

Fiscal Year 2026 NIH Professional Judgment Budget for Alzheimer's Disease and Related Dementias Research: Advancing Progress in Dementia Research



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NIH Director's Message

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 2026 (FY26). This document outlines a funding proposal as well as examples of the future research efforts that can be pursued with additional investment in FY26. Each of the research initiative examples described builds upon recent scientific advancements and leverages 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, Alzheimer's and related dementias research has advanced at a remarkable pace over the past several years. NIH appreciates these efforts that are only possible through meaningful collaboration among the research community, industry, and the broader public, as well as the considerable contributions of research participants and care partners without whom the field could not have advanced to where it is today. NIH is committed to building upon this momentum to accelerate research breakthroughs for people living with dementia and their loved ones.

Accompanying the release of this prospective Professional Judgment Budget is the NIH Alzheimer's and Related Dementias Research Progress Report. This year's edition summarizes key dementia research advances from the last year, from therapeutic interventions to cognitive assessments and biomarkers, to care and caregiving research, and more.

NIH-funded researchers have made significant advances in the last several years, including the identification of new genetic, behavioral, environmental, and lifestyle risk and protective factors associated with dementia.

Increased understanding of such factors has and will continue to inform additional research, including the development and evaluation of a wide range of behavioral and lifestyle interventions to reduce dementia risk. For example, building on a growing body of work that suggests hearing loss may be a risk factor for dementia, an NIH-funded clinical trial tested whether a hearing aid intervention had an impact on cognition. Results showed that hearing aids appeared to reduce cognitive decline over three years in a group of older adults with specific risk factors for dementia. These findings reinforce earlier studies that suggest hearing loss is an important public health target to reduce dementia risk.

Advances in the understanding of key risk and protective factors are also driving progress in therapeutic development. For example, scientists are uncovering rare forms of genes that may help protect against Alzheimer's that are already inspiring development of potential therapeutics. NIH-funded researchers are also exploring how genetic factors in diverse populations, including those with Down syndrome, can help to inform new interventions to benefit these populations and others who are impacted by these diseases.

In addition, NIH-funded research is accelerating the development of improved diagnostic tools to help clinicians diagnose Alzheimer's and related dementias and identify specific disease stages to improve dementia treatment. As one example, with support from NIH small business funding, C2N Diagnostics released a second-generation blood test in 2023, PrecivityAD2, that combines measures of amyloid and tau proteins — hallmarks of Alzheimer's — to help physicians make an accurate and timely diagnosis. Because they do

not require specialized equipment (e.g., PET scanners), blood tests like PrecivityAD2 have the potential to lower costs and increase access to diagnostic tools for Alzheimer's. Newly emerging biomarkers can help detect the complex processes underlying Alzheimer's and related dementias in diverse populations at early and presymptomatic stages, enabling more effective and personalized prevention and treatment.



Monica M. Bertagnolli, M.D.
Director
National Institutes of Health

A Road Map for the Future

NIH aims to capitalize on this progress to advance the development of effective diagnostics, risk reduction strategies, and treatments for Alzheimer's and related dementias, as well as quality care for those living with these diseases. The FY26 NIH Professional Judgment Budget for Alzheimer's Disease and Related Dementias Research presents a path forward: a prospective look at the research opportunities that could be pursued with additional investment. Within this document, we describe the additional resources needed to pursue exciting new research opportunities and accelerate progress toward effective prevention and treatment of Alzheimer's and related dementias.

Introduction

Annual Budget Estimate

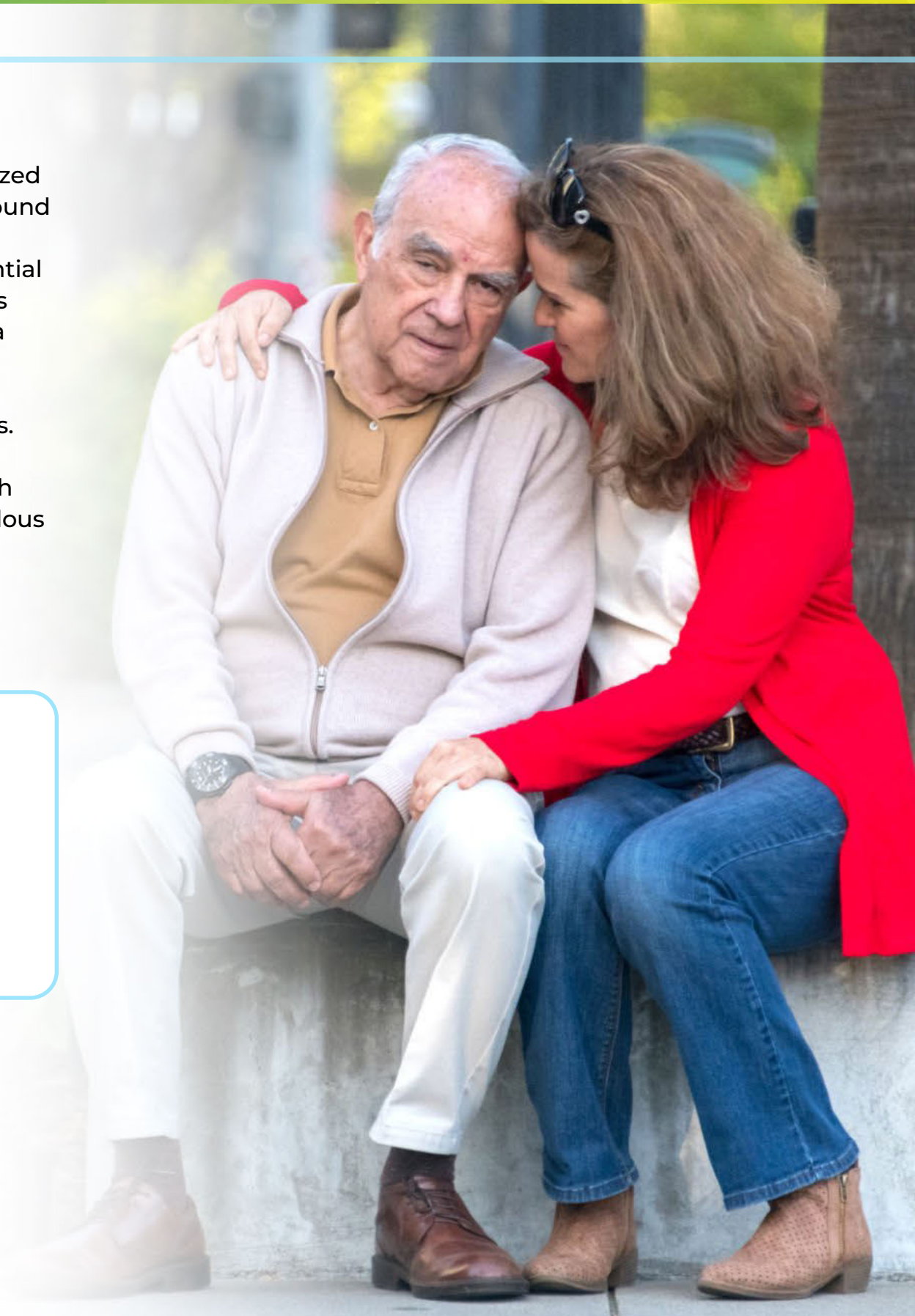
This budget proposal outlines the additional funding needed in FY26 to advance NIH-supported research toward achieving the goals outlined by the National Plan to Address Alzheimer's Disease. The professional budget estimate includes \$113 million in additional resources for new research, with the overall resources needed totaling \$3.98 billion. The projected cost of resources needed in FY26 for new research is \$445 million. This estimate is reduced by \$332 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 FY26 budget is \$113 million.

