Looking Forward: Opportunities to Accelerate Alzheimer’s and Related Dementias Research

Innovations in Prevention, Treatment, and Care Research
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SPOTLIGHTS: KEY OPPORTUNITIES

- Precision Environmental Health Approach to Risk Reduction and Prevention for Alzheimer’s Disease and Related Dementias .............. 12
- Leveraging Technologies That Enable Characterization of Individual Cells to Advance Dementia Research ......................... 20
- Using Artificial Intelligence to Accelerate Drug Development for Alzheimer’s and Related Dementias .............................. 25
Bypass Budget: At a Glance

NIH Director’s Message

This year, we commemorate the 10th anniversary of the National Plan to Address Alzheimer’s Disease (“National Plan”), which was mandated by the National Alzheimer’s Project Act (NAPA). As we reflect on the significant advancements and progress in Alzheimer’s and related dementias research — made possible by robust and sustained investments from Congress — we acknowledge the crucial work that must continue to expand to bring us closer to meeting the first goal of the National Plan: to prevent and effectively treat these devastating disorders.

Scientific progress to date has yielded important insights about Alzheimer’s and related dementias. As a result, our trajectory toward finding effective treatments has never been more promising. Now is the time to leverage the momentum gained to date and to continue innovation and discovery that will yield new opportunities for improved diagnostics, prevention, treatments, and support for people living with dementia and their loved ones.

I am pleased to present the National Institutes of Health (NIH) Professional Judgment Budget for Alzheimer’s Disease and Related Dementias Research for Fiscal Year (FY) 2024.

“Now is the time to leverage the momentum gained to date and to continue innovation and discovery.”

Lawrence A. Tabak, D.D.S., Ph.D.
Acting Director
National Institutes of Health
NIH Director’s Message, continued

Building on Success

Since the passage of NAPA and the increased investment in Alzheimer’s and related dementias research, NIH has accelerated and expanded the scope of its science — and its accomplishments — in several critical fields:

» Genomics. Ten years ago, we knew of just a handful of genetic areas associated with Alzheimer's disease. That number has grown to more than 70 today. These genomic advances are already informing new pathways and, in some cases, the testing of interventions that target these pathways, in both animal models and humans.

» Disease Mechanisms. Research has revealed that most dementia cases in older adults exhibit multiple disease pathologies. “Mixed” dementias therefore appear to be the rule, not the exception. These important findings have shifted the way the field has thought about therapeutic development and have elevated the importance of applying a precision medicine approach for dementia treatment.

» Diagnostics. In the early 2000s, researchers could confirm an Alzheimer’s disease diagnosis only at autopsy. Now researchers can measure disease burden through brain scans and are developing more affordable and less invasive tools, including blood biomarker tests, to diagnose and distinguish different forms of dementia. Better diagnostics not only aid in the development of more refined clinical trials but also help people living with the disease plan for the future, until effective treatments are available.

» Risk/Resilience Factors and Prevention. We now know there are several risk and resilience factors that may play a role in the development of dementia. One example is blood pressure control: Recent studies showed that intensive high blood pressure control significantly reduces the occurrence of mild cognitive impairment, a precursor to dementia in some individuals. NIH has taken steps to share these findings with the public through efforts like the Mind Your Risks® campaign.

» Care and Caregiving Research. Building on NIH’s longstanding commitment to enhance care for the millions of Americans currently living with dementia, NIH funded a national research infrastructure in 2019 to support pragmatic trials, or real-world clinical trials that take place where people live and routinely receive care. This effort is designed to spur innovation to meet the challenges of complex care management and improve the lives of individuals living with dementia, their care partners, and loved ones. Conducting this research in care settings will aid in diversifying clinical trial participation and help to ensure that positive findings can be broadly implemented.

» Cutting-Edge Infrastructure. NIH has established robust infrastructure to advance understanding of disease mechanisms and identify and validate potential targets for therapeutics. This includes the newly launched intramural Roy Blunt Center for Alzheimer’s Disease and Related Dementias (CARD) Research on the NIH campus in Bethesda, Maryland, where NIH intramural researchers work side by side with visiting investigators from around the globe on specific projects intended to accelerate the translation of scientific findings into real-world applications. CARD is designed to complement efforts of the extramural community by leveraging the unique resources available on the NIH Campus, including the NIH Clinical Center, to address scientific gaps. In addition, CARD offers multiple opportunities for early-career investigators to hone skills needed for the translation of discoveries into therapies through collaboration with top researchers in the field.

I look forward to sharing additional details about the exciting developments and recent scientific advances in NIH’s next Alzheimer’s and Related Dementias Research progress report, to be released in November 2022.
A Roadmap for the Future

To advance closer to effective diagnostics, prevention, and treatments for Alzheimer’s and related dementias, as well as quality care for those living with these diseases, we must continue to prioritize promising basic, translational, and clinical research. The FY 2024 Professional Judgment Budget for Alzheimer’s Disease and Related Dementias presents a way forward: a prospective look at the research opportunities that could be pursued with additional investment. Within this narrative, we describe the additional resources needed to pursue exciting new research opportunities that can help accelerate progress toward the goals of the National Plan. Examples of investment priorities are organized along six research 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 FY 2024. In addition, we emphasize significant cross-cutting research efforts centered on equity and inclusion. NIH recognizes the need to actively support efforts to address health equity in dementia research given existing disparities in the prevalence and impact of these diseases in historically marginalized communities. Also, a growing body of evidence shows that diversity in science fosters innovation and discovery and improves research quality. Our focus on equity and inclusion is critical to ensuring the rigor of our research and U.S. leadership in the global scientific community. We underscore NIH’s long history of investments to understand and address these important issues and outline additional ways NIH will seek to achieve equity and inclusion in research.
Annual Budget Estimate

This budget proposal outlines the additional funding needed in FY 2024 to advance NIH-supported research toward achieving the goals outlined by the National Plan. The professional budget estimate includes $321 million in additional resources for new research, with the overall resources needed totaling $3.87 billion. The projected cost of resources needed in FY 2024 for new research is $498 million. This estimate is reduced by $177 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 2024 budget is $321 million.

