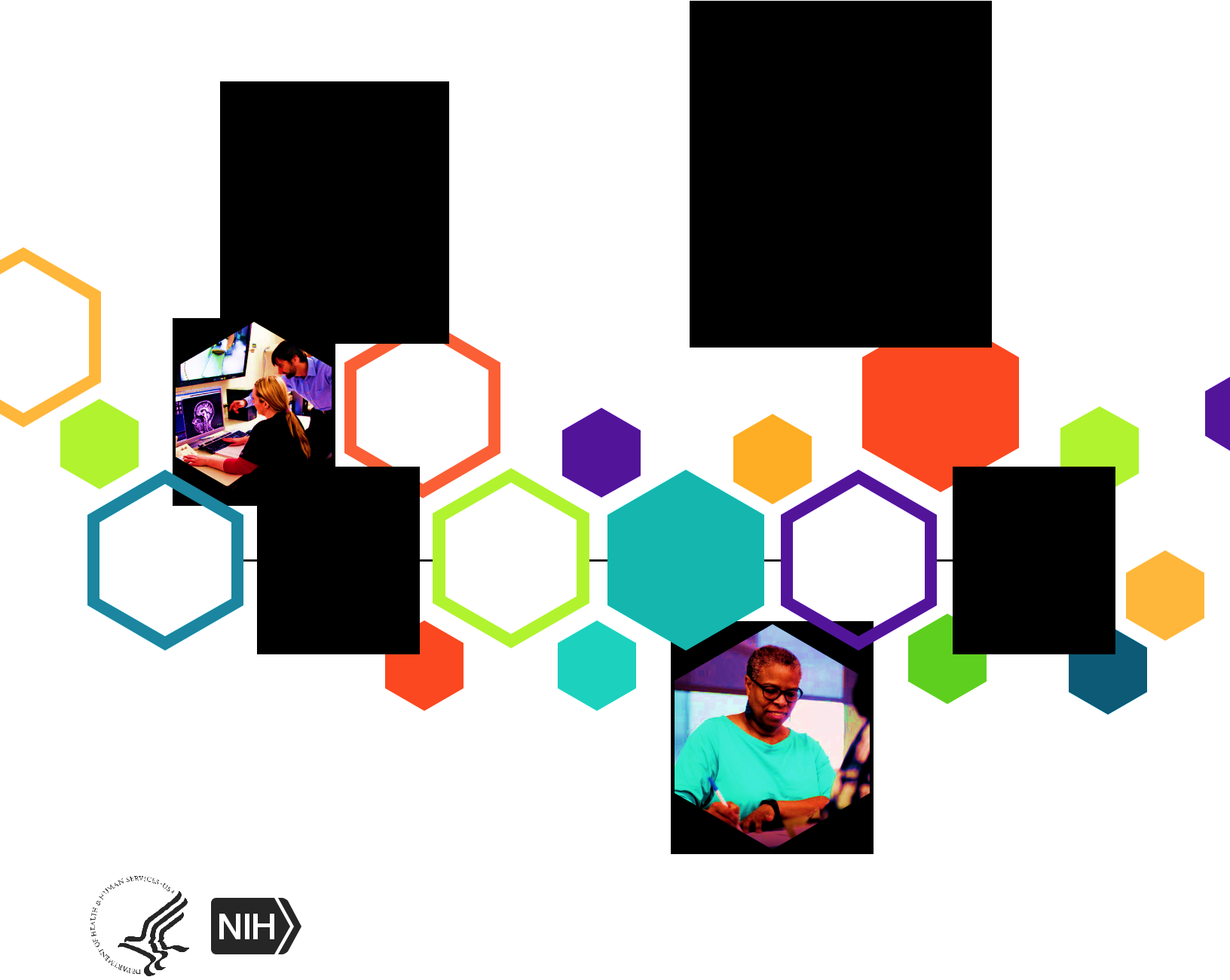
NIH BYPASS BUDGET PROPOSAL FOR FISCAL YEAR 20XX

Together We Succeed

**Accelerating Research on Alzheimer’s Disease & Related Dementias**

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National Institutes of Health

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**TOGETHER WE SUCCEED: ACCELERATING RESEARCH ON ALZHEIMER’S DISEASE AND RELATED DEMENTIAS**