Impact

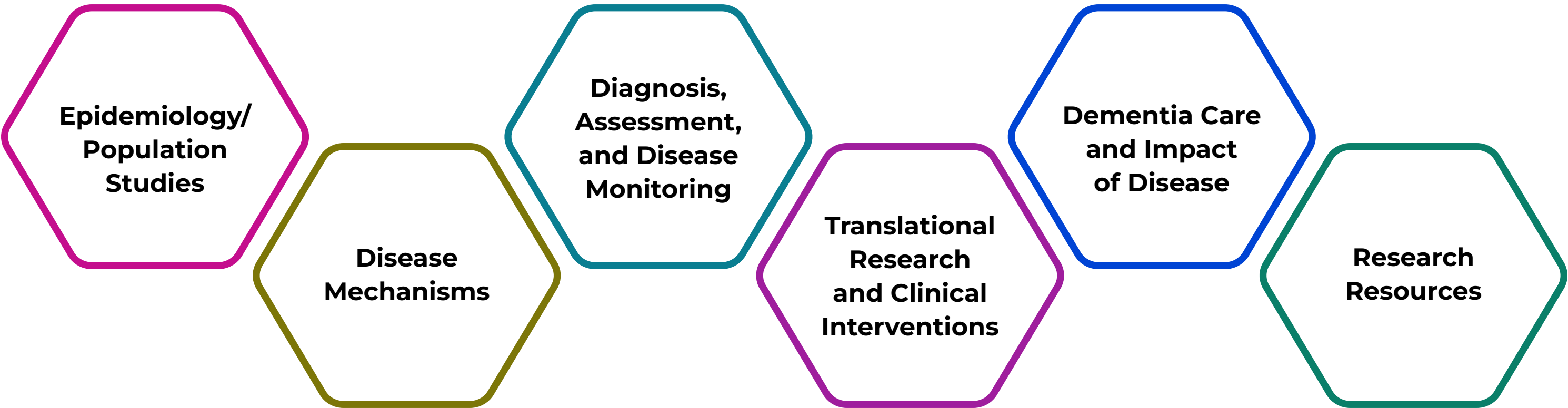
An estimated 6.9 million Americans are currently living with Alzheimer's, and these numbers are projected to increase as the nation's population ages. NIH is focused on turning new discoveries into health to meet the needs of those currently living with Alzheimer's as well as individuals living with related dementias or mixed dementias (having two or more forms of dementia at the same time). This public health challenge takes a tremendous emotional, physical, and financial toll on those living with these diseases, their families, and their care partners, underscoring the urgent need for effective diagnostics, risk reduction strategies, treatments, and care.

NIH has made remarkable progress in our understanding of these diseases and has revolutionized how they are diagnosed by health care providers around the country. In addition, NIH is funding hundreds of clinical trials to develop the next generation of potential therapeutic interventions, including drug candidates aimed at a range of novel disease targets as well as a variety of behavioral and lifestyle interventions. NIH has also made key advances in care and caregiving for those living with dementia and their care partners. 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 6.9 million Americans are currently living with Alzheimer's, and these numbers are projected to increase as the nation's population ages.



Examples of investment priorities are organized along six areas:



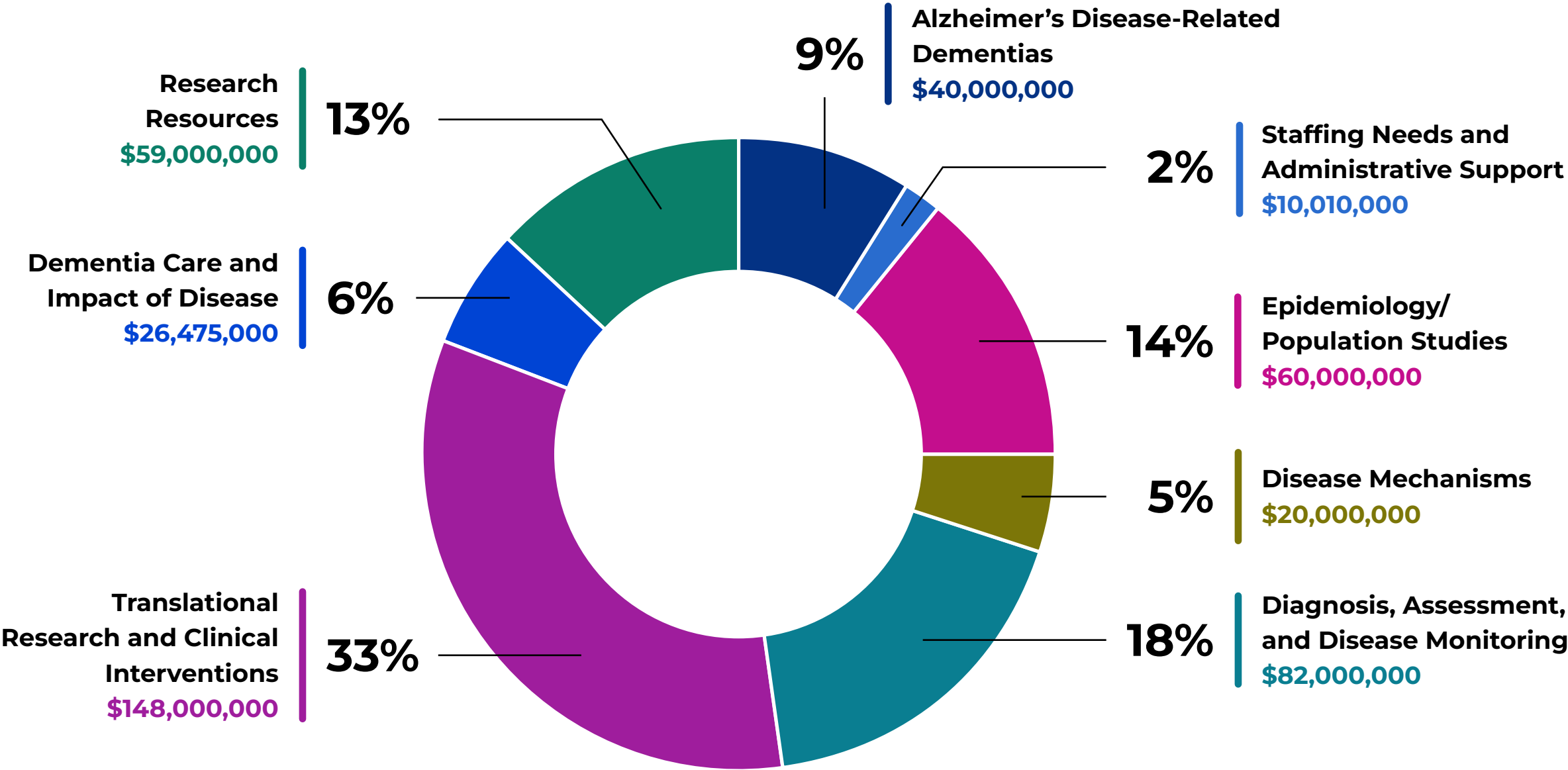
Across these six areas, we highlight three bold endeavors (“Spotlights”) that NIH seeks to accomplish with increased Alzheimer’s and related dementias research investment in FY26. In addition, we emphasize significant crosscutting efforts centered on community-engaged research. NIH recognizes the importance of engaging a broad range of communities, including those that have been historically underrepresented, in research aimed at advancing dementia diagnosis, prevention, treatment, and care efforts. Importantly, community engagement provides the opportunity to improve health equity through inclusion and retention of participants, including those from diverse backgrounds, in the research process.