Impact

More than six million Americans are currently living with Alzheimer’s disease, and it is predicted that more than 13 million will be living with the disease by 2060. In addition, many people have other forms of dementia, such as Lewy body dementia, frontotemporal dementia, and vascular cognitive impairment/dementia. NIH is focused on turning new discoveries into health to meet the needs of the millions living with and at risk for these diseases as well as their care partners. With increased investment, NIH will bring the field closer to effectively preventing, detecting, and treating these challenging and complex disorders.
### Professional Judgment Budget FY 2024

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<tr>
<td><strong>Total Costs for New AD/ADRD Research</strong></td>
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Less: Funding from completed projects that is now available for new AD/ADRD research

| Additional FY 2024 Resources Needed for New AD/ADRD Research      | **$321,237,000** |

### Total Resources Needed

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<td>ADDITIONAL FY 2024 Resources Needed for New AD/ADRD Research</td>
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<td><strong>Total FY 2024 Resources Needed for AD/ADRD Research</strong></td>
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1. Baseline estimate represents the Alzheimer’s Disease including Alzheimer’s Disease Related Dementias (AD/ADRD) category from the Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC) website. This category includes Alzheimer’s disease, frontotemporal dementia, Lewy body dementia, and vascular cognitive impairment/dementia. Individual disease baseline estimates are available on the RCDC website. The annual estimates reflect amounts that change as a result of science, actual research projects funded, and the NIH budget.

2. In FY 2024, the projected cost of resources needed for new and evolving research to meet the 2025 treatment/prevention goal is $498 million. The estimate is reduced by $177 million in funding from completed projects that is now available for new research initiatives. As a result, the additional resources needed for new research in the FY 2024 budget are $321 million.
Professional Judgment Budget FY 2024, continued

Distribution of FY 2024 Total Projected Costs Across Research Areas

- **Research Resources**: $80,800,000 (16%)
- **Dementia Care and Impact of Disease**: $41,000,000 (8%)
- **Epidemiology/Population Studies**: $75,000,000 (15%)
- **Alzheimer's Related Dementias**: $40,000,000 (8%)
- **Staffing Needs and Administrative Support**: $9,437,000 (2%)
- **Disease Mechanisms**: $65,500,000 (13%)
- **Diagnosis, Assessment, and Disease Monitoring**: $44,000,000 (9%)
- **Translational Research and Clinical Interventions**: $142,500,000 (29%)

Total Projected Costs: $498,237,000*

Less: Funding from completed projects $177,000,000

Additional Resources Needed for New Research: $321,237,000

*In FY 2024, the projected cost of resources needed for new and evolving research to meet the 2025 treatment/prevention goal is $498 million. The estimate is reduced by $177 million in funding from completed projects that is now available for new research initiatives. As a result, the additional resources needed for new research in the FY 2024 budget are $321 million.
With increased investment, NIH plans to fund additional longitudinal studies designed to better understand how, for a given individual or group, different genetic, behavioral, social, cultural, and other environmental factors affect risk for and protection from Alzheimer’s and related dementias.
State of the Science

Longitudinal studies follow groups of people over time, making them a powerful tool for understanding the aging process. These studies not only shed light on what constitutes normal aging but also help to identify the role of specific factors in contributing to age-related health and function, including cognitive decline and dementia. NIA supports the longest-running study of aging in America, the Baltimore Longitudinal Study of Aging (BLSA); and several other longitudinal studies, including the Health and Retirement Study (HRS), the Alzheimer’s Biomarkers Consortium — Down Syndrome (ABC-DS) project, and additional studies focused on dementia in historically marginalized populations, discussed in more detail below.

The HRS, which repeatedly surveys a national sample of older adults and emphasizes appropriate representation of historically marginalized populations, is the largest and most comprehensive longitudinal study of older adults in the United States. To date, it includes more than 20,000 adults ages 50 and older and covers a broad range of health and functional measures, including those relevant to Alzheimer’s and related dementias. The HRS also collects data on childhood conditions and adult socioeconomic status. As a result, the HRS has become the model for a suite of longitudinal aging studies in several other countries. To facilitate cross-national comparisons and enable harmonization of data about brain changes across studies, NIA funded in 2016 the development and deployment of the Harmonized Cognitive Assessment Protocol (HCAP), a state-of-the-art standardized protocol for assessing cognitive function that allows one to estimate the prevalence of mild cognitive impairment and dementia in large nationally representative samples. Such a standardized approach enables researchers to measure and understand dementia risk in the HRS and other ongoing longitudinal studies of aging around the world by using methods and content that are as similar as possible across studies.

Longitudinal studies are most helpful when they include a diverse set of participants that represents the broader population. In recent years, NIH has undertaken efforts to increase the diversity of populations within its U.S. longitudinal research. In particular, NIH has supported initiatives to increase the representation of Black and Hispanic individuals, who are at greater risk of developing dementia, in these studies. For example, NIA launched the Health & Aging Brain Study: Health Disparities (HABS-HD) in 2022 as the first large-scale, community-based project to simultaneously research the key biomarkers associated with Alzheimer’s disease in African Americans, Mexican Americans, and non-Hispanic Whites. NIA also increased the inclusion of underrepresented populations in longitudinal studies, including the HRS. Likewise, the National Institute of Neurological Disorders and Stroke (NINDS) is expanding the longstanding Reasons for Geographic and Racial Differences in Stroke (REGARDS) project, which has historically examined health disparities in stroke, to investigate health disparities in dementia and cognitive impairment. Additional longitudinal data are needed to build on this progress and comprehensively understand how different factors influence disease burden across populations.