July 29, 2019

On behalf of the National Institutes of Health (NIH), I am pleased to present our Fiscal Year (FY) 2021 Professional Judgment Budget, commonly referred to as a Bypass Budget, for Alzheimer’s disease and related dementias. In addition to the NIH funding proposal, this document provides an extensive array of current and cutting-edge research accomplishments and an outline of efforts to capitalize on the investments made in the Alzheimer’s disease and related dementias research enterprise. You will also learn about the ongoing involvement needed by everyone— people living with these devastating diseases, caregivers, researchers, clinicians, government, academia, industry, and not-for-profit organizations—to achieve the national goal of effectively treating or preventing Alzheimer’s disease and related dementias by 2025.

Due to recent advances as well as lessons learned from recent clinical trial failures, we are indeed gaining traction toward addressing this public health crisis, one that has profoundly affected our Nation as well as the global community. With expanded FY 2021 funding, NIH will build on the current momentum by continuing to support a broad range of treatment targets. These include, but importantly are not limited to, amyloid and tau and reflect the accelerating pace of discovery that has identified new and diverse targets for translation into therapeutic strategies. The unprecedented excitement of discovery continues to inspire many of the sharpest and most creative scientific minds in the field. These innovators are working tirelessly on ways to rethink and reconstruct the research enterprise into one that enables the discovery and dissemination of desperately needed interventions for people at all stages of disease.

NIH’s diverse and comprehensive efforts are spearheading progress on a number of fronts:

* Deepened understanding of genetic risk factors for Alzheimer’s disease and related dementias, with more genes linked to disease risk in 2018 than in all previous years combined
* Expanded population and epidemiological research to better understand disease risk and protective factors
* Insight into new disease mechanisms in less understood areas, such as sleep and the microbiome
* Improved biological and behavioral markers to detect and diagnose Alzheimer’s disease and related dementias more efficiently and effectively
* Investment in target validation and drug design to accelerate the time to human testing
* Expanded translational infrastructure programs that facilitate rapid sharing of data and research models to enhance collaboration as well as rigor and reproducibility

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* Intensified and expanded research on care and services, fueled by the infusion of new funding as well as the first National Research Summit on Dementia Care

In the 4 years since our first Alzheimer’s disease and related dementias Bypass Budget and the 7 years since our first NIH Alzheimer’s Disease Research Summit and initial National Plan to Address these diseases—and through a number of summits since that time—we have made unparalleled progress in understanding the science of Alzheimer’s disease and related dementias as well as dementia care and services. Our two most recent summits resulted in nearly 100 additional recommendations to chart our course forward. Setting sail for new horizons requires continued investment.

The FY 2021 Professional Judgment Alzheimer’s disease and related dementias budget estimate includes $354 million in additional resources for new research, with the overall resources needed totaling $2.822 billion. To build this budget, NIH took into account multiple factors. First, the FY 2020 estimate for Alzheimer’s disease and related dementias spending, based on the President’s budget, is $326 million below the FY 2019 estimated (enacted) funding level. The FY 2021 estimate includes funding to compensate for this reduction and adds the $354 million noted above in additional resources needed for new research. As a result, the total FY 2021 Professional Judgment Budget is $680 million above the FY 2020 President’s budget. NIH also considered funding that is projected to become available after completion of previously funded research initiatives, and that is reflected in the $354 million estimate.

It is a challenging but critical time in Alzheimer’s disease and related dementias research. We must continue to expand upon intense efforts that are helping to unlock the mysteries and mechanisms of these devastating diseases. While the path toward prevention and treatment continues to present complex challenges, we can now dare to think in terms of true precision medicine in the realm of Alzheimer’s disease and related dementias—the possibility of treating a specific person with the right intervention at the right time. With continued commitment and support, we have a realistic hope of realizing that vision.

Sincerely yours,



Francis S. Collins, MD, PhD

Director, National Institutes of Health

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**INTRODUCTION**

The Nation’s Alzheimer’s disease and related dementias research program has never been more robust—or more promising. Thanks to recent, critical increases in congressional appropriations, the National Institutes of Health (NIH) investment in research for treatment, prevention, and care will surpass an estimated $2 billion in Fiscal Year (FY) 2019. This unprecedented support has brought tangible progress, revealing more clearly the mechanisms and mysteries of dementia. It has enabled us to develop and test novel and potentially more effective therapies at the



earliest possible time, and greatly intensified the search for new and better ways to provide medical care and long-term support and services for people living with these devastating diseases, their families, and caregivers.