FY26 Additional and Total Resources Needed for AD/ADRD Research

Professional Judgment Budget FY26 Additional Resources Needed	Amount
Epidemiology/Population Studies	\$60,000,000
Disease Mechanisms	\$20,000,000
Diagnosis, Assessment, and Disease Monitoring	\$82,000,000
Translational Research and Clinical Interventions	\$148,000,000
Dementia Care and Impact of Disease	\$26,475,000
Research Resources	\$59,000,000
Alzheimer's Disease-Related Dementias	\$40,000,000
Staffing Needs and Administrative Support	\$10,010,000
Total Costs for new AD/ADRD Research	\$445,485,000
Less: Funding from completed projects that is now available for new AD/ADRD research	(\$332,000,000)
Additional FY26 Resources Needed for New AD/ADRD Research	\$113,485,000
Professional Judgment Budget FY26 Total Resources Needed	Amount
FY24 NIH Estimate (based on FY24 enacted dollars) for AD/ADRD Research Spending (baseline estimate)	\$3,871,000,000
Additional FY26 Resources Needed for New AD/ADRD Research	\$113,485,000
Total FY26 Resources Needed for AD/ADRD Research	\$3,984,485,000

In FY26, 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 \$445 million. The estimate is reduced by \$332 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 FY26 budget are \$113 million.

Distribution of FY26 Total Estimated Costs Across Research Areas



Total Projected Costs:
\$445,485,000

Less: Funding From
Completed Projects
\$332,000,000

Additional Resources
Needed for New
Research:
\$113,485,000

In FY26, 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 \$445 million. The estimate is reduced by \$332 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 FY26 budget are \$113 million.

Epidemiology/ Population Studies

With increased investment, NIH plans to expand research on genomic analyses of Alzheimer's and related dementias.



Family-Based Genomic Analyses of Alzheimer’s and Related Dementias

State of the Science

People who have family members living with dementia may be at increased risk of developing the disease themselves. This predisposition may be due to genetic or environmental factors or to a combination of the two. With participation from affected families, ongoing research at NIH is uncovering key factors that may affect risk of or resilience to Alzheimer’s.

For example, researchers are sequencing all of the genes (called the genome) of each member of some families with a history of dementia. Sequencing provides important information on the genetic contributions to familial Alzheimer’s and facilitates genome-wide association studies (GWAS) — powerful tools for identifying key genetic associations in dementia and enabling studies to target these genetic areas.

Genetic associations include influences from three sources:

- **Direct genetic effects.** The genes of a person can influence an outcome due to inherited genetic variation. For example, whether a person has a trait like dimples depends on whether they possess the genes for that trait.
- **Indirect genetic effects.** The environment a person experiences can be influenced by the genetics of others, especially parents. For example, the home environment created by parents is partially caused by parents’ own genetics, including through genes that were not passed to the child.
- **Demographic influences.** Additional nongenetic factors can influence an outcome. For example, people often choose mates with similar traits, like educational attainment, culture, or religious or spiritual beliefs.

Importantly, GWAS typically include samples from many unrelated individuals. As a result, these studies often cannot differentiate between direct (based on one’s own genes) and indirect (influenced by the genes of others) genetic effects. In addition, the samples used in typical GWAS are often limited to a single genetic-ancestry group instead of diverse populations to reduce the number of variables that influence the genetic associations being studied.

GWAS that use samples from within a family (e.g., sibling pairs, parent-child trios) can separate direct and indirect genetic effects and are better able to control for the influence of demographic factors. However, few GWAS studies currently have this within-family design, hindering both the accuracy of GWAS findings and their application to diverse populations.

Future Directions

With additional investment, NIH will fund studies that leverage existing resources and methods to better understand direct and indirect genetic effects as they relate to dementia risk and resilience. NIH will also fund efforts to expand within-family samples in ongoing studies and explore new data collection efforts that enhance data availability from underrepresented populations. This research, along with a growing body of research that includes whole genome sequencing, analyses of proteins and other molecules, and biomarkers in families from diverse populations, will help to define subtypes of disease and guide the field toward investigating causal effects of genes, identifying more accurate genetically driven therapeutic targets, and understanding the various ways in which genes indirectly influence social and behavioral risk factors for dementia.



Spotlight: Key Opportunities

Oral Health and Risk of Cognitive Impairment and Dementia

Complex interactions between genetic, environmental, and lifestyle factors shape the risk of developing Alzheimer’s and related dementias. Due to their relative modifiability, several lifestyle factors have been identified as attractive targets for interventions aimed at reducing risk for mild cognitive impairment and dementia. For example, high blood pressure and hearing impairment, two key modifiable lifestyle factors, have long been under investigation in this context.

More recently, oral health has emerged as a modifiable lifestyle factor that may contribute to risk for cognitive impairment and dementia. Recent evidence suggests that poor oral health is associated with greater risk for dementia. For example, a study led by NIH researchers found that some measures of periodontitis — a form of gum disease — are associated with increased risk of developing and dying from dementia. This study identified several species of bacteria that may play a role in this association. These and related findings suggest that preventing or treating oral disease may present a strategy for preventing or treating dementia, though the mechanisms underlying the association between oral health and dementia are currently unknown.