In recent years, NIH has undertaken efforts to increase the diversity of populations within its U.S. longitudinal research.
Future Directions

Leveraging existing longitudinal studies, NIH plans to fund new research examining the role of social determinants of health — including education, socioeconomic status, adverse childhood experiences, and physical environment — in Alzheimer’s and related dementias. In particular, NIH expects to support new analyses of data from the international studies harmonized to the HRS, focusing on data from low- and middle-income countries as representative cohort studies for rapidly growing subpopulations in the United States. For example, NIH could support research that facilitates comparisons of the health dynamics of older Mexicans enrolled in the Mexican Health and Aging Study with comparably aged Mexican-born migrants in the U.S. and second-generation Mexican Americans enrolled in the HRS. Such cross-national analyses will advance understanding of how different genetic, behavioral, social, cultural, and other environmental factors affect risk of and resilience to Alzheimer’s and related dementias, enabling the development of appropriate dementia risk reduction strategies.
A person is exposed to a myriad of environmental factors over the course of a lifetime, from the food and water they ingest to the air they breathe and the social, financial, and psychological environments they experience. The totality of a person’s lifetime exposures to external factors is known as the exposome. These environmental exposures can have a direct effect on human health. As one example, pollen in the air can be a trigger for allergies. However, some people have genetic risk factors that may make them more or less susceptible to environmental exposures. For instance, some individuals have no reaction to pollen, whereas others experience severe allergy symptoms. This interaction of genetic and environmental factors plays a key role in shaping human health.

It is important to appreciate that this “exposome” is unequally distributed across communities and can contribute to inequities in health outcomes. For example, environmental toxicants like air pollution, pesticides, and metal toxins disproportionately affect communities of color. These substances have also been linked to several neurodegenerative disorders, including Alzheimer’s and related dementias.

The growth of advanced computing in recent years has now made it possible to measure aspects of the exposome and their relationship to human health. However, the mechanisms by which these elements of the exposome affect dementia risk are still largely unknown.
NIH anticipates advancing research in this emerging area by supporting coordinated centers for exposome science with the goal of addressing the urgent need for research infrastructure that explores the role of various physical, chemical, social, psychological, and economic exposures in Alzheimer’s and related dementias and how these exposures differ across populations.

To this end, NIH will employ a multipronged approach through the establishment of key infrastructure and centralized resources. For example, NIH plans to establish a research consortium to better understand the impact of environmental exposures on brain health and the development of dementia. Specifically, this consortium will include the use of relevant mouse models of late-onset Alzheimer’s disease to examine the consequences of early and midlife environmental exposures on several aspects of late-life brain health. In addition, NIH will fund research using cutting-edge cellular and tissue models — including small platforms that mimic human organs and diseases known as microphysiological systems (MPS) — to better understand the exposome in human cells and tissues (see Research Resources for more information on MPS).

The research consortium anticipates utilizing these new models to identify signatures of toxicant and other environmental exposures in body tissues. Identifying these signatures will inform the development of noninvasive biomarkers, such as imaging or blood biomarkers, that can indicate exposure. A key goal is to collect exposure data from broad, diverse human populations.

NIH will also enrich existing longitudinal studies with biomarkers and other measures indicating not only environmental exposures but also the body’s response to these exposures. Additionally, NIH will leverage several non-Alzheimer’s and related dementias longitudinal studies for which exposure data is already available by adding dementia-specific biomarkers and outcome measures, such as cognitive assessment. Furthermore, given the unequal distribution of exposome elements across communities, NIH will utilize diverse and demographically representative studies to create rich data resources reflecting the effect of environmental exposures across the lifespan in diverse groups of individuals. NIH plans to establish a centralized hub for accessing, harmonizing, and sharing environmental data and individual exposure data to help explain the relationship between exposures across the lifespan and the risk of Alzheimer’s and related dementias. This hub will also support researchers in developing new common data elements and validated measures to accelerate the study of the role of the exposome in dementia risk, such as by enabling comparisons across multiple longitudinal studies.

NIH plans to establish a CENTRALIZED HUB for accessing, harmonizing, and sharing environmental data this work is expected to advance the field of dementia research in several critical ways. First, it will improve understanding of how environmental factors affect health disparities in Alzheimer’s and related dementias. It will also lead to the identification of novel risk factors for these diseases. Furthermore, exposome research will offer the opportunity to develop precision medicine approaches for the treatment of Alzheimer’s and related dementias as well as inform strategies for dementia risk reduction and disease prevention.
Disease Mechanisms

With increased investment, NIH will fund research that explores underlying molecular and cellular processes, including the functional role of the many genetic variations that have been recently linked to Alzheimer’s and related dementias (functional genomics), and other fundamental research to develop innovative therapies (including novel immunotherapies) to treat these diseases.
**Functional Genomics**

With increased investment, NIH plans to accelerate research exploring the functional role of the many genetic variations that have been recently linked to Alzheimer’s and related dementias.

**State of the Science**

Genomics research has revolutionized biomedical research by uncovering the genetic basis of many complex diseases. Studies that scan the genome — the complete set of genes a person has — including genome-wide association studies (GWAS) conducted as part of the *Alzheimer’s Disease Sequencing Project (ADSP)*, have been highly successful in identifying genetic variations that may play a role in the development of AD. More than 70 regions of the genome associated with Alzheimer’s have been identified so far, but how variations in these genetic regions affect the function of molecules or cells in the body or confer risk for Alzheimer’s is largely unknown. In fact, discerning genome function remains a persistent scientific bottleneck that has limited progress toward fully understanding dementia disease mechanisms. Adding to the complexity, several Alzheimer’s-related dementias have a genetic basis involving genomic regions and functional pathways, some in common with and some distinct from Alzheimer’s disease. Understanding processes triggered by genetic variations associated with dementia is necessary to enable development of therapeutics based on genetic drivers of these complex diseases.

