive issues long after their initial infection. However, the connection between dementia and viral or bacterial infection remains unclear. Recently, scientists working at the NIH Roy Blunt Center for Alzheimer's Related Dementias (CARD) in Bethesda, Maryland, reported finding significant associations between neurodegenerative disorders and previous viral infections (other than COVID-19) that required hospital visits. For example, diagnoses of several disorders, including dementia, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), were linked to hospitalizations due to pneumonia-causing flu viruses.

However, the mechanisms underlying these associations are not well understood. One possible mechanism may involve brain inflammation. The CARD study found that individuals who had previous brain inflammation caused by a virus, a condition known as viral encephalitis, were at least 20 times more likely to be diagnosed with Alzheimer's than those who did not experience viral encephalitis. To date, few studies have investigated how viruses may trigger long-lasting brain inflammation and lead to disease development.

Furthermore, a growing body of research suggests that COVID-19 may trigger brain inflammation. For example, recent NIH-funded studies in mice and hamsters found that COVID-19 induces brain inflammation. While more research is needed to understand the impact of COVID-19 on the brain in humans, approximately 20% to 30% of COVID-19 survivors have reported persistent COVID-19-related cognitive issues. Although these issues are more common in people who experienced severe COVID-19 that

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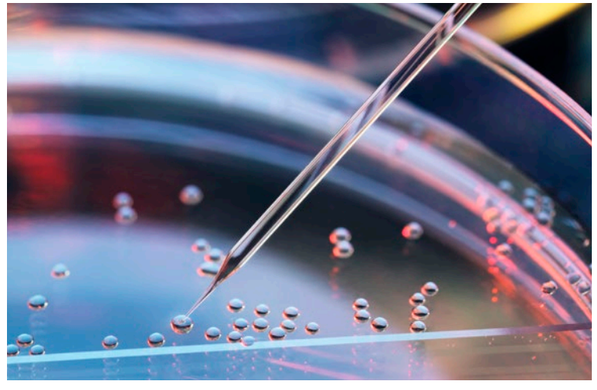
required hospitalization, even individuals who experienced mild COVID-19 symptoms report cognitive issues, commonly referred to as “brain fog,” which can persist for weeks, months, or even years.

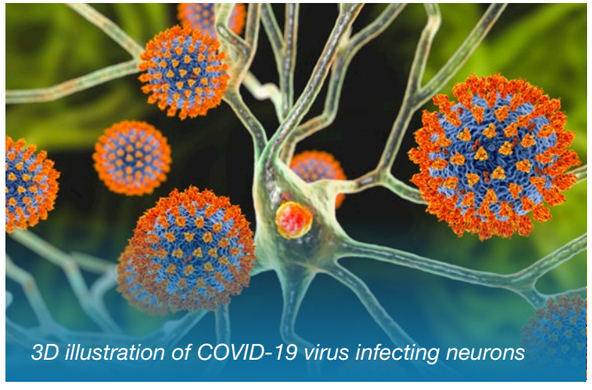
Given the scale of the COVID-19 pandemic to date, and the fact that hundreds of thousands of Americans are hospitalized with flu and other common viruses each year, it is critically important to enhance our understanding of the role of viral infection on brain health and the development of neurodegenerative diseases. More specifically, there is an acute need for research focused on identifying the basic mechanisms that underlie changes in dementia risk associated with viral infection.

To address this need, NIH researchers plan to employ three complementary approaches to explore how viruses, including the virus causing COVID-19, contribute to dementia risk. First, CARD has generated advanced cellular models of dementia using stem cells derived from “reprogrammed” ordinary cells such as blood or skin cells. By exposing these cellular models to select viruses associated with dementia risk, CARD researchers will be able to collect data on how virus exposure impacts the inner workings of the cell. These data will help inform additional studies examining the interplay of environmental factors with genetics, including how virus exposure may affect genetic risk for Alzheimer’s disease.

CARD researchers also plan to use the information gleaned from cellular models to help guide work on human tissue samples. Researchers intend to examine postmortem brain samples voluntarily donated by people who had Alzheimer’s and/or a related dementia upon their death. These samples enable researchers to investigate the relationship between viral infection, brain inflammation, and dementia risk.

In addition, NIH researchers, including those at CARD, will aim to uncover links between viruses and neurodegeneration by leveraging datasets from longitudinal population-based studies of aging. These large, long-term studies follow cohorts of people over many years and have enabled tremendous scientific progress in understanding the factors that influence healthy aging and age-related disease. Researchers will be able to use data from these studies to investigate how a history of viral infection impacts the brain over time, such as by examining longitudinal brain imaging data.





3D illustration of COVID-19 virus infecting neurons

To complement the work of NIH researchers, NIH also anticipates supporting external scientists investigating the relationship between COVID-19 infection and dementia risk. Specifically, NIH plans to fund studies using animal, cell culture, and/or human tissue models to elucidate the mechanisms by which COVID-19 influences dementia risk. This work will also help researchers better understand the effects of COVID-19 on the brain. Such an initiative would also advance broader understanding of the basic mechanisms underlying cognitive impairment and dementia.

Disease Mechanisms

With increased investment, NIH aims to fund research exploring how RNA and protein changes, as well as communication within cells between mitochondria and the nucleus, influence onset and progression of dementia.