The potential link between poor oral health and dementia risk can be compounded by the challenges associated with obtaining quality oral health care

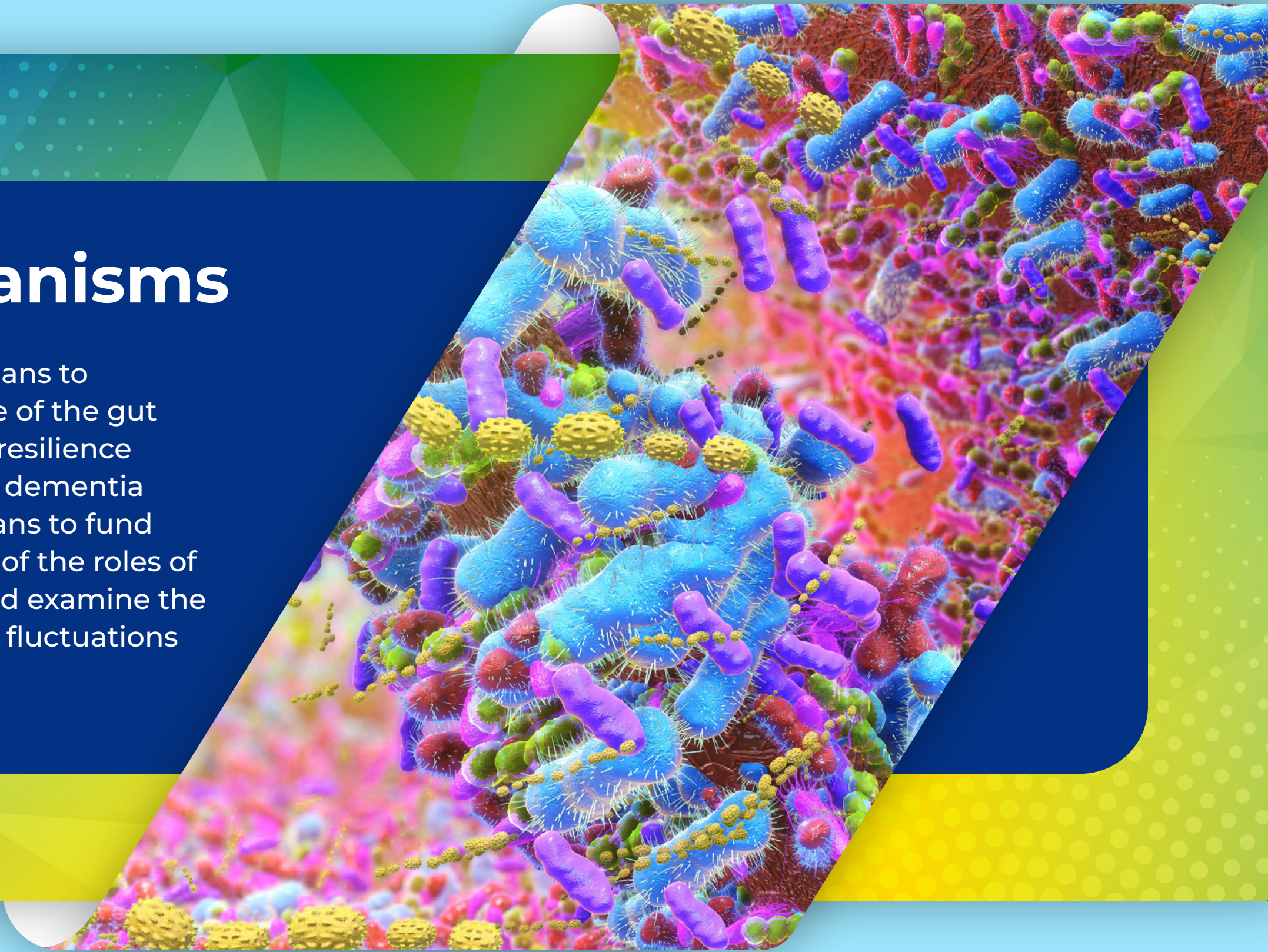
and practicing good oral hygiene. For example, access to oral health care across the life course may be limited by gaps in dental coverage and a lack of local oral health care providers. People living with dementia may encounter the added difficulty of maintaining consistent oral hygiene practices in the face of declining memory and cognition. Indeed, people living with dementia tend to have poor measures of oral health and hygiene across several indicators, which can pose further risks to overall health and quality of life.

With additional investment, NIH plans to fund research that advances understanding of the association between oral health and dementia. Large-scale studies in diverse cohorts could reveal how other factors (e.g., genetics, comorbidities) influence the interaction between oral health and dementia. NIH also anticipates funding research to examine the biological mechanisms linking poor oral health to dementia, which can help identify key disease pathways and potential targets for interventions. NIH also plans to address the need for efficacious behavioral and social interventions to improve oral health and hygiene among people at risk for or living with dementia. Cumulatively, additional investment in this area will directly address the possibility that improving oral health may serve as a viable tool for reducing the risk and impact of dementia.



Disease Mechanisms

With increased investment, NIH plans to expand research exploring the role of the gut microbiome in dementia risk and resilience and the roles of brain immunity in dementia development. Additionally, NIH plans to fund efforts to enhance understanding of the roles of abnormal proteins in dementia and examine the mechanisms underlying cognitive fluctuations associated with dementia.



Contribution of Gut Microbiome to Dementia

State of the Science

Our intestines are home to a universe in miniature known as the gut microbiome: a busy ecosystem composed of trillions of bacteria, fungi, and other microbes. The organisms in a healthy gut microbiome work together to digest food, support the immune system, and maintain our overall health. However, when the gut microbiome becomes unbalanced due to illness, diet, exposure to toxins, or for other reasons, the consequences may affect the entire body — including the brain.

The gut microbiome is in constant communication with the brain via a chemical highway known as the gut-brain axis. Disruptions in this system can have a profound impact on brain health. For example, an analysis of publicly available data of more than 2,000 brain samples from the NIH-funded AD Knowledge Portal provided evidence that microbial waste products, which can travel through the bloodstream and enter the brain, may play a role in Alzheimer’s. Other research suggests that the gut microbiome may be involved in the development of gastrointestinal disorders, such as Crohn’s disease and inflammatory bowel disease — which may, in turn, be associated with increased risk for dementia and other neurodegenerative diseases, although the specific mechanism(s) have yet to be determined.

Future Directions

Additional investment will enable NIH to fund expanded efforts to understand the role of the gut microbiome and associated microbial products in Alzheimer’s and related dementias and to develop therapeutic approaches targeting alterations in the microbiome. NIH will also fund efforts to understand molecular changes in the central nervous system in individuals with chronic gastrointestinal disorders.