**Future Directions**

With increased investment, NIH will usher in the next generation of functional genomics approaches, including innovative and scalable genomic technologies, high-resolution cell imaging, and streamlined experimental workflows. Much of this work is expected to build on and enrich the existing ADSP infrastructure, including the ADSP Functional Genomics Initiative established in 2020 to systematically identify and elucidate the functional roles of genetic elements in how Alzheimer’s and related dementias begin, develop, and present in different individuals and populations. These efforts will facilitate exploration of the functional genome of Alzheimer’s disease to identify drivers of dementia and underlying disease mechanisms. This work is particularly crucial to understanding impacts of genomic versus non-genomic risk in people living with dementia — especially those disproportionately affected by the disease, including women and Black/African and Hispanic/Latino Americans. NIH will usher in the next generation of functional genomics approaches, including innovative and scalable genomic technologies, high-resolution cell imaging, and streamlined experimental workflows.
Novel Immunotherapies

With increased investment, NIH intends to support fundamental research to develop innovative immunotherapies to treat Alzheimer’s and related dementias.

State of the Science

Accumulations in the brain of specific proteins, such as amyloid and tau, are the hallmarks of Alzheimer’s disease. A category of drugs known as monoclonal antibodies, which help remove these proteins, are currently being tested for their ability to slow or prevent Alzheimer’s disease. These drugs work largely by identifying protein aggregations and triggering the body’s own immune defenses to clear the proteins, a form of immunotherapy known as passive immunotherapy. In clinical trials, some of these drugs have been effective in clearing amyloid protein deposits from the brain. However, none of these therapies have yet demonstrated clear clinical benefits, such as slowing of cognitive decline, though several trials of monoclonal antibodies are ongoing.

Other immunotherapies focus on boosting specific components of the immune system to fight disease. Novel immunotherapies have produced remarkable results in treating some forms of blood cancer, such as leukemia. One form of this, known as chimeric antigen receptor T-cell (CAR-T) therapy, modifies specific immune cells, called T cells, with the ability to find and destroy cancer cells. Because this approach involves tailoring T cells to seek out specific types of target cells, it could potentially be repurposed to treat other diseases, including dementias.

Senescent cells are one such promising target for novel immunotherapies. As humans age, some cells can lose their normal function, such as the ability to divide and replicate. Although they lack normal cellular capabilities, these senescent cells remain active and continue to release chemicals that may damage neighboring cells and contribute to age-related diseases and disorders, including neurodegeneration. NIH-supported investigators have found that treatment with senolytics, compounds that selectively remove senescent cells, extended lifespan and healthspan in aging mice and even preserved cognition in a mouse model of Alzheimer’s disease. Although several drugs show promise as senolytics, further investigation is needed to identify those that are the safest and most effective for use in treating age-related diseases, including Alzheimer’s and related dementias.

Future Directions

NIH is planning to fund research that bridges these areas of study by adapting novel immunotherapies to target cells and proteins thought to play a role in the development of Alzheimer’s and related dementias. First, NIH will focus on advancing CAR-T immunotherapies that offer promise in selectively seeking out and removing senescent cells in the brain that may contribute to dementia. Second, NIH will advance research on a comparable type of immunotherapy, called CAR-M, that works in a similar fashion to CAR-T but enhances a different kind of immune cell, called a macrophage. Macrophages are primarily responsible for clearing protein aggregations in the brain. NIH could fund basic research to reveal whether CAR-M can successfully enhance macrophages to better target and remove accumulations of proteins, including amyloid and tau, that are associated with Alzheimer’s and related dementias.

Additional investment will advance innovation in this field by funding research to develop proof-of-principle for these immunotherapies. Specifically, NIH will support the establishment of protocols and best practices for enhancing immune cells in dementia-relevant ways. NIH will also fund efforts to demonstrate not only that immune cells can be readily and reliably modified but also that modified cells can engage specific targets of interest. Furthermore, NIH will seek to verify that CAR-T and CAR-M therapies produce the desired effect (e.g., clearance of senescent cells), as well as to understand how long CAR-T and CAR-M cells remain in the body after administration. By funding research in this area, NIH has the potential to advance novel and powerful treatment strategies for Alzheimer’s and related dementias.

A macrophage cell stretching its “arms” engulfing two particles, possibly pathogens, in a mouse (Credit: The original uploader was Obli at English Wikipedia)
With increased investment, NIH seeks to develop the next generation of biomarkers to enable detection and diagnosis even earlier than is now possible, and to distinguish different forms of dementia from one another.
State of the Science

A little more than two decades ago, scientists could definitively diagnose someone with Alzheimer’s disease only by examining brain tissue after death. Today, research has advanced to support the possibility of reaching the same diagnoses through a simple blood test or a noninvasive imaging test, such as a positron emission tomography (PET) scan. Importantly, these biomarker tests — which help measure changes associated with disease — are still largely used by researchers in the lab and not yet in hospitals or doctors’ offices. More work is needed to ensure these tests are sensitive and reliable indicators of Alzheimer’s disease or a related dementia, including mixed pathologies, and can be scaled for use in everyday clinical settings.

Another active line of research is focused on what we can infer about changes in cognitive status from tasks done on mobile devices or from background sensor data on these devices or others in our homes. These sensitive and noninvasive “digital biomarkers” may hold unique promise in detecting earlier changes in function, in a scalable and cost-effective way.

Currently, the AT(N) framework outlines the “common language” used by researchers to identify, develop, and validate Alzheimer’s disease biomarkers in clinical and observational studies. This framework derives its name from the primary hallmarks of Alzheimer’s disease: Amyloid plaques, Tau tangles, and Neurodegeneration. Although AT(N) has helped facilitate understanding of the disease process, it has limitations that additional research will help to address. For example, the framework does not account for multiple etiology dementias (dementia with multiple underlying causes). In addition, historically marginalized communities have not been well represented in research underlying each biomarker, so there remains a need to investigate these biomarkers across different racial and ethnic groups. Knowing how the AT(N) biomarkers differ across these groups will better inform the continued development and use of this framework. Although NIH is supporting studies that are aimed at better understanding health disparities of brain aging and Alzheimer’s disease biomarkers using this framework, such as through the Health and Aging Brain Among Latino Elders (HABLE) Study, there is a critical need for an expanded framework that goes beyond amyloid, tau, and neurodegeneration to fully appreciate the complexities of these diseases.
To further bridge the gap between discovery work and therapeutic development, NIH will fund rigorous analytical and clinical validation studies on a range of new candidate biomarkers and functional assessments to measure and predict the success of potential treatments. Such biomarker research will advance efforts to diagnose disease early, track disease progression, select a diverse range of participants for and design clinical trials, and measure response to potential treatments.