**What’s at Stake**

We are now able to undertake intensified, accelerated efforts to address the demographic and scientific challenges before us. As many as 5.6 million Americans age 65 and older are estimated to be living with Alzheimer’s disease, the most common form of dementia [(Hebert et](https://www.ncbi.nlm.nih.gov/pubmed/23390181) [al., 2013](https://www.ncbi.nlm.nih.gov/pubmed/23390181)). Many more under age 65 are affected by frontotemporal dementia or genetic forms of early- onset Alzheimer’s. Millions of people, some with and some without Alzheimer’s, are affected by vascular cognitive impairment/dementia, Lewy body dementia (LBD), or mixed forms of these diseases. This prevalence reflects an emerging consensus that mixed dementia is the rule rather than the exception. The Centers for Disease Control and Prevention ranks Alzheimer’s disease as the sixth leading cause of death among people age 65 and older and third for those age 85 and above [(Heron, 2018](https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_06.pdf)).

Several large population studies suggest that the percentage of older people with dementia, including Alzheimer’s disease, has been declining, possibly as a result of higher levels of educational attainment and better high blood pressure treatment, two risk factors for dementia. However, millions of Americans remain at risk. The absolute numbers of affected individuals will continue to rise in the coming decades ([Larson et al., 2013](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4130738/)) as the number of “oldest old”—people age 85 and older, who are at the highest risk of dementia—continues to climb. The growth of this age group is expected to accelerate with the continued aging of the population, increasing from approximately 5.8 million in 2010 to 19 million in 2050 [(Vincent and](https://www.census.gov/content/dam/Census/library/publications/2010/demo/p25-1138.pdf) [Velkoff, 2010](https://www.census.gov/content/dam/Census/library/publications/2010/demo/p25-1138.pdf)). At the same time, health conditions that often emerge at midlife and are known risk factors for later development of dementia, such as uncontrolled hypertension and diabetes, also remain common [(Barnes and Yaffe, 2011](https://www.ncbi.nlm.nih.gov/pubmed/21775213)).

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The impact on families and caregivers, who provide much of the care for people with dementia, is of utmost concern. While caregivers may find the experience to be deeply rewarding, they can also feel exhausted, overwhelmed, isolated, and/or distressed at the mental, emotional, physical, and behavioral aspects of providing care. NIH- supported investigators estimate that family caregivers spend an average of around 92 hours per month—the equivalent of more than 2 full work weeks—on in-home caregiving of adults ages 65 and older with dementia. For spouses, that figure rises to about 145 hours per month [(Kasper et al., 2015](https://www.ncbi.nlm.nih.gov/pubmed/26438739)).

The financial costs of dementia care are among the highest for any disease. In the last 5 years of life, total health care spending for people with dementia was 57 percent greater than the costs associated with other diseases, including cancer and heart disease. This analysis, by NIH-supported researchers, estimated total health care spending at $287,000 for those with probable dementia and $183,000 for those with other diseases, including heart disease and cancer [(Kelley et al., 2015](https://www.ncbi.nlm.nih.gov/pubmed/26502320)).

**Planning for Prevention, Treatment, and Care**

As more individuals, families, health care providers, and communities experienced the epidemic of Alzheimer’s and related dementias, the Nation took notice. In 2011, the [National Alzheimer’s](https://aspe.hhs.gov/national-alzheimers-project-act#NAPA) [Project Act](https://aspe.hhs.gov/national-alzheimers-project-act#NAPA) (NAPA) became law. It declared prevention, treatment, and care to be a priority for the United States and ordered creation of a [National Plan to Address Alzheimer’s Disease .](https://aspe.hhs.gov/national-plans-address-alzheimers-disease) Later, as part of the FY 2015 appropriations act, Congress further mandated that NIH prepare a Professional Judgment Budget for Alzheimer’s and related dementias for each fiscal year through 2025 to calculate the funding necessary to meet the research goals of the National Plan.