Transcriptome, Proteome, and Dementia

With increased investment, NIH aims to fund research exploring the roles of the transcriptome and the proteome in the onset and progression of dementia.

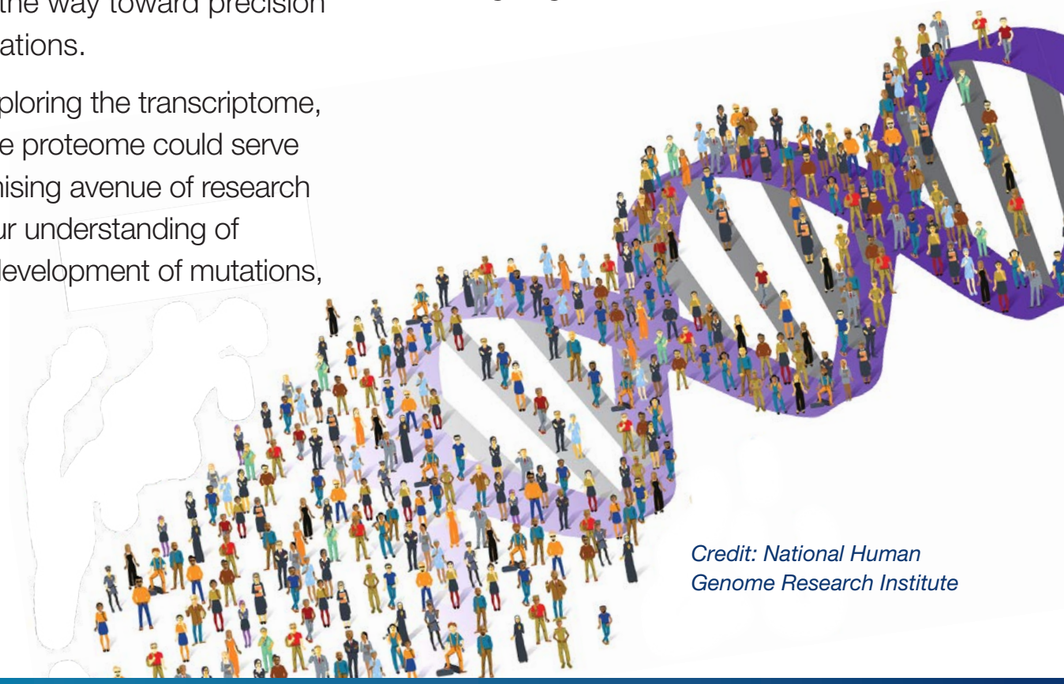
State of the Science

The human genome is the blueprint of life, holding the instructions that inform development and functioning. The genome consists of DNA, which carries the instructions for how to make the various proteins of the body. The transcriptome is the complete set of RNA in the body and serves as a bridge between DNA and proteins. RNA conveys the instructions for producing proteins from DNA to the cell machinery where proteins are produced through a process called transcription. The entire set of proteins produced in the body is known as the proteome.

Recent advances have enabled scientists to detect and characterize changes, or modifications, to RNA molecules. Emerging evidence suggests that these changes to the transcriptome may have a significant impact on the maintenance of health and development of disease, including the development of neurodegenerative disorders such as Alzheimer's and related dementias. The significance of such RNA modifications in brain development and neuron function is just beginning to be appreciated, and the extent and diversity of RNA modifications and their role in neurodegenerative diseases remain largely unexplored. This presents new opportunities for discovering diagnostic markers and novel mechanistic insights into brain aging and dementia.

Understanding the role of RNA and RNA modifications in processes implicated in neurodegenerative disease could also inform new treatment strategies. RNA-based therapeutics, which can modulate biological pathways to treat a specific condition, hold great promise as effective treatments for disease. Advances in our understanding of the implication of RNA and RNA modifications on dementia may ultimately pave the way toward precision medicine applications.

In addition to exploring the transcriptome, exploration of the proteome could serve as another promising avenue of research for advancing our understanding of dementia. The development of mutations, improper RNA processing, and misfolding or modification of proteins, among other abnormal processes, can result in "aberrant," or abnormal, proteins. The accumulation of aberrant proteins is a defining characteristic of a number of neurodegenerative disorders, such as Alzheimer's and related dementias. Improving our understanding of the mechanisms underlying changes to the proteome and their role in neurodegenerative diseases will be important for developing effective therapies. As the pivotal Phase 3 trial for lecanemab showed, approaches that target the production or aggregation of aberrant proteins or that promote their clearance or degradation can have a significant, albeit to date modest, benefit in slowing cognitive decline.



Credit: National Human Genome Research Institute

Alzheimer's and related dementias are complex diseases involving numerous biological processes. Research that integrates the study of the genome, transcriptome, and proteome, as well as the exposome, will allow for the identification of new disease pathways that will advance our ability to develop better diagnostics and treatments for these diseases.

Future Directions

With increased investment, NIH plans to fund innovative research to better understand and characterize the modifications in RNA that are associated with brain aging and dementia. Understanding these modifications and their effects on biological processes will uncover new insights and inform strategies to estimate disease risk, predict disease trajectory and severity, and develop new therapies. NIH also anticipates funding research to better understand the role of aberrant proteins in Alzheimer's and related dementias through combined exploration of the genome and proteome. This will include the development and application of unique tools to identify and analyze aberrant proteins and potentially identify new disease pathways.