**Future Directions**

With further investment, NIH will expand the existing AT(N) framework into a more comprehensive form that incorporates Alzheimer’s disease-related dementias and multiple etiology dementias, as well as better assessment of the behavioral, psychological, and functional changes that occur along the disease trajectory. NIH will also fund the systematic evaluation and incorporation of additional biomarkers into the AT(N) framework to uncover underlying mechanisms and pathways that may differ across individuals based on race, ethnicity, gender, and other factors. To complement an improved framework, NIH will fund the development of cutting-edge tools and multimodal approaches — involving fluid, imaging, and digital tests — that can detect several disease-associated markers at once and differentiate among multiple forms of dementia. For example, NIH will extend ongoing research to identify and validate new PET tracers as biomarkers to detect the presence of additional protein abnormalities linked with Alzheimer’s disease-related dementias. To further bridge the gap between discovery work and therapeutic development, NIH will fund rigorous analytical and clinical validation studies on a range of new candidate biomarkers and functional assessments to measure and predict the success of potential treatments. Such biomarker research will advance efforts to diagnose disease early, track disease progression, select a diverse range of participants for and design clinical trials, and measure response to potential treatments.
Our understanding of Alzheimer’s and related dementias will be revolutionized by being able to study these diseases at the scale of individual cells.

Leveraging Technologies That Enable Characterization of Individual Cells to Advance Dementia Research

In 1610, Galileo’s publication of *Sidereus Nuncius* changed our understanding of the cosmos by revealing that the Milky Way was comprised of individual stars. In much the same way, our understanding of Alzheimer’s and related dementias will be revolutionized by being able to study these diseases at the scale of individual cells. Just as the telescope was the tool that enabled a paradigm shift in astronomy, a new set of techniques known as single-cell analysis enables researchers to examine the composition and function of individual cells. These techniques, largely advanced by NIH’s [Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative](https://www.braininitiative.nih.gov/), not only can facilitate comparisons across cells but also can help shed new light on disease dynamics. For example, single-cell analysis can help reveal how vulnerable specific types of cells are to the accumulation of proteins such as amyloid, tau, alpha-synuclein, and TDP-43. Single-cell analysis can also uncover the interactions between cells both in normal brain aging and in the development of Alzheimer’s and related dementias, as well as how differing types of cellular dysfunction can lead to different forms of dementia. New advancements in single-cell analysis offer novel opportunities to develop research tools and identify innovative, personalized therapeutic options. For example, NIH-funded researchers affiliated with the BRAIN Initiative recently developed a new method of single-cell analysis that
enables investigators to examine multiple genetic and molecular components together instead of one at a time.

NIH anticipates leveraging the BRAIN Initiative’s Cell Census Network to help accelerate the development of new insights and tools for dementia research. NIH will link BRAIN Cell Census Network activities to new efforts to conduct single-cell profiling and generate a deeper understanding of how individual cells function and interact with one another when healthy and in various stages of dementia. In particular, insights from single-cell profiling can enhance our knowledge of the complex molecular and cellular pathologies of Alzheimer’s and related dementias, making it possible to pursue the next generation of high-performance biomarkers in blood, cerebrospinal fluid, other body fluids, or tissues. This approach will also facilitate the identification of novel therapeutic targets and enable a precision medicine approach to diagnosing, treating, and preventing these diseases, a “participant-centric” approach that results in each person getting the right treatment in the right place at the right time for them.

To be most useful, these data must represent the broader population of the U.S. NIH will fund efforts to conduct robust single-cell analysis using cells from diverse groups of individuals. NIH is working now to ensure that when the tools and protocols for single-cell profiling have matured, there will be cells from a representative U.S. population available for analysis, obtained following appropriate informed consent and ethics policies. In particular, the HRS is collecting and cryo-preserving cells from participant blood samples for future use, and additional investments will be necessary to ensure the availability of cells for years to come.

Single-cell analysis will generate tremendous amounts of new data on Alzheimer’s and related dementias, a single human brain is comprised of nearly 200 billion cells. Factoring in data on the function and composition of these cells, alongside the integration of this material with existing clinical and other data, means that vast quantities of information will be produced during the course of this work. To ensure that these data are housed appropriately and made available to the broader research community, NIH will fund an open-access data sharing infrastructure that facilitates curation, analysis, and mining of these data.

By facilitating discoveries at the scale of individual cells, NIH will help to elucidate the unique contributions of cells and networks, alone and in combination, to Alzheimer’s and related dementias. The integration of this information will aid in the development of risk reduction strategies and novel therapeutic targets for the treatment and prevention of these complex diseases.

A single human brain is comprised of 200 BILLION CELLS
With increased investment, NIH intends to fund the development of advanced tools and data resources to rapidly screen and identify novel therapeutics to pursue a precision medicine approach to treating and preventing dementia.
State of the Science

At the heart of dementia research progress has been the effort to find a prevention or effective treatment for these complex disorders. We now know that one drug or therapeutic is unlikely to be successful for all individuals, in part because research has shown that Alzheimer’s disease often co-occurs with related dementias and other neurodegenerative disorders, such as Parkinson’s disease. Consequently, researchers expect that a range of treatments and approaches tailored to individuals will likely be required to halt and reverse the effects of these diseases.