The first National Plan was released in 2012 by the Secretary of Health and Human Services, based on contributions by a range of public and private stakeholders. It articulated an accelerated and collaborative mission to find effective ways to treat or prevent dementia by 2025 and to improve clinical care and long-term care services and support. The National Plan is updated annually.

NIH played an essential role in the overall Plan’s development and now takes the lead in planning and implementing its research goals. To that end, NIH has put in place a formal and inclusive strategic planning process. This effort relies on formal and informal communications and conferences with the scientific, medical, and care communities, as well as with individuals living with dementia, formal and informal caregivers, health care providers, advocates, regulators, and others. Major international research summits hosted by NIH are a primary planning resource. They focus on 1) treatment and prevention of Alzheimer’s disease, 2) treatment and prevention of Alzheimer’s disease-related dementias (ADRD), including vascular cognitive impairment/dementia, LBD, and frontotemporal disorders, and 3) better approaches to care, services, and support. In a 3-year rotation by topic, the research summits are held annually. Participating experts provide recommendations, which reflect extensive summit-related discussion and input from a wide range of stakeholders, to guide future Alzheimer’s and related dementias research efforts.

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All of these activities, including the summit recommendations, inform research implementation milestones, which show in detail how NIH intends to meet the goals of the National Plan and what has been achieved so far. Planning and implementation are led by the [National Institute](https://www.nia.nih.gov/) [on Aging](https://www.nia.nih.gov/) (NIA), the primary NIH institute for the study of Alzheimer’s disease and age-related cognitive change, and the [National Institute of Neurological Disorders and Stroke,](https://www.ninds.nih.gov/) which focuses its dementia research on Alzheimer’s disease-related dementias. A broader trans-NIH group of institutes and centers collaborates to bring all potentially relevant NIH programs into the fight against Alzheimer’s and related dementias.

NIH also operates a database of research supported by public and private organizations worldwide. An important planning tool to catalogue the global research investment in Alzheimer’s disease research, the [International Alzheimer’s and Related Dementias Research](https://iadrp.nia.nih.gov/) [Portfolio](https://iadrp.nia.nih.gov/) (IADRP), is designed to foster collaboration and coordination, as well as to avoid duplication of effort in Alzheimer’s research.

**Alzheimer’s Disease-Related Dementias Summit**

NIH held its third [Alzheimer’s Disease-Related Dementias (ADRD) Summit](https://meetings.ninds.nih.gov/?ID=21149) March 14- 15, 2019. This summit, one of the three triennial dementia research planning efforts led by NIH, brought together dementia experts, individuals living with related dementias, caregivers, families, and advocacy groups to reprioritize, revise, and update the research recommendations developed at the 2016 summit. The 2019 ADRD Summit included sessions focusing on: FTD, LBD, vascular cognitive impairment/dementia, multiple etiology dementias, health disparities, nomenclature, and emerging topics such as dementia risk due to traumatic brain injuries and TDP-43 proteinopathy in AD/ADRD. Research recommendations from the ADRD Summit will be incorporated into the National Plan as research milestones early next year and will help inform future AD/ADRD research investments.

**Meeting the Scientific Challenge**

This year’s annual bypass budget proposal highlights the most recent scientific progress in NIH’s quest for effective ways to prevent and treat Alzheimer’s disease and related dementias. To build on that progress, we offer this Professional Judgment Budget for additional NIH funding in FY 2021 to address the most pressing research needs and scientific opportunities. While the funding increases of the last 5 years have done much to advance AD/ADRD research, there is much more to be done.

The substantial increases in funding for Alzheimer’s disease and related dementias research over the last several years have enabled us to expand and upgrade every aspect of our comprehensive research program, including:

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* Population and epidemiological research to better understand disease risk and protective factors
* Basic science studies in genetics and biological mechanisms of disease
* Development, testing, and validation of biomarkers, including imaging and fluid-based, to detect and diagnose disease, follow progression, and measure the effectiveness of treatments
* Translational drug discovery, development, testing, and clinical trials of promising therapies as early as possible in the disease process
* Assessment of care needs and investigation of better approaches for individuals living with dementia, caregivers, and health care providers

This all-encompassing program relies on a sophisticated, high-tech infrastructure built by NIH to support data collection and “big data” analysis; develop cellular and, when necessary, animal models for testing; and facilitate discovery and evaluation of new interventions. Described more thoroughly throughout this report, this infrastructure and some individual research projects feature creative partnerships among NIH and other federal agencies, foundations, other nongovernmental organizations, and pharmaceutical and biotech companies. Such collaborations leverage related efforts and promote the organizations’ shared missions to provide relief as soon as possible for people with dementia and their families.