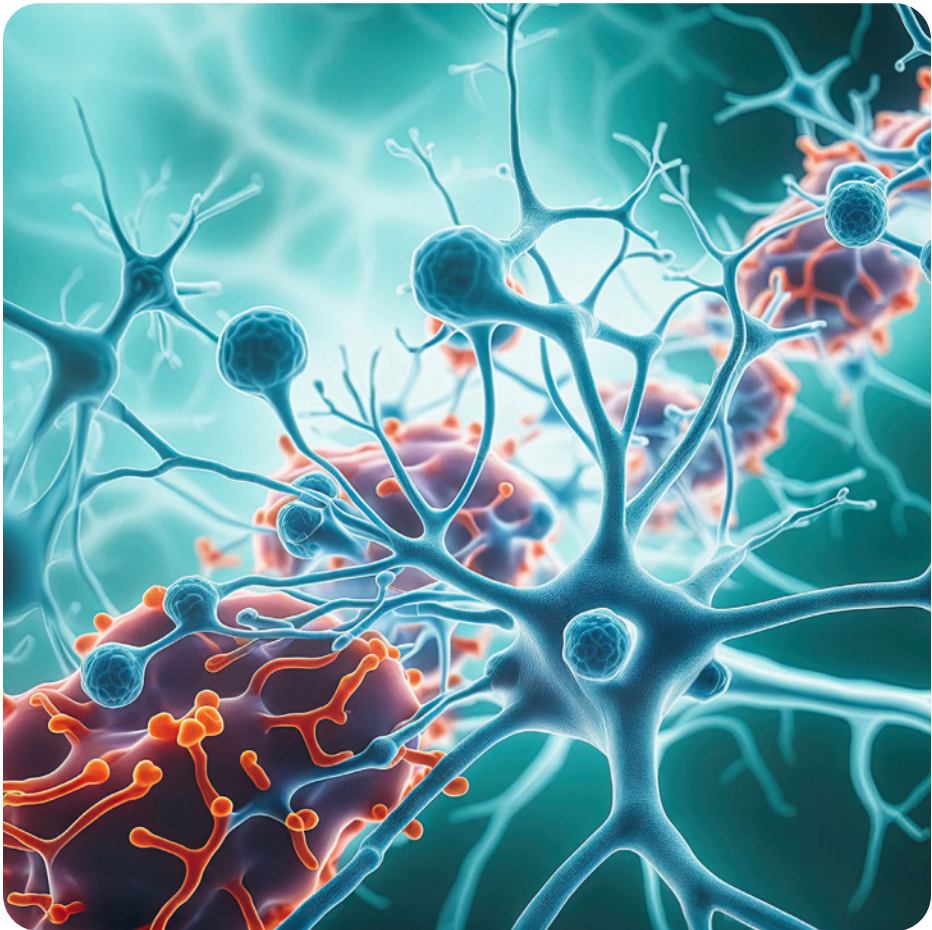
Brain Immunity in Development of Alzheimer’s and Related Dementias

State of the Science

The time course of cognitive decline in dementia closely parallels the degeneration and loss of neurons — brain cells that orchestrate the nervous system’s myriad functions. Neurons are not the only cell type in the brain, however. Neurons receive wide-ranging support from another class of brain cells known as glia. First thought to serve a minor role as a glue that holds neurons together, glia are now better understood to play major roles in expediting signals sent between neurons, recycling molecules involved in these signals, and refining brain development, among other essential processes.

One major glial cell type, the microglia, serves as the brain’s principal immune cells. In this capacity, microglia constantly monitor the brain for exposure to potentially harmful agents or materials, such as viruses, bacteria, and cellular debris. When functioning normally, microglia help to dispose of detected threats by enveloping and digesting them and by informing immune cells from outside of the brain to escalate the immune response. The glial role in healthy brain immunity also extends to astrocytes, another glial cell type, which help to regulate the entry of nonresident immune cells into the brain.

Mounting evidence suggests that dysfunction of the brain’s immune system contributes to the development and progression of dementia. For example, impairment of microglia’s ability to detect and dispose of protein deposits that precede Alzheimer’s appears to underlie some of the genetic risk associated with the disease. Microglia dysfunction may also accelerate the spread of toxic forms of the protein tau, a hallmark of Alzheimer’s. However, a deeper understanding of the role of glial cells and brain immunity in dementia is needed to advance the development of potential therapeutic approaches.



Future Directions

With additional investment, NIH aims to bolster research to identify and describe biological mechanisms that implicate the brain’s immune system in the development of Alzheimer’s and related dementias. In addition to expanding knowledge of glial biology in health and disease, NIH-supported work will help delineate how disease influences interactions between glia and neurons. NIH plans to support studies that leverage both new in vivo animal models of disease and in vitro cell models to achieve detailed mechanistic insights. Ultimately, this work will help inform the design of sensitive biomarkers for improved diagnosis and disease monitoring and more precise therapeutic strategies.

Expanding Understanding of Proteins in Alzheimer’s and Related Dementias

State of the Science

Abnormal protein deposits are consistent hallmarks of disease in brains of individuals living with dementia. The development of specialized molecular tools to detect these protein aggregates in people forms the basis of modern diagnostic protocols. These tools are also invaluable in research for understanding how protein deposits relate to fundamental disease processes.

However, some proteins can assume different shapes and structures, only one or a few of which may be recognized by a given tool. This can have diagnostic consequences: If a specific tool cannot detect each of the various shapes a protein may take, then certain collections of the protein — even those that play critical roles in driving disease — can be invisible to clinicians and researchers. The structural variability of a protein may also contribute to disease progression, as some forms of dementia-associated proteins appear to go unrecognized by cells that typically defend the brain against toxic debris. While recent progress has begun to reveal the deep structural diversity of dementia-associated proteins, considerable work is still needed to achieve a full accounting of this diversity.

In addition, some proteins can operate in a dysfunctional manner or appear outside of their usual places within a cell. For example, in healthy cells, a protein known as TDP-43 resides in the nucleus and plays an important role in regulating how RNA is processed. However, TDP-43 can move from the nucleus, and abnormal forms of TDP-43 can build up elsewhere in the cell.

Recent research has identified TDP-43 dysfunction and mislocalization as contributing to the development of neurodegenerative diseases, including Alzheimer’s and related dementias. However, it remains unclear how



TDP-43 becomes dysfunctional, what molecular and cellular consequences result from this change, and how abnormal functioning of TDP-43 ultimately leads to the loss of brain cells that manifests clinically as dementia.

Future Directions

With additional investment, NIH will fund work to improve the identification and characterization of structurally diverse protein aggregates implicated in the development of Alzheimer’s and related dementias and, in doing so, better understand their roles in neurodegeneration. These efforts will enable the development of more precise diagnostic tools and therapeutics capable of selectively engaging the protein forms most central to disease progression.

NIH also plans to utilize additional investment in this area to accelerate research on TDP-43 dysfunction and mislocalization to better understand their role in neurodegeneration and dementia. The foundational knowledge generated by this support could lead to therapies that cut across the several forms of dementia for which pathological roles of TDP-43 have been recognized.

Understanding Mechanisms of Cognitive Fluctuations in Dementia

State of the Science

Clinically, Alzheimer’s and related dementias are marked by cognitive decline over time. However, this downward cognitive trajectory can involve fluctuations — sporadic episodes of altered, typically reduced, cognitive function. These alterations can persist for varying lengths of time, from minutes to days. Besides impairing the daily functioning of people living with dementia, the unpredictability of cognitive fluctuations can amplify the strain placed on caregivers and makes it difficult for researchers to interpret the outcomes of clinical trials aimed at boosting cognitive function.

Though cognitive variations are prevalent in some dementias, little is known about their origin. Some studies have shown that cognitive fluctuations can co-occur with broad patterns of electrical activity in the brain, suggesting that such activity may contribute to alterations in cognition. However, the significance and mechanisms of these activity patterns are unclear. More fundamentally, researchers do not yet know whether processes other than those associated with dementia also contribute to cognitive fluctuations or if the mechanisms underlying these alterations differ with various factors (e.g., type of dementia, risk genes).

Future Directions

With increased investment, NIH will foster research to identify and examine potential mechanisms for cognitive fluctuations in dementia. Identification of the underlying mechanisms will provide targets for the development of effective interventions. An improved understanding of these mechanisms could also enable prediction and monitoring of cognitive fluctuations, allowing people living with dementia and their care partners valuable time to prepare and adjust for periods of elevated burden.