Building on the successes of programs like NIA’s Alzheimer’s Drug Development Program (ADDP) and Accelerating Medicines Partnership® for Alzheimer’s Disease (AMP® AD), NIH aims to expand the therapeutic pipeline by advancing precision medicine approaches for dementia. In a precision medicine model, the timing, types of treatments, and/or combination of treatments are tailored to an individual’s burden of disease, and the field is already advancing in this direction. For example, efforts to collect information about the biological molecules underlying Alzheimer’s and related dementias, including genetic material through genomics studies, are generating tremendous amounts of new data. The advent of newer diagnostics and biomarkers makes it possible to collect data from broader, more diverse populations on the presence of brain proteins implicated in the development of disease. Artificial intelligence (AI) and machine learning (ML) methods, as well as new computational modelling approaches, offer novel ways to more rapidly assess these data. Innovative resources of these kinds are critically needed to accelerate discovery and enable a more personalized approach to dementia treatment.

NIH aims to expand the therapeutic pipeline by advancing precision medicine approaches for dementia.
Future Directions

With additional investment, NIH plans to advance the therapeutic pipeline by making available a broad range of resources, including basic science and applied research tools, that support precision medicine and prevention strategies. These resources include funding for the development of new, standardized platforms for screening and preclinical testing of dementia therapeutics, such as small biological models that mimic aspects of the body or disease known as microphysiological systems (see Research Resources). Other infrastructure elements will support the development of novel therapeutics such as gene editing, whereby the onset or progression of disease is changed by altering a person’s genes. Such a unique therapeutic approach may be a particularly promising option for individuals with Alzheimer’s disease-related dementias, as several common and rare genetic variants have been identified as potential therapeutic targets.

Another approach to advancing the therapeutic pipeline is to leverage large investments in digitizing medical and health records. For example, data platforms that provide the research community with access to real-world data from clinical visits, including prescribed drugs and other treatments, may facilitate the discovery of opportunities for repurposing drugs and conducting future pragmatic trials. By extending these data sources to include information about demographics and environmental exposures, NIH can generate opportunities to uncover potential risk or resilience factors that can aid in the development of novel, effective treatments. The inclusion of larger and more representative populations in these datasets will also enable researchers to identify diverse participants for recruitment in clinical trials and examine a range of treatment approaches.

While we investigate avenues for treatment, it is also important to explore effective ways to prevent Alzheimer’s and related dementias. Detecting and addressing vascular risk factors, like blood pressure, early is a promising area for dementia prevention. NIH plans to fund large-scale pragmatic trials of preventive approaches focused on enhancing vascular health to reduce dementia risk, including non-pharmacological approaches like diet and exercise. Additionally, NIH aims to advance non-pharmacological work toward the realm of precision medicine by supporting a research resource to identify common data elements, improve trial design features, and promote collaboration across research teams to understand which behavioral or lifestyle interventions work best, for whom, and under what circumstances. NIH is poised to bring these powerful new technologies and tools to fruition across the entire research enterprise and to realize the goal of changing the course of dementia and providing optimized treatments for every individual.
Using Artificial Intelligence to Accelerate Drug Development for Alzheimer’s and Related Dementias

Traditionally, the process of preclinical drug design starts with researchers screening vast numbers of small molecules and testing their effects on disease-associated targets. This can be a slow and expensive process that, despite evidence-based strategies, only infrequently produces positive outcomes. Fortunately, through the rapid growth in the data sciences, artificial intelligence (AI) and machine learning (ML) methods — tools once considered to be science fiction — have opened new doors to accelerate key steps involved in drug development. AI/ML offers great potential to speed up some of the most costly and challenging steps of the drug design and development process. These methods can increase the odds of finding the best candidate drugs; in fact, it is now possible to rapidly screen billions of drug candidates to find those that will most precisely interact with specific targets without having to physically make and test the candidates in the lab. This technology not only accelerates the identification process but does so with a great deal of precision, thereby reducing failure rates of pinpointed candidates.

To get to more effective treatments for dementia faster, NIH will expand the capabilities of the existing translational research program and initiate the new AI for Drug Discovery program. This computer-aided drug design program will develop and apply AI/ML methods to accelerate drug design for Alzheimer’s and related dementias treatment and prevention. The program will create advanced analytical and research tools that will be made available to researchers in academia and biotech/pharma for more effective drug discovery. It will also complement the efforts of NIH’s TaRget Enablement to Accelerate Therapy Development for Alzheimer’s Disease (TREAT-AD) centers, which have the goal of advancing novel targets into drug discovery by developing high-quality, open-source target-enabling research tools. The future of drug discovery is here: AI/ML will bring us closer to finding safe and effective therapies for these diseases.
With increased investment, NIH aims to fund research that addresses barriers to integrated care and advances knowledge on the economic impact of care and caregiving.
State of the Science

While we work to develop successful treatments, people currently living with Alzheimer’s and related dementias need quality care that maintains their safety, promotes human dignity and autonomy, and can be delivered in a fiscally responsible manner. NIH recognizes these needs and has a long history of supporting care and caregiving research to better understand the impact of dementia on people living with these diseases as well as on their care partners and society.

As of March 2022, NIH is supporting more than 190 clinical trials of dementia care and caregiving interventions. This includes those in formal care settings, such as skilled nursing facilities, as well as those in home or informal care settings. Several recently launched studies are pragmatic trials, which take place where people already live and receive care. Many of these are being conducted through the NIH IMbedded Pragmatic Alzheimer’s disease (AD) and AD-Related Dementias (ADRD) Clinical Trials (IMPACT) Collaboratory, which was established in 2019 to develop the nation’s capacity to accelerate care intervention research and ensure real-world applicability of models. In addition to supporting the Collaboratory, NIH is supporting an array of care-related interventions, including research on two care models that were recently identified by the National Academies of Science, Engineering, and Medicine as ready for implementation in real-world settings, under conditions that enable further study and evaluation to inform future implementation.