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Nuclear-mitochondrial Crosstalk

With increased investment, NIH aims to explore the role of crosstalk between mitochondria and the nucleus in the onset and progression of dementia.

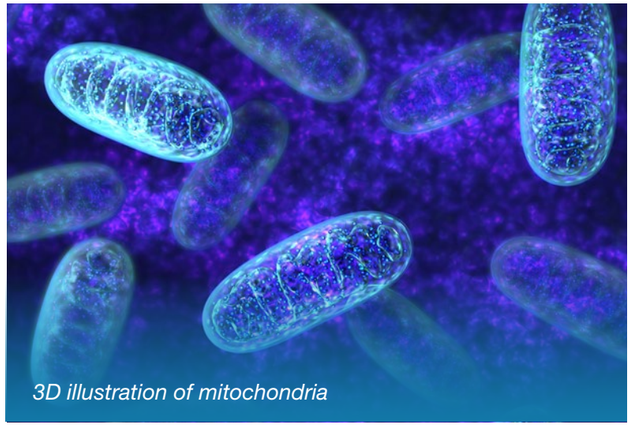
State of the Science

Mitochondria are often referred to as the powerhouse of the cell, producing energy for essential cellular functioning through a process called metabolism. Mitochondria rely on numerous other parts of the cell to metabolize energy sources and properly function. Although mitochondria have their own DNA, most mitochondrial proteins are synthesized based on DNA contained within the cell nucleus, the cell's control center which contains most genomic information. As these proteins are critical to mitochondrial function, the stability of mitochondria relies heavily on communication with the nucleus. Despite their known interconnection, little is known about how the crosstalk between the mitochondria and the nucleus impacts overall cell health.

A decline in mitochondrial quality and activity is a hallmark of brain aging and of Alzheimer's and related dementias, but more work is needed to understand how metabolic changes lead to disease onset and progression. Emerging evidence suggests that the communication between the nucleus and mitochondria may play a pivotal role. Exploring crosstalk between the mitochondria and nucleus could help identify new disease pathways that can be targeted by therapeutics.

Future Directions

With increased investment, NIH plans to fund research that explores the role of communication between the nucleus and mitochondria in dementia. This work includes research to develop foundational knowledge on the crosstalk between the nucleus and mitochondria in brain cells called neurons, along with the development of novel tools and methods to probe this relationship as it pertains to the onset and progression of dementia. NIH also plans to expand existing research infrastructure responsible for conducting genetic sequencing of DNA in the cell's nucleus to conduct mitochondrial DNA and RNA sequencing to provide additional insights into mitochondrial genetic mutations that may affect this crosstalk. The goal of these initiatives is to identify new mechanisms and pathways that could serve as targets for therapeutics to prevent and/or treat neurodegeneration associated with dementia.



3D illustration of mitochondria

SPOTLIGHT:
Key Opportunity

Protecting the Brain's Blood Vessels and the Blood-Brain Barrier to Prevent and Enhance Treatment of Dementia

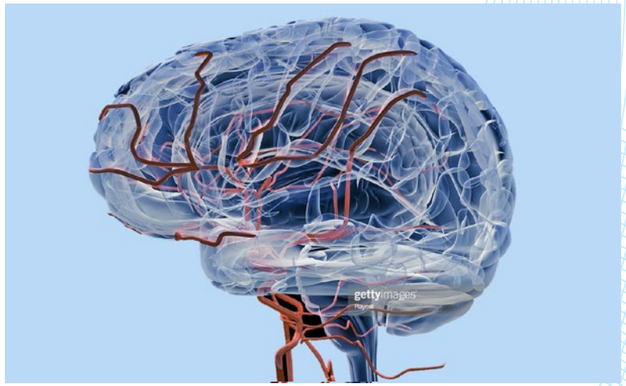
For years, observational research data pointed to high blood pressure during midlife as a risk factor for dementia. Evidence from the NIH-funded SPRINT-MIND trial further strengthened this link by indicating that intensive blood pressure control can reduce a person's risk of developing mild cognitive impairment, a common precursor to dementia, and slow the development of lesions in the brain. Also, while the total number of people with dementia (or incidence) continues to grow in the United States, the proportion of older adults with dementia (or prevalence) has been shown to have decreased in recent decades — and new evidence from an NIH-funded study of dementia trends suggests that this decline in dementia prevalence may be a result of improved cerebrovascular health, or the health of the brain and its blood vessels. How blood flow, as well as blood vessel and cardiac health, contributes to the start and severity of dementia is an important area of research, collectively known as vascular contributions to cognitive impairment and dementia (VCID).

One critical aspect of VCID research is understanding the blood-brain barrier, or the network of blood vessels that protects the brain against harmful substances while selectively allowing vital substances such as oxygen to reach the brain. In aging brains, the blood-brain barrier starts to break down, and a growing body of research suggests this breakdown can have major impacts on brain changes that underlie dementia. Taking steps to investigate new ways to understand the blood-brain barrier and its role in VCID has major implications for dementia treatment and prevention strategies.