**Recent Advances, New Initiatives**

The complexity of Alzheimer’s disease and related dementias remains daunting. We now know there are multiple influences on these diseases, which, while broadly common, are unique to a given individual. Ultimately, we want to devise a precision medicine approach to treatment and care, which will enable us to determine a person’s risk and tailor a mix of interventions most effective for that person.

This remarkable period of scientific growth and discovery—and a continued high level of effort—will help us reach this goal. This report presents a small fraction of the latest findings by scientists nationwide who are engaged in the fight against Alzheimer’s disease and related dementias. It also describes select programs and new initiatives to move promising discoveries to the next level. There is significant progress on several fronts:

* **Deeper understanding of genetic risk factors for Alzheimer’s, dementia with Lewy bodies.** In 2018 alone, the number of genetic risk factors found to be implicated inAlzheimer’s disease was larger than what had been identified in all previous years combined. This amazing pace of discovery is evidenced by new research that revealed an additional five new risk genes and confirmed 20 known others. And, for the first time, researchers have been able to report findings from a large-scale genome-wide association study of dementia with Lewy bodies, which found associations with genes common to multiple neurodegenerative diseases and others involving pathways that may be unique to this condition. A collaborative, international infrastructure of large databases from dozens of population and genetics studies is the basis for accelerated progress in genetics.

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These types of discoveries have led to the evolving concept of “genetic hubs” for dementia, in which clusters of genes in common pathways with similar function contribute to disease risk. Emerging hubs include pathways involved in cholesterol metabolism, neuroinflammation, cellular immunity, and endocytosis. Technological advances now allow for pathway analyses to focus on optimal targets for the design of new drugs.

* **Revealing disease mechanisms.** New studies point more specifically than ever before tohow brain function may be compromised in dementia. Scientists examining the microbiome, which is of interest in relation to various diseases, describe how disruptions in the “gut-brain axis” might contribute to cognitive impairment by altering levels of serum bile acids. Other investigators tracked how sleep deprivation contributes to the release, accumulation, and spread of tau into tangles in brain areas important for memory. Researchers also reported on the misfolding of a protein called TDP-43 as a broad influence on neurodegenerative disease, suggesting that its impact should be assessed in the future across studies in dementia. Insights such as these are vital to understanding specific mechanisms that cause Alzheimer’s and related dementias and, together with genetics discoveries, are an important step in the development of effective drug and other treatments.
* **Better biological, behavioral markers to detect and diagnose disease.** The identificationand use of clinical, imaging, genetic, and biochemical biomarkers is literally redefining Alzheimer’s disease. It is now possible, in a research setting, to use brain imaging and measures of tau and amyloid in cerebrospinal fluid to diagnose Alzheimer’s and to use these markers to gauge the biological effects of interventions being tested in clinical trials. As these approaches continue to be refined and validated, new studies are looking at easier and less expensive approaches to biomarker detection, including brain and blood metabolites associated with disease pathology and progression. These types of studies could lead the way to easier biomarker measures for study participants and researchers as they aim to greatly speed tracking in clinical trials. Eventually, biomarker approaches could make their way into everyday clinical practice for the earliest detection of disease, before the symptoms of dementia become evident.
* **Accelerating drug design to human testing.** The path from target and biomarkeridentification to the development and testing of a drug that can be evaluated in humans is often referred to as the “Valley of Death.” Extensive NIH efforts to avoid this chasm are starting to pay off, in part by working to more precisely align drug development directly with disease mechanisms. A new effort to make animal models more predictive in initial phases of testing has generated eight new mouse models of late-onset Alzheimer’s disease, and human adult stem cells are helping to generate tissue models of brain cell interactions. A vibrant drug discovery and development enterprise features more than 30 novel drugs for Alzheimer’s and related dementias in different stages of development for more than 12 different targets. Furthermore, the signature Accelerating Medicines Partnership–Alzheimer’s Disease program this past year identified 100 novel candidate targets, sharing data widely so that the scientific community can begin target validation and preclinical testing of promising approaches.