Other NIH-funded care research focuses on ways to improve community-level integration of medical care, home-based care, and other long-term assistance for people living with dementia. Such integration is essential for people living with dementia to live in the setting of their choice while ensuring access to necessary services. Yet people living with dementia are still faced with fragmented care and a lack of care coordination today. Furthermore, there is wide variation across U.S. states in payment and policies that support care coordination and integration, and evidence suggests that racial and ethnic minorities as well as rural residents are less likely to have access to well-integrated care. More research in this area is crucial to promote the safety, quality of care, and quality of life for people living with dementia, as well as to reduce costs.
Future Directions

To address these issues and support broader implementation of promising care practices, NIH plans to launch a new research consortium to integrate multiple sources of existing data, such as that from state- and privately-funded inpatient and long-term care settings as well as home- and community-based services. The goal is to better understand and assess care integration across a variety of settings. In addition, the consortium will enable meaningful comparisons between available care programs across the country, develop and disseminate best practices in care integration across settings, and elucidate causal factors that may drive disparities in health care for people living with dementia. NIH will also fund economic research exploring how incentives impact the direction of care (e.g., transferring a patient to a hospital unnecessarily to redirect costs to Medicare), regardless of ideal care practices. By determining how incentives can be optimized for dementia care, improvements in quality of and access to care will be made alongside reductions in cost.

Alzheimer’s and related dementias are devastating disorders. Continued investments in care and caregiving research offer the opportunity to enhance safe, quality care for people living with dementia; improve the well-being of affected individuals and their care partners; and better understand the economic impact of these diseases on individuals and society.
With increased investment, NIH plans to develop and share cutting-edge resources, including new preclinical research tools, to enable the biomedical research community to address scientific challenges and accelerate efforts to prevent and treat Alzheimer’s and related dementias.
State of the Science

Scientific progress in dementia research requires a robust set of resources and infrastructure to enable new insights into disease pathology and inform rigorous and reproducible preclinical and clinical testing. For example, through NIA’s Model Organism Development & Evaluation for Late-Onset Alzheimer’s Disease (MODEL-AD) consortium, researchers develop, validate, and make broadly available the next generation of animal models for the study of late-onset Alzheimer’s disease. Although animal models will continue to play a critical role in research, new cell-based tools offer the promise of increased predictive power in a more cost-effective package. One exciting new set of research tools are microphysiological systems. As described above, these systems mimic key features of the human body and disease in a microenvironment and include such platforms as miniaturized organs called organoids, organs-on-chips, and stem cells derived from ordinary cells that have been “reprogrammed.” NIH-funded dementia researchers are already creating standardized stem cell resources and “disease-in-a-dish” models that more closely mimic aspects of Alzheimer’s disease. MPS may represent key research tools holding promise to support precision therapeutic development for Alzheimer’s and related dementias.

NIH also supports infrastructure and related policies to facilitate data and sample sharing arising from a variety of initiatives, including the NIA Genetics of Alzheimer’s Disease Data Storage Site (NIAGADS), which collects and curates genetic data produced from domestic and international research studies, and Biospecimen Exchange for Neurological Disorders (BioSEND), which banks human tissue and blood samples for research across several neurological disorders, including frontotemporal dementias and Lewy body dementias. Other efforts to compile and harmonize data on cognitive aging — such as the HCAP (featured above), part of the long-running HRS — have empowered collaboration and discovery by enabling data sharing across the globe. The Artificial Intelligence and Technology Collaboratories for Aging Research (AITC) program has brought us into the next generation of science for improving care and health outcomes for individuals living with dementia, as well as their care partners, by serving as a national resource to promote development and implementation of AI approaches and technology through partnerships with industry, healthcare systems, and various other stakeholders. Additionally, on the NIH campus in Bethesda, Maryland, collaboration is flourishing at the new Roy Blunt Center for Alzheimer’s Disease and Related Dementias Research, where NIA and NINDS intramural scientists are working alongside a cadre of visiting researchers to accelerate translational dementia research. These research resources are enabling key advances in the field, and additional infrastructure will accelerate discovery and bring us closer to finding an effective treatment or prevention for these complex diseases.

While animal models will continue to play a critical role in research, new cell-based tools offer the promise of increased predictive power in a more cost-effective package. One exciting new set of research tools are microphysiological systems.

Researchers view engineered 3-D vascularized neural tissues from a brain tissue chip. (Credit: Andy Manis, Morgridge Institute for ResearchInspired Engineering, Harvard University)
Future Directions

With additional investment, NIH plans to expand and enhance existing infrastructure to continue to meet research challenges. NIH will establish interdisciplinary centers focused on the development, characterization, and validation of new translational research tools, including MPS models of dementia. These multicomponent centers will also be responsible for rapidly disseminating MPS data and tools to the research community for use in preclinical testing. NIH will continue to strengthen data sharing efforts, with the aim of building a comprehensive and publicly accessible inventory of longitudinal epidemiology studies with harmonized data relevant for Alzheimer’s and related dementias research. Finally, with proposed funds, NIH will build a new centralized online hub to help investigators connect to all available NIH-funded resources, including protocols, samples, and data. This “one-stop shop” will accelerate research and invigorate collaboration across the dementia research field by removing barriers to access and facilitating sharing of key resources.

By developing and sharing powerful, cutting-edge resources with the broader research community, NIH will ensure investigators have the tools to address scientific challenges and pursue promising opportunities to treat and prevent these diseases.

NIH will ensure investigators have the tools to address scientific challenges and pursue promising opportunities to treat and prevent Alzheimer’s and related dementias.
Cross-Cutting Area: Health Equity & Inclusion Science

Though a great deal of scientific progress has been made in understanding Alzheimer’s and related dementias, we must ensure that these advancements are beneficial to all individuals affected by these diseases. Because pivotal scientific achievements occur when diverse minds collaborate, NIH is committed to diversifying the scientific workforce and ensuring that all supported research activities are designed and conducted in a manner and environment that promotes diversity, equity, inclusion, and accessibility. As acknowledged throughout this proposal, continued scientific progress requires an intentional integration of health equity and inclusion across all components of the research enterprise.