More specifically, understanding the brain's complex system involving the blood-brain barrier and the brain's blood vessels could

How blood flow as well as blood vessel and cardiac health contributes to the start and severity of dementia is an important area of research, collectively known as vascular contributions to cognitive impairment and dementia (VCID).

help researchers identify new treatments as well as address side effects of other disease-modifying drugs, including the anti-amyloid immunotherapies lecanemab, which received traditional (full) approval from the FDA in July 2023 based on a demonstrated effect in slowing cognitive decline, and aducanumab, which received accelerated approval from the FDA in 2021 based on a surrogate (amyloid clearance from the brain) rather than a clinical endpoint. A significant percentage (>20%) of participants in clinical trials for these immunotherapies experienced adverse events known as amyloid-related imaging abnormalities (ARIA). These are detected using magnetic resonance imaging (MRI) and indicate fluid retention and/or 'microbleeds' in the brain. Most ARIA cases were asymptomatic, but some participants with ARIA experienced clinical symptoms indicating more serious concerns like brain bleeds, swelling, and inflammation. Given these adverse reactions, many patients with VCID have been excluded from clinical trials of



anti-amyloid therapies, as this dementia type is often indicative of preexisting damage to the brain's blood vessels. More research is needed to understand whether these therapeutics can be given safely and effectively in VCID populations or whether these therapies can be modified to help protect the blood-brain barrier during treatment.

NIH plans to launch a set of initiatives to further study the brain's complex system involving the blood-brain barrier and related factors influencing its response to anti-beta-amyloid immunotherapies. Researchers will seek to further understand the genetic, molecular, and cellular factors influencing the response of the blood-brain barrier and blood vessels to passive immunotherapies targeting beta-amyloid proteins in the brain. Additionally, NIH will promote discovery of cellular and molecular mechanisms underlying adverse events, including brain bleeds and swelling. The overall goal is to find ways to protect the brain's vasculature system during immunotherapy interventions that target brain amyloid. NIH also plans to establish a collaborative, team science-based center focused on multifaceted approaches to advancing the science of VCID at a broader level.

Diagnosis, Assessment, and Disease Monitoring

With increased investment, NIH seeks to advance digital health and biomarker technologies for more sensitive detection of cognitive decline and dementia.

State of the Science

Recent advances in dementia biomarkers, such as brain imaging and blood tests, have improved the ability of researchers and clinicians to detect these diseases and provide more precise and earlier diagnoses. These recent developments have also helped to reduce the cost and time needed to screen participants for clinical trials, which are essential for advancing efforts toward a precision medicine approach to treating dementia.

However, Alzheimer's and related dementias affect many cognitive processes, such as memory and thinking, and the ways in which cognitive decline manifests can vary widely. Current methods to measure cognitive decline are not sensitive enough to capture the diverse behavioral changes resulting from cognitive impairment that appear in daily life. This can lead to potential delays in diagnosis. As a result, there is a need for new, more sensitive methods of cognitive assessment that can take into account multiple activities at one time and comprehensively capture the many ways in which dementia-related cognitive impairment appears. Digital health technologies — including systems such as smartphone applications that use software and sensors to monitor an individual's activities for health care and related uses — could provide a powerful way to capture the various and complex behavioral changes associated with progressive cognitive impairment.

Analyzing this complex behavioral data, gathered using sensing technologies, requires machine learning methods designed to analyze large, diverse streams of data and identify specific trends and patterns. Digital health technologies, coupled with machine learning-supported analysis, have the potential to capture enough population-level and individual-level variability to identify the range of behavioral patterns of cognitive impairment across varying stages of dementia as well as person-specific changes.

Future Directions

With further investment, NIH plans to fund research that will develop new digital health technologies and machine learning tools for analysis of multimodal data from such devices to advance the detection of cognitive impairment and dementia across diverse populations. This includes studies that employ sensors from smartphones, wearables, and other personal devices to generate rich datasets that can be used to facilitate better and earlier identification of behaviors indicative of cognitive decline. These data will be harmonized across NIH programs and platforms to facilitate a broad range of analyses and better explain the relationship between progression of dementia and behavioral changes. NIH also plans to fund cross-sectional and longitudinal studies to better understand how cognitive decline manifests in one or more behaviors as people go about their daily lives. These studies will be able to capture variabilities and identify which behaviors may distinguish people with normal brain aging from those who will develop mild cognitive impairment, Alzheimer's disease, and related conditions.

Increased investments in this area will also enhance efforts to develop biomarkers to enable the detection and diagnosis of dementia in neurodiverse populations, such as individuals with autism spectrum disorder (ASD). The use of multimodal data, including imaging and fluid biomarkers, clinical/cognitive assessments, and genetics, will help researchers characterize the manifestation of dementia in people living with ASD and generate the foundational knowledge necessary to develop precision medicine strategies tailored to the needs of this understudied population.

With further investment, NIH plans to fund research that will develop new digital health technologies and machine learning tools. . . . This includes studies that employ sensors from smartphones, wearables, and other personal devices.

Translational Research and Clinical Interventions

With increased investment, NIH plans to link powerful new technologies and approaches with existing knowledge bases to develop novel interventions to effectively treat and/or prevent Alzheimer's and related dementias.