Diagnosis, Assessment, and Disease Monitoring

With increased investment, NIH plans to expand research efforts to identify disease-associated proteins and develop approaches to support decision-making for early dementia diagnosis and risk disclosure.



Next-Generation Technology To Identify Alzheimer's and Related Dementias-Associated Protein Structures in Biological Settings

State of the Science

Recent identification of minute differences in the structures of proteins associated with Alzheimer's and related dementias has expanded recognition of the complexity of these diseases. These advances offer the potential to accelerate the development of a precision medicine approach to treatment and prevention, as even tiny differences in disease-related proteins may suggest alternative diagnoses, novel therapeutic targets, or new treatment strategies. Detailed knowledge of a protein's structure may also facilitate the design of molecules that bind to the protein and, when viewed with sensitive brain imaging technologies, serve as biomarkers for the disease subtype associated with the protein.

To date, efforts to resolve the fine structural details of proteins have relied upon protein samples extracted from cells and tissues or reproduced under artificial

conditions. These approaches facilitate high-resolution imaging, but the proteins may not appear as they would in their normal biological settings. As a result, there is a need to connect protein structures identified through conventional methods to Alzheimer's and related dementias to how these same proteins appear within the body in both healthy individuals and in those with dementia. Emerging structural biology technologies such as cryogenic electron tomography now make it possible to study the structures of proteins while embedded within tissue, potentially providing more accurate and relevant results.

Future Directions

With additional investment, NIH will fund research to develop and use methodologies for exploring the structural biology of dementia-related proteins in native (healthy and pathological) cellular settings. Findings from these studies will enable and inform the development of more accurate and sensitive biomarkers for Alzheimer's and related dementias.

Spotlight: Key Opportunities

Clinically Meaningful Change and Outcomes That Matter

Two drugs targeting the underlying disease pathology of Alzheimer’s have received traditional approval from the U.S. Food and Drug Administration (FDA): lecanemab in July 2023 and donanenamb in July 2024. Several other promising treatment options are currently being evaluated in clinical trials. While exciting and encouraging, this progress has also revealed new challenges and questions around how to measure whether a potential treatment is effective over the course of a clinical trial and beyond in a “clinically meaningful” way.

In general, a clinically meaningful improvement refers to a change or delay in symptoms that people living with dementia or their care partners consider to be valuable. From a research perspective, consideration of clinically meaningful improvements is essential for developing effective treatments.

One of the major challenges in understanding clinically meaningful outcomes for dementia research is that individuals experience dementia differently. Other factors like comorbidities, severity of impairment, age of onset, culture, and social and financial concerns also lead to variability in what changes are deemed meaningful for an individual.

Work led by the broader research community has shed important light on these outcomes, though there remains a need to further explore the research

outcomes that matter most to people living with or at risk for dementia and their care partners, such as memory, function, independence, health, and engagement in meaningful activities. An essential piece of this research is continuous collaboration with the lived experience community, which is uniquely qualified to identify desired outcomes and ascribe meaning to changes in symptoms. It is also important to hear from those who may not be experiencing symptoms of cognitive decline right now but could in the future.

With additional investment, NIH plans to fund collaborative, person-centered research to equitably identify outcomes that matter most to those impacted by dementia across multiple modalities, including cognitive function, physical health, and social and emotional well-being. Importantly, this work is intended to build on and complement prior and ongoing efforts carried out by the broader dementia community on clinically meaningful outcomes. Funding will support the development and validation of novel research tools and assessments that incorporate key priorities of people living with dementia and their care partners. This approach includes providing follow-up results to participants in an easy-to-understand format tailored to a participant’s needs and preferences, enabling them to make the most informed decisions for themselves and their loved ones. Notably, progress in defining and measuring meaningful outcomes may also accelerate the development of more personalized approaches to dementia prevention, treatment, and care, by better understanding what matters most in different contexts.



Translational Research and Clinical Interventions



Advancing the Next Generation of Innovative Clinical Trials of Novel Therapeutic Candidates

With increased investment, NIH plans to accelerate transition of drug candidates from phase 1 to phase 2 trials, expand the use of newly available biomarkers in trials, and enhance efforts to recruit and retain clinical trial participants, including those from diverse populations.

State of the Science

There have been exciting recent advances in the field of dementia therapeutics, including the FDA approval of two drugs for the treatment of early Alzheimer's. However, we know now that different types of dementia will likely require different types of treatments, including some that may eventually target an individual's unique disease characteristics — much like the cancer treatments that are available today. NIH funds efforts that support the development of multiple therapeutic options to prevent and treat Alzheimer's and related dementias. For example, NIH-funded drug development programs have led to 20 new drug candidates that have entered phase 1 and phase 2 trials, representing the next generation of potentially disease-modifying therapies. More than 30 additional drug candidates, aimed at a broad range of disease mechanisms and targets, are in preclinical development. NIH is committed to advancing research to develop new targets, interventions, and trials to maximize opportunities for successful treatment and prevention options that work for all populations.

Future Directions

With additional investment, NIH will accelerate efforts to advance innovative clinical trials for the next generation of dementia therapeutics. For example, NIH will build on recent efforts to streamline the transition of novel drug candidates (those with targets other than amyloid or tau) from phase 1 to phase 2 trials, expanding and strengthening the drug development pipeline. NIH will also enhance clinical trials, including those for combination therapies and repurposed drugs, using new and more sensitive biomarkers (e.g., blood and digital biomarkers), which can help facilitate faster, less expensive clinical trial recruitment of appropriate participants most likely to benefit from the trials, including of people from populations historically underrepresented in research. This will also advance more robust tracking of disease progression and response to therapeutic interventions. NIH will also expand comprehensive approaches to recruit and retain clinical trial participants that represent the communities most likely to be affected by Alzheimer's and related dementias.



Integrating Multiple Data Types To Enable Precision Medicine

With increased investment, NIH plans to integrate multiple data types across the research pipeline to support the development and application of a precision approach to prevent and treat Alzheimer's and related dementias.

State of the Science

Precision medicine approaches aim to provide to individuals the right treatment at the right time for them. These approaches depend on the availability of robust data to help researchers and clinicians understand dementia risk, disease trajectory, and more. For example, an individual's risk of and resilience to dementia is influenced by several factors, including but not limited to sex, genetics, and environmental exposures. As a result, researchers recognize the need to apply a precision medicine-based approach — which takes risk and resilience factors into account — to diagnosing, preventing, and treating these diseases.

Scientists now know of at least 80 genetic areas associated with Alzheimer's, up from just 10 areas in 2010. In addition, researchers have found that the genetic areas associated with Alzheimer's, and the risk or protection they confer, may vary across ancestral populations. For example, one variant of the *apolipoprotein E* gene, called *APOE4*, can increase the risk of developing Alzheimer's, but this change in risk differs across racial and ethnic populations. As scientists uncover more genetic areas — and genomic variation across populations — associated with Alzheimer's and related dementias, there is an increasing need to clarify the functional impacts of these genomic variations and deepen understanding of the key pathways that lead to disease.