To move the needle, NIH is already engaging with communities, listening to and understanding needs, and taking actionable steps toward changing culture and addressing inequities. Much of this work is being conducted through NIH’s UNITE initiative, established in 2021 as an agency-wide effort to identify and address structural racism both within NIH-supported research and in the broader scientific community, as well as complementary internal efforts at NIA related specifically to dementia. For example, NIA’s Alzheimer’s Disease Research Centers (ADRCs), which have been a powerful force in conducting cutting-edge research to detect, treat, and prevent dementias; improving care for people living with these diseases; and promoting awareness of Alzheimer’s and related dementias nationwide for decades, have taken steps to deepen relationships with communities through the establishment of new centers focused specifically on enhancing collaborations with diverse populations. In addition, NIH continues to engage with communities at a particularly high risk for developing dementia, including individuals with Down syndrome, to ensure research considers their unique needs and promotes appropriate and meaningful inclusion in clinical trials.

In the years to come, NIH will further expand efforts to understand the causes and consequences of health disparities, as well as the potential modifiable factors to reduce or mitigate these disparities, guided in part by the NIA Health Disparities Research Framework. For example, NIH will conduct research to identify and reduce gaps in the timely and accurate diagnosis of Alzheimer’s and related dementias in historically marginalized populations by improving the utility of existing assessment tools for use in diverse populations, as well as developing new approaches for...
harmonizing culturally tailored measures across large datasets. NIH is also committed to ensuring that researchers are building trust with communities as they recruit and enroll diverse participants in clinical studies. To truly shift the existing landscape, accountability is essential.

NIH has begun — and will continue — to closely track enrollment and retention in clinical studies in near real time to ensure investigators are meeting requirements and to ultimately enable a precision medicine approach to dementia treatment and prevention. For example, NIA has established a new Clinical Research Operations & Management System (CROMS) to allow for near real-time monitoring of trial enrollment. This system will enable NIH and other researchers to glean best practices for recruitment as well as to intervene when investigators are faced with enrollment or retention challenges. NIH has also embarked on a review of Alzheimer’s and related dementias clinical trial resources to identify existing gaps and opportunities in its infrastructure. With increased investment, NIH will address identified infrastructure challenges — such as enhancing community engagement efforts and recruitment and inclusion planning — and ensure that the agency is funding rigorous research that produces outcomes to inform the health and well-being of all individuals.

NIH is also committed to advancing the most innovative scientific ideas from investigators of all ethnic, racial, and cultural backgrounds. To ensure such a pipeline, NIA has released a series of funding opportunities geared toward diversifying the aging and dementia research workforce and an entrepreneurial challenge to build diversity and innovation. To encourage young scientists in the field, NIH has assembled a wealth of training opportunities, including grant awards, diversity supplements, and NIA’s Butler-Williams Scholars Program, a unique weeklong summer program offering an opportunity for emerging investigators to learn from diverse scientists and advance their knowledge of aging research.

New in 2022, through its CARD Intramural Research Program, NIH also established a two-year master’s-level fellowship program for early-career scientists to advance expertise in the data sciences. With increased investments, NIH will continue to support young and diverse scientists through existing programs as well as new fellowship and training programs. More specifically, increased investment provides NIH with the opportunity to establish new cross-disciplinary career development programs in dementia research for underrepresented early-stage scientists.

By threading equity and inclusion through all components of our research endeavors, NIH will advance our understanding of how the risk, prevalence, symptoms, and development of Alzheimer’s and related dementias differ across populations. NIH also works to further understand how the use and accuracy of biomarkers may vary across and within the broader population to enable a precision medicine approach to detecting and treating Alzheimer’s and related dementias for all people. Prioritizing equity and inclusion in research will ensure the identification of effective interventions for dementia that meet the needs of the diverse U.S. population.

PRIORITIZING EQUITY and inclusion in research will ensure the identification of effective interventions for dementia that meet the needs of the diverse U.S. population.
Conclusion

In the 10 years since the launch of the National Plan to Address Alzheimer’s Disease, NIH has made tremendous progress in Alzheimer’s and related dementias research, fueled by many years of generous investments by Congress. As described in this professional judgement budget, NIH will build on this momentum by using new investments to capitalize on novel and emerging opportunities to advance the field of dementia research.

Thanks to robust investments over the past several years, the landscape of Alzheimer’s and related dementias research looks very different now than it did 10 or 20 years ago. In the early 2000s, researchers could confirm an Alzheimer’s disease diagnosis only via autopsy. Thanks to publicly funded research supported by NIH, clinicians today can access and use new technologies that measure the brain changes that occur in the Alzheimer’s disease process and aid in making a definitive diagnosis in living people.
We are committed to advancing research in bold new ways that deepen our understanding of dementia, accelerate the development of novel therapeutics, and deliver innovative approaches to support people living with dementia.

These advances in imaging technology have revolutionized the diagnosis of Alzheimer’s disease and enabled researchers in academia and the private sector to recruit participants, including those at risk of dementia who do not yet have symptoms, for clinical trials of potential therapeutics. NIH investments are poised to revolutionize the field yet again by enabling the development of next-generation biomarkers that enable earlier, more accurate diagnoses and significantly reduce barriers to clinical trial recruitment and enrollment.

In addition, NIH funding has fueled the basic science investigations behind the discovery of immunotherapies such as monoclonal antibodies. These discoveries enabled the private sector to advance development of novel drug candidates meant to address the underlying causes of Alzheimer’s and related dementias. Pivotal clinical trials testing the first wave of potentially disease-modifying immunotherapies, built on NIH-supported discoveries, will be wrapping up in the very near future. Just as there are several options for treating the many types of cancer, different types of dementia will require different kinds of treatments. These immunotherapies are likely to be just a few of multiple clinical strategies that will be needed to treat these diseases across the population.

As we take stock of these remarkable years of discovery, we are inspired by the scientists, clinical trial participants, caregivers, and many other stakeholders whose hard work and dedication are helping to tackle these devastating diseases. That is why we are committed to advancing research in bold new ways that deepen our understanding of dementia, accelerate the development of novel therapeutics, and deliver innovative approaches to support people living with dementia and their care partners. With sustained funding, we will continue to create and take advantage of new opportunities to propel research forward and bring us closer to the NAPA goal of preventing and effectively treating Alzheimer’s and related dementias.