State of the Science

Research discoveries of the last several decades have underscored that an array of factors contribute to the onset and progression of Alzheimer's and related diseases. With this increased knowledge, researchers have recognized the need to apply a precision medicine approach to diagnosing, preventing, and treating these diseases — that is, a "participant-centric" strategy that results in each person getting the right treatment in the right place at the right time for them. To that end, NIH currently supports work to identify and develop therapies for a wide range of targets, ranging from genetic factors underpinning disease to hormones involved in circadian rhythm and sleep. Efforts are also underway to examine the effects of combining drugs with lifestyle interventions, among other approaches.

NIH supports the discovery and development of new drug candidates for a diverse portfolio of therapeutic targets through a series of specific funding initiatives. Since 2012, 18 new therapeutic agents developed with NIH support have transitioned into clinical development and are currently in Phase 1 or Phase 2 clinical trials. More than 20 additional preclinical drug candidates are currently in development. In addition, NIH currently funds more than 200 active clinical trials testing new or repurposed drug candidates, as well as various lifestyle and other non-drug interventions, for the treatment or prevention of Alzheimer's and related dementias. This includes trials conducted by the Alzheimer's Clinical Trials Consortium, the NIA-supported network that is designed to expand studies for dementia therapies across the disease spectrum, with a focus on increasing participant diversity.

These and other NIH programs and clinical trials generate tremendous amounts of data and biosamples that can help inform future therapeutic development for dementia. Researchers can now take advantage of advances in data analytics to review these data and glean important insights, such as why certain individuals might respond to a particular treatment while others do not.

These advanced analytic methods also make it possible to examine data from other NIH-funded research programs and repositories, including those focused on other diseases and conditions, to help

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identify new therapeutic options for dementia. For example, the National Cancer Institute's Program for Natural Product Discovery is one of the world's largest, most diverse libraries of products found in nature, including compounds derived from plants, fungi, and other organisms. Through this program, NIH makes samples that can be leveraged to support the discovery and development of novel natural products as drug candidates for dementia treatment and prevention readily available to the research community.

While technology has the power to reveal new findings within existing datasets, it also offers brand-new techniques for treating disease. For instance, new gene-editing technologies such as CRISPR have the power to selectively add, remove, and alter parts of the genome responsible for changes in disease state and behavior. Preclinical research has shown promise in using CRISPR to alter a genetic variant and related disease progression in a form of frontotemporal dementia. Such gene-editing approaches could lead to significant breakthroughs for individuals known to have a genetic form of dementia and have the potential for treating or even preventing cognitive decline altogether.

Research technology is advancing at an unprecedented pace, creating new opportunities for treatment and prevention of dementia every day. Yet there is a need for researchers to couple this technology with existing knowledge bases to deliver novel, promising interventions.

Future Directions

With additional investment, NIH plans to expand funding for the discovery and development of effective therapeutics for dementia in multiple ways. First, NIH anticipates supporting research to leverage data and biosamples to build computational models that can help predict how new and existing drugs impact disease progression and responsiveness to treatment. NIH also expects to fund research that employs integrated approaches to identify novel drug candidates for dementia, including harnessing natural products chemistry and investigating the potential use of repurposed drugs currently used to treat other conditions, as well as combination therapies. Furthermore, NIH plans to support research that tests the efficacy of novel therapeutic approaches such as gene editing in preclinical models of dementia — for example, in genetic-based forms of frontotemporal dementia and other Alzheimer's-related dementias. Findings from this research can help inform the design of future precision medicine clinical trials and ultimately result in safer and more effective therapies for all.

SPOTLIGHT:
Key Opportunity

Developing measures to enable large-scale clinical trials of promising lifestyle and behavioral interventions

Research indicates that changes in the brains of people living with Alzheimer's disease begin much earlier than recognizable changes in behavior or cognition. These findings underscore the importance of intervening early and identifying effective prevention strategies, which could help eliminate the pain and suffering associated with disease and may have fewer risks and costs than dementia treatment. Several modifiable risk factors have been associated with dementia, possibly pointing to potential targets for prevention trials of lifestyle and behavioral interventions. For example, a robust body of work, including a randomized clinical trial, indicates that intensive blood pressure control significantly reduces the occurrence of mild cognitive impairment, a precursor to dementia in some individuals. Other lifestyle interventions, many of which are currently under study, may offer additional promising avenues for effective prevention of dementia, and NIH plans to develop new tools to accelerate clinical research in this evolving area, including research on improving adherence to interventions.

Enhancing Trials of Diet and Nutrition

Among several lifestyle and behavioral interventions that may impact dementia risk are changes in diet and nutrition. Research suggests that healthy diets such as the Mediterranean diet and the Dietary Approach to Systolic Hypertension (DASH), both aimed at reducing blood pressure, may be associated with cognitive benefits. In addition, a related diet known as Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND) — a largely plant-based diet emphasizing green leafy vegetables and avoidance of items higher in saturated and trans fats — has been associated with slower cognitive decline and lower levels of a key protein, amyloid, that is a hallmark of Alzheimer's disease.