Researchers are also working to develop precision medicine approaches for people living with Alzheimer's and related dementias. Most individuals living with dementia will experience neuropsychiatric symptoms (NPS), also known as behavioral and psychological symptoms of dementia (BPSD), such as depression, anxiety, apathy, irritability, and changes in sleep. In addition, these individuals often experience impaired and altered behavior patterns. Despite the prevalence of these symptoms, there remain significant gaps in understanding how such symptoms develop in the context of cognitive impairment. Further, little is known about the relationships between and variability in NPS/BPSD, altered daily behavior patterns, and cognitive impairment.

Future Directions

With additional investment, NIH anticipates expanding research to enable precision genomic medicine for Alzheimer's and related dementias, including funding studies to characterize and understand how the genome affects the risk and development of dementia in diverse ancestral populations and across dementias. This effort will leverage findings from the Alzheimer's Disease Sequencing Project and other genetic efforts to establish causal links between genomic variation and specific disease characteristics and trajectories. Knowledge gleaned from this work will ultimately inform discovery of novel diagnostic and therapeutic targets to enable precision genomic medicine for Alzheimer's and related dementias.

NIH also aims to fund efforts to gather and process novel big data from multimodal sensors and existing disparate datasets using machine learning and artificial intelligence approaches to yield new sensitive methods to detect and explain behavioral and psychological symptoms of dementia, understand the contexts in

which they arise, and inform symptom treatment and care. These efforts will also be aimed at comprehensively characterizing 24-hour real-world behaviors and their underlying causes, across the spectrum of cognitive impairment, in a manner that has not been accomplished previously. Importantly, these data — and the research tools necessary to analyze and explore this information — will serve as an invaluable resource for additional future studies of behavior and dementia.

Advancing the Development of Dementia Therapeutics by Harnessing Mechanisms To Cross the Blood-Brain Barrier

State of the Science

The blood-brain barrier is an important structure that helps keep potentially dangerous substances out of the brain while allowing the entry of nutrients, oxygen, and other key compounds. Many drug candidates in development are unable to cross the blood-brain barrier. As a result, the blood-brain barrier poses a significant challenge for the delivery of therapeutics for Alzheimer’s and related dementias directly to the brain, where they may have higher efficacy and fewer side effects. Recently, researchers found that use of focused ultrasound, a rapidly evolving noninvasive technology, enabled the delivery of anti-amyloid immunotherapies across the blood-brain barrier by temporarily “opening” this barrier. Additionally, foundational work funded by NIH has also shown that it may be possible to facilitate delivery of some therapeutic compounds, which cannot cross the blood-brain barrier on their own, to the brain by attaching them to other substances that can cross the barrier. Accelerating efforts to generate a deeper understanding of the blood-brain barrier in both

healthy individuals as well as those living with dementia can inform the development of novel therapeutic compounds and delivery approaches.

Future Directions

With additional investment, NIH anticipates funding research to accelerate efforts to deepen our understanding of the structure and function of the

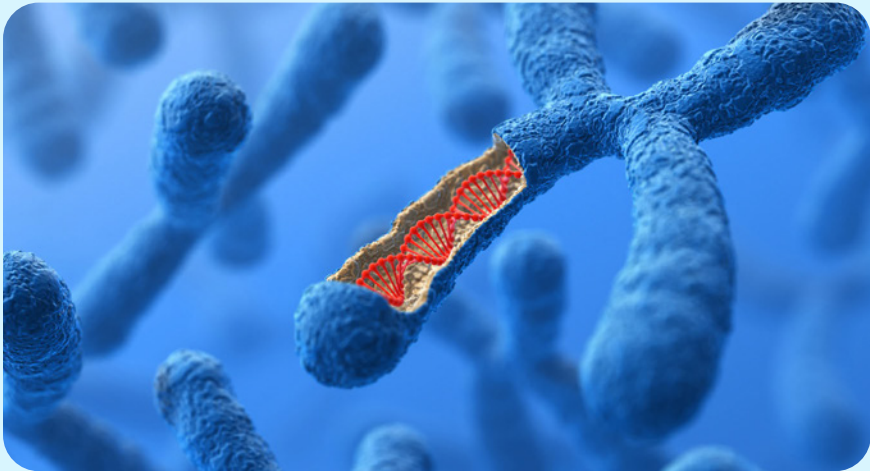
blood-brain barrier in healthy adults and people living with dementia. NIH also expects to fund research to identify and develop ways to safely and effectively move both existing therapeutics and new drug candidates across the blood-brain barrier.

Spotlight: Key Opportunities

Harnessing Protective Mechanisms To Advance Therapeutics for Alzheimer’s and Related Dementias

Researchers have identified several gene variants that are associated with increased risk of Alzheimer’s. However, scientists have also uncovered rare gene variants that may help protect against the disease. In recent years, NIH-funded researchers have identified two new protective gene variants that confer resilience against Alzheimer’s: a variant of the *RELN* gene called *RELN-COLBOS* and a variant of the *APOE* gene called *APOE3 Christchurch* (abbreviated *APOE3ch*). Understanding how these rare variants protect against dementia can help open new avenues for developing effective interventions for disease prevention. *APOE3ch*-inspired antibodies are already being investigated for their potential to inform the development of new Alzheimer’s therapeutics. However, there remain significant gaps in understanding the mechanisms of protection against dementia, including how these mechanisms are influenced by genes and the environment.

With additional investment, NIH will accelerate research toward a deeper understanding of the molecular mechanisms by which gene-environment interactions lead to cognitive resilience in individuals across diverse populations with various types of high dementia risk, including age, genetic risk, presence of cardiovascular risk factors, or presence of specific dementia biomarkers. This work will also help inform the development of resilience-based therapeutics for disease prevention and the development of new biomarkers for resilience.



Dementia Care and Impact of Disease

With increased investment, NIH plans to expand research on development and exploration of innovative care interventions and dementia care models.



State of the Science

Just as critical as ongoing efforts to pursue breakthroughs in prevention and treatment for Alzheimer’s and related dementias are efforts to ensure that the millions of Americans currently living with these diseases receive quality, person-centered care. To complement ongoing prevention and treatment work, NIH funds researchers who are actively developing and testing dementia care and caregiving interventions and care models to improve the quality of life of those living with dementia and their care partners.

One important research area focuses on better understanding the daily behavior patterns and routines involved in care. Enhanced knowledge of these patterns among both care recipients and care partners could provide an opportunity to develop strategies that involve collaboration between individuals and their care partners to foster increased reciprocity, communication, and empathy. These strategies may allow care partners to anticipate future needs and prevent potential behavioral and/or other issues from arising or escalating. In addition, efforts to develop wellness strategies that facilitate coping and recovery would benefit from enhanced knowledge of daily behavior patterns. Such strategies require more knowledge of the multitude of typical daily behavior patterns of both the individual receiving care and the care partner, as well as information on care-recipient/care partner needs.