Furthermore, NIA-funded investigators are currently studying the effects of a modified Mediterranean-Ketogenic diet, which may also lead to changes in amyloid levels and other biomarkers of Alzheimer's disease. While these and other dietary and nutritional interventions are promising, more research is needed to determine whether they can actually prevent dementia and, if so, which mechanisms underlie their efficacy. At the same time, nutritional interventions have unique challenges in design and execution. For example, nutrition studies often must rely on self-reported

nutritional intake, such as food questionnaires and journals, as opposed to more objective measures of nutrient levels such as biomarkers. Biomarkers, such as those that can be obtained via imaging (e.g., magnetic resonance imaging) or through simple blood tests, can enable more precise monitoring of changes in nutrients over time, help scientists more readily determine specific levels of nutrients associated with cognitive benefits, and aid researchers in better understanding the factors driving differences in how individuals respond to various diets. However, there is a remaining need for more reliable and less expensive biomarkers for use in these studies.

To this end, NIH plans to fund efforts to discover, develop, and validate imaging and blood-based biomarkers of nutrition. By developing these critical biomarkers, NIH will help enhance and accelerate dementia prevention trials of dietary and nutrition interventions.

Measures for Lifestyle Intervention Trials at Midlife

Observational studies suggest that targeting dementia risk factors at midlife or earlier can help prevent or at least delay significant cognitive and functional impairment later in life. In fact, a recent clinical trial found that intensive blood pressure control can reduce the risk for mild cognitive impairment, often a precursor to dementia. However, most dementia clinical trials involve adults ages 60 and older and feature the use of biomarkers and measures of cognitive function that have been developed and validated for older adults.

Cognitive and other changes in midlife may be more subtle than those seen later in life, so more sensitive ways to measure these changes, in as near real time as possible, are needed. In addition, biomarkers and other measures can — with proper validation — act as "surrogate" outcomes, obtained in the span of weeks or months, that meaningfully predict future clinical outcomes and effectively shorten clinical trial timelines. Importantly, these measures need to be rigorously validated in populations with diverse racial/ethnic, cultural, and educational backgrounds to maximize their utility and impact. As a result, there is a significant opportunity and need to identify, develop, validate, and make broadly available measurement tools to enable and facilitate robust midlife dementia prevention trials, including trials focused on adherence to interventions.

Therefore, NIH plans to establish an extramural research network that fosters innovative approaches in the development and use of validated measures, methods, and other research tools customized for individuals with different needs and linked to real-world function. These new and refined research resources optimized for use in midlife will be accessible to both the individuals impacted by Alzheimer's and related dementias and the broader research community. Researchers will be able to use these resources to both inform the design and facilitate the implementation of new trials to test promising dementia prevention interventions at earlier stages of life than ever before.

Dementia Care and Impact of Disease

With increased investment, NIH plans to expand research on palliative care and measure the impact of telehealth on care for people living with dementia.

State of the Science

While researchers continue to pursue breakthroughs in prevention and treatment for Alzheimer's and related dementias, the millions of Americans currently living with these diseases need and deserve quality, person-centered care now. NIH continues to support research to rigorously develop and test dementia care and caregiving interventions, improve the integration of care across multiple settings, and understand the economic impact of care on individuals, families, and society. In support of those efforts, NIH recently hosted the latest national Dementia Care and Caregiving Research Summit in early 2023, providing an opportunity to identify gaps and opportunities in dementia care and caregiving research and inform future research priorities.

NIH has long prioritized dementia care across the disease course. One key form of specialized care is palliative care, which is focused on improving quality of life for people with serious illness regardless of age. Palliative care may include but is not synonymous with end-of-life and hospice care. In fact, palliative care, which may be initiated as early as the time of diagnosis, is meant to treat symptoms including pain and distress, promote care that aligns with the goals of the individual, and facilitate care coordination. While there has been significant growth in palliative care research for people living with dementia and their care partners, enhanced coordination among researchers is necessary to advance the field.

Many forms of dementia care, including palliative care, may take place in a variety of locations, such as at home, at a provider's office, or in specialized care facilities, and NIH funds dementia care research that examines the delivery and efficacy of care across these settings. However, in the early stages of the COVID-19 pandemic, there were major shifts in the provision of health care. Significant reductions in in-person care were accompanied by shifts to telehealth services. While there has been some return to in-person delivery of care, telehealth is expected to remain a common care delivery method for the foreseeable future. This has potential implications for people living with dementia and their care partners. While studies have examined telehealth utilization for adults in general, comparatively little has been done in terms of understanding telehealth utilization and efficacy for people living with dementia. Moreover, people living with dementia — particularly individuals who belong to minoritized communities or live in rural areas — may face barriers to receiving care via virtual care modalities. Recent policy changes have introduced new restrictions on access to telehealth, such as requiring that individuals have an established relationship with their provider (e.g., through an in-person examination or provider consultation with another physician who has an ongoing provider-patient relationship). There is a need to understand the health impacts of a shift to telehealth and the recent implementation of new telehealth restrictions on people living with dementia and their care partners.

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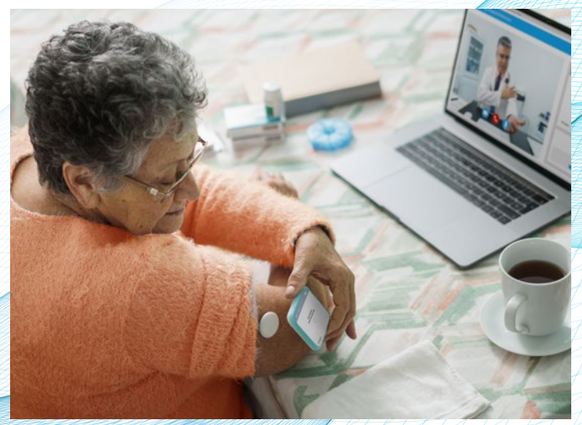


Future Directions

With increased investment, NIH plans to enhance care research in two key ways. First, NIH aims to expand and intensify strategic coordination of palliative care research by establishing a multi-institute research consortium. This new infrastructure will provide the research community with an opportunity to leverage prior successes to build a collaborative pipeline of researchers and studies that emphasize a life course approach to palliative care for serious illness, including Alzheimer's and related dementias. In addition, this new consortium will serve as a foundation for other relevant palliative care research activities that go beyond dementia care. This enhanced coordination may help lead to practice-changing interventions that could be deployed across the health care system.

In addition to expanding palliative care research, NIH intends to fund research aimed at measuring the impact of telehealth on care access, cost, equity, and quality for people living with dementia and their care partners. This work will help address the evidence gap regarding the extent to which telehealth meets the needs of people living with dementia and identify opportunities to optimize dementia care delivery.

Research Resources

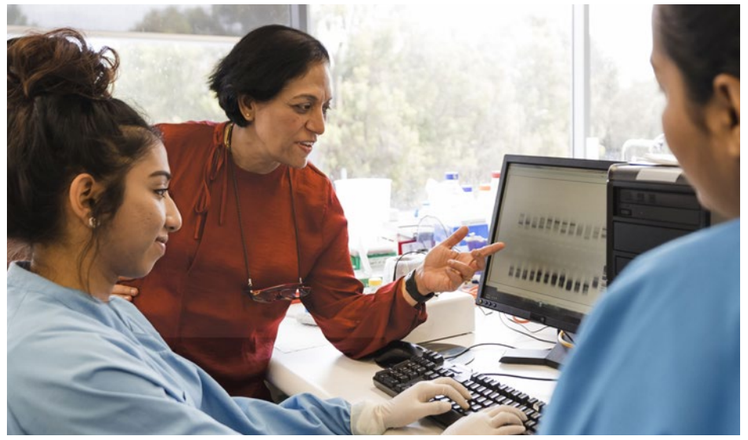
With increased investment, NIH plans to establish new technology-based, team science infrastructure to enhance data and resource sharing opportunities and accelerate efforts to prevent and treat Alzheimer's and related dementias.

State of the Science

Advances in technology have fundamentally changed the way in which science is conducted. Research teams are now generating new data and insights faster than ever before using computational tools including AI/ML. For example, researchers with CARD are using AI/ML to develop scalable and openly accessible tools to help researchers understand and analyze complex genomic datasets. The broader research community is also increasingly connected, with researchers accessing data through shared resource repositories, including the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS), a national genetics repository designed to facilitate access to genotypic data for the study of dementia; and the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System, a system that brings together comprehensive datasets to advance knowledge about traumatic brain injury (TBI) and post-TBI dementia. The increased availability of scientific data, coupled with the development of powerful computational tools and opportunities for collaboration, has the power to facilitate scientific discovery on a scale once considered impossible.

New opportunities for data sharing, computational tool development, and collaboration underscore NIH's long-standing commitment to making the results of NIH-funded research available. In an extension of this commitment, NIH released a new data sharing policy in 2023 aimed at enhancing the rigor, reproducibility, and transparency of research findings. This policy is designed to build upon existing infrastructure and open a wide range of new data sharing opportunities to further accelerate the pace of biomedical research.

While the new data sharing policy is an important step forward, more work is needed to successfully share and manage the abundance of new data within the broader research community. In particular, there is a lack of interoperability among research datasets that can lead to duplicative efforts and costly expenses. Especially with the advent of larger, more complex, and more rapidly accumulating data sets (collectively known as "big data"), new research infrastructure is needed now to help centralize the curation, harmonization, and distribution of data in a cost-effective manner. Fortunately, advancements in technology provide the research community with an opportunity to



modernize data sharing and management efforts through cloud-based computing platforms and other digital resources. In addition to reducing costs and ensuring more equitable access to datasets and tools, such resources have the power to unlock new clues about the underlying causes of dementia and identify new targets for prevention and therapeutic interventions.

Future Directions

With increased investment, NIH intends to enhance data and resource sharing opportunities for the dementia research community. Leveraging existing resources, NIH anticipates supporting the development of new cloud-based systems to host datasets and shared workspaces so that investigators can more efficiently generate valuable insights. These resources will be geared toward facilitating seamless sharing of U.S.-based and international data within an equitable framework and fostering robust collaborations. Through new investments, NIH also plans to develop new digital resources that promote interdisciplinary, team science collaboration and leverage and enhance centralized brain banks and informatics systems, such as FITBIR to study post-TBI dementia. NIH is committed to enhancing and broadening access to data and developing infrastructure to equip the next generation of investigators with cutting-edge tools and resources to make advancements toward precision prevention and treatment of Alzheimer's and related dementias.