In addition, the impact of caregiving can vary among individual care partners due to diverse and dynamic factors such as how far the disease has progressed and where care is received. For example, findings from NIH-funded research indicate that informal family caregivers of people living with Alzheimer’s and related dementias are 1.5 times more likely to report substantial physical difficulty in administering care than caregivers of people without dementia. In addition, in some care settings, care partners are simultaneously responsible for multiple



care recipients at different stages of the disease, creating additional strain. There is an acute need for effective strategies that can alleviate the problem of elevated strain associated with dementia caregiving.

Additionally, NIH continues to fund efforts to evaluate dementia care models to support people living with dementia and their care partners. For example, years of NIH-funded research helped inform the development of team-based care approaches known as collaborative care models. In July 2023, the Centers for Medicare & Medicaid Services announced a new voluntary dementia care model, the Guiding an Improved Dementia Experience (GUIDE) Model. This collaborative care approach aims to improve the quality of life of people living with dementia, reduce strain on their unpaid care partners, and enable people living with dementia to remain in their homes and communities using a comprehensive package of care coordination and care management, care partner education and support, and respite services. It is important to evaluate the effectiveness of novel dementia care models, including

GUIDE, to improve care for those currently living with dementia as well as outcomes for caregivers. NIH-funded researchers can play a critical role in understanding the impact of these dementia care models on people living with dementia and their care partners.

Future Directions

With increased investment, NIH plans to fund the development of approaches that explore the interplay among individual care partner and care-recipient behavior patterns and preferences to enable innovative care models that are efficient and can be tailored to anticipated or evolving situations and needs in a timely manner. These efforts will include development of approaches to facilitate contextual and behavioral data analytics and insights to identify patterns and environmental triggers that can be leveraged to yield improved daily care management. This information can be used to help identify and evaluate interventions to enhance physical and mental well-being for both people living with dementia as well as formal and informal care partners.

In addition, NIH intends to fund efforts examining the impact of dementia care models, including the GUIDE model, on the health and well-being of people living with dementia and their care partners. NIH-funded efforts could explore the impacts of the GUIDE model across multiple stages of implementation (e.g., early versus later years of GUIDE) and explore research areas that go beyond what formal GUIDE evaluations will assess (e.g., evaluating changes in caregiver burden, beneficiary satisfaction, and other outcomes that matter to people living with dementia and their care partners). This research could include identifying the best outcome measures for GUIDE programs to add to their required data collection, exploring use of alternate data sources, and identifying the specific services and programs that make a difference for those living with dementia and their care partners.

Research Resources

With increased investment, NIH plans to expand efforts to enhance data in existing data resources.



State of the Science

NIH has established and maintains several centralized resources to provide access to robust information, including clinical and demographic data, medical records, and biospecimens, to the broader research community. For example, the NIH NeuroBioBank provides a centralized resource aimed at the collection and distribution of human postmortem brain tissue and a central point of access for researchers to the extensive collections of high-quality biospecimens within its biorepositories. The NIH NeuroBioBank has worked collaboratively with the NIH-funded Alzheimer’s Disease Research Centers to ensure the dementia research community can access donated postmortem tissue for Alzheimer’s and related dementias research. However, some databases and repositories would benefit from enhanced integration of data to maximize usefulness for researchers.

Just as high-quality biospecimens and related resources have advanced dementia research by enabling scientists to better understand the brain, genetic tests and fluid biomarkers have revolutionized the dementia field by enabling researchers to accurately and reliably collect information about dementia risk and resilience, determine disease progression, and measure and track response to treatment. Further refinement of these tools, such as by increasing the amount of information these tools can collect or by making them less invasive and less expensive, is important

to sustaining progress in dementia research. One powerful way to help refine biomarkers and genetic tests is to expand the collection of this data from existing clinical studies of dementia, some of which were launched prior to the availability of these novel tests. This approach represents a significant opportunity to maximize the utility of NIH-funded clinical studies to enhance understanding of the clinical presentation of dementia, as well as validate biomarkers that provide important information about disease progression and response to treatment.

Future Directions

With increased investment, NIH plans to fund efforts to enhance data in existing data resources. With richer, more comprehensive data, researchers will be able to answer additional and more complex research questions and improve the rigor and quality of their research studies, so the addition of these data could substantially enhance Alzheimer’s and related dementias research.

NIH also plans to fund efforts to expand the capacity and utility of established clinical studies to validate dementia biomarkers and collect data on genetic status. These investments will help fill an important gap in the dementia clinical science enterprise, providing more foundational information on the utility of these biomarkers for clinical research, clinical trials, and, ultimately, to enable precision medicine in dementia clinical practice.



Crosscutting Area: Community-Engaged Research



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NIH recognizes the importance of engaging a broad range of communities, including those historically underrepresented in research, in Alzheimer's and related dementias research aimed at advancing diagnosis, prevention, treatment, and care efforts. Community engagement provides the opportunity to advance health equity through inclusion and retention of participants, including those from diverse backgrounds, in all aspects of the research process. This approach is critical to better understanding and addressing the drivers of persistent health disparities in dementia. In community-engaged research, scientists or research teams use community engagement strategies to develop research questions, design studies, collect data, interpret results, and disseminate findings as they relate to the specific community's health. In addition to ensuring equitable inclusion in research studies, partnering with the community supports the development of sustainable interventions and the translation of study results into practice.

NIH continues to develop, update, and disseminate important resources for clinical research to increase engagement, recruitment, and retention of research participants and their care partners, including those from diverse backgrounds, as well as provide funding for clinical research studies to build the robust community partnerships needed to increase research participation. For instance, NIH has funded efforts to develop and test community collaborations focused on increasing clinical

research participation of underrepresented racial and ethnic groups, sexual and gender minorities, and members of under-resourced and/or rural communities. As one example, NIH funds the Engaging Communities of Hispanics/Latinos for Aging Research Program, a collaborative effort that brings together researchers, agencies, and communities to target key recruitment factors in aging research. This program includes efforts to increase engagement of Hispanics/Latinos in Alzheimer's and related dementias research. As another example, NIH funds the Community-Engaged Health Equity Research in Neuroscience Initiative to advance clinical trial readiness utilizing a multipronged approach to advance community-engaged health equity research across all neurological disease areas within populations that experience health disparities. The initiative supports collaborations, education, and capacity building to conduct such research.

With increased investment, NIH plans to fund new efforts to build capacity for community-engaged Alzheimer's and related dementias research. These efforts will include research to understand and address the drivers of dementia health disparities in diagnosis, treatment, and outcomes. This research will enable the development of new community-based strategies to enhance the recruitment and retention of research participants, address the research needs of all communities, and develop sustainable, culturally tailored interventions.



Conclusion

NIH has made tremendous progress in research on Alzheimer's and related dementias prevention, diagnosis, treatment, and care, fueled by many years of generous investments by Congress. NIH will continue this momentum, using new investments to capitalize on novel and emerging opportunities to advance the field of dementia research.

Importantly, this progress would not have been possible without the collaboration and commitment of a dedicated community of individuals and organizations, including people living with dementia, care partners, families, advocates, Congress, clinicians, researchers, and others. The examples of research opportunities outlined within this professional judgment 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 pursue promising new research initiatives that will bring us closer to the goal of preventing and effectively treating Alzheimer's and related dementias.