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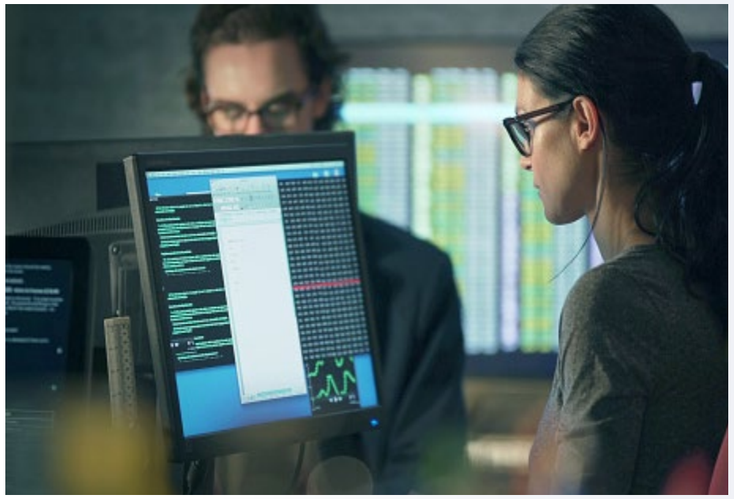

Cross-Cutting Area: International Studies

Alzheimer's and related dementias are a significant global health burden, estimated to affect more than 55 million people worldwide. NIH has supported several international studies that have produced crucial data and findings that have helped to accelerate many high-priority areas of dementia research, including identifying risk factors for dementia and novel targets for treatment and prevention interventions. NIH support has also facilitated groundbreaking clinical trials of dementia therapeutics that would not have been possible without international participation.

In one example, a rare genetic form of Alzheimer's known as dominantly inherited Alzheimer's disease causes memory loss and dementia in individuals in midlife, typically while they are in their 30s to 50s. This genetically inherited form affects less than 1% of the total population of people with Alzheimer's, but individuals who are carriers of the genetic variations associated with the disease are generally clustered within large families around the world. NIH-funded researchers are working with 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, to learn more about disease progression and responsiveness to potential treatments. This has been critically important for the conduct of dementia prevention trials, which typically must involve many individuals and take place over a very long period of time, because participants are recruited before symptoms begin. Researchers do not know at the outset of these trials which individuals will develop dementia or when symptoms might appear, which could be many years later. Because individuals in this family have an approximate idea about whether and when they may develop dementia, their participation in prevention trials has been invaluable. Moreover, thanks to the participation of members of this family, researchers have now identified at least two gene variants — including one identified in May 2023 — that offer protection against the onset of dementia in individuals who would otherwise develop Alzheimer's in middle age, offering potential targets for therapeutic development.

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Additionally, identification of this family and the gene of interest would not have been possible without the scientific expertise and community knowledge of researchers in Colombia, who also led subsequent clinical trials with substantive participation by members of this family. Confronting a global health issue like dementia requires a critical mass of researchers who have the necessary knowledge and experience in health problems specific to their region and who understand the cultural, social, and environmental contexts of their local communities. Importantly, local researchers are more likely to have earned the trust of their communities, which is needed to successfully conduct clinical trials and other health research.

Growing this important pool of researchers — particularly in low- and middle-income countries (LMICs), where nearly two-thirds of people living with dementia reside — is vital to sustaining progress in the search for effective prevention and treatment options for Alzheimer's and related dementias. Increased investment provides NIH with the opportunity to establish career development programs for early-career and established researchers in LMICs. This support will not only build local capacity for dementia research but also advance the science more broadly.

NIH has also made substantial investments to measure and understand dementia risk within ongoing longitudinal studies of aging around the world. By capturing data on the social, economic, cultural, and environmental circumstances people age in, these long-term studies can provide researchers with crucial information about the factors affecting dementia risk over the life course. These data also make possible cross-national comparisons, which have tremendous promise in helping inform interventions in the United States and globally to improve health. However, cross-national analyses have been relatively limited thus far. These studies require researchers to not only learn how to use multiple datasets from several countries but also learn about varying country contexts. Expanding the pool of researchers, including those with local contextual knowledge who are equipped to conduct cross-national studies, will help advance the field of dementia research. To this end, NIH seeks to reduce barriers that limit the conduct of cross-national studies by supporting training opportunities, including short courses, that help researchers develop the necessary skills to conduct such studies.

Now more than ever before, science is a global enterprise. The participation of dedicated researchers and people living with dementia from around the world benefits research on Alzheimer's and related dementias, helping bring us all closer to effectively treating and preventing these devastating disorders.

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Conclusion

NIH has made tremendous progress in Alzheimer's and related dementias research, fueled by many years of generous investments by Congress. NIH is excited to continue this momentum and further accelerate dementia research in FY 2025 and beyond. Importantly, this progress would not have been possible without the collaboration of a dedicated community of individuals and organizations, including people living with dementia, care partners, families, advocates, Congress, clinicians, researchers, and others. Together, we are enhancing our understanding of and developing new ways to prevent and effectively treat these diseases.

The examples of research opportunities outlined within this professional judgement budget build on this collaborative effort and demonstrate NIH's commitment to strategically funding research projects that leverage existing infrastructure and utilize cutting-edge technologies to fill gaps in knowledge and advance the field. With sustained funding, NIH will be able to support promising new research that will propel the science forward and bring us closer to the goal of preventing and effectively treating Alzheimer's and related dementias.