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As of spring 2019, NIH supported approximately 200 clinical trials on a wide range of interventions aimed at Alzheimer’s and cognitive decline. Targets for drug trials are moving into a next generation. While amyloid continues to be a target of clinical investigation, of the 41 pharmacological trials supported by NIA, 26 are looking at other targets. More than 80 current trials test nonpharmacological interventions, while an additional 60 are aimed at care and caregiving for people with dementia.

* **Intensifying research on care, services.** Fueled by the infusion of new funding, as well asthe first National Research Summit on Dementia Care, Services, and Supports for Persons with Dementia and Their Caregivers in 2017, NIH is expanding and upgrading its crucial research program on care and services. The summit process resulted in 58 recommendations, and NIH in response quickly took steps to solicit related applications. New initiatives include expansion of NIA’s Edward R. Roybal Centers for Translational Research in the Behavioral and Social Sciences of Aging to focus on interventions for dementia care and support, establishment of a new Alzheimer’s Disease and Alzheimer’s Disease-Related Dementias Health Care Systems Research Collaboratory to organize studies within and among health care systems, and an opportunity to examine how community-based services can be used more effectively by people with dementia and caregivers who have not been able to take advantage of such services.

**Expanding a Multidisciplinary Army of Investigators**

The explosion in scientific opportunity has required NIH to engage more scientific minds in the Alzheimer’s and related dementias research mission. The expert cadre of scientists who have for many years dedicated their careers to dementia, aging, and brain research have been able to do more with the support provided. Still, given the challenges, we need to expand their ranks and so have reached out to and engaged talented scientists not previously involved in Alzheimer’s and related dementias research. Efforts included 1) inviting researchers with non-AD/ADRD grants to apply for supplemental funding if their ongoing work could effectively contribute to AD/ADRD research and 2) encouraging both early- stage and established investigators who are new to the field to engage with AD/ADRD research.

Working with colleagues across NIH, NIA issued a notice for researchers holding grants from other NIH components to apply for supplemental funding for research relevant both to Alzheimer’s and related dementias and to the topic of their existing grants. The result: In FY 2018, approximately 300 supplements totaling more than $132 million were awarded to investigators representing 25 NIH institutes, centers, and offices. Examples included:

* A gene-environment study of the association between early-life exposure to air pollutants and later-life development of Alzheimer’s-related pathology (National Institute of Environmental Health Sciences)
* A study examining the relationships among psychosocial stress due to discrimination, markers of vascular risk, and cognitive function in early middle-aged, African-American women (National Heart, Lung, and Blood Institute)
* A study to identify trends in infection management and palliative care in facility-bound AD/ADRD patients at the end of life (National Institute of Nursing Research)

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* A study to develop and test a new imaging technique that maps oxygen metabolism in the brain, with a goal of improving our understanding of how oxygen is delivered and consumed in healthy and diseased brains, such as those with AD/ADRD pathology (National Institute of Neurological Disorders and Stroke)
* A study adapting neurotransmitter sensors to detect AD/ADRD target proteins (National Eye Institute)
* A study of a possible molecular basis for the clinical associations among obesity, diabetes, and Alzheimer’s disease (National Institute of Diabetes and Digestive and Kidney Diseases)

An internal NIA analysis found that between 2015 and 2018, approximately one-quarter of its Research Project Grant (R01) equivalent awardees in AD/ADRD were either NIH-designated New Investigators (this was their first competitive NIH grant) or Early-Stage Investigators (this was their first competitive NIH grant, and they were within 10 years of their terminal degree). In addition, approximately one-third of the R01 Alzheimer’s awardees had not previously applied for such funding from NIH, as almost half of them were established investigators previously pursuing other lines of study. NIH anticipates that these investigators’ success in securing funding will help ensure an active pipeline of energetic researchers looking at AD/ADRD from new perspectives for years to come.

**Budgeting in FY 2021 to Fight Dementia**

In summer 2015, NIH prepared its first-ever Professional Judgment Budget for Alzheimer’s and related dementias, as required in Public Law No. 113-235, the Consolidated and Further Appropriations Act, 2015, SEC. 230, which states:

Hereafter, for each fiscal year through fiscal year 2025, the Director of the National Institutes of Health shall prepare and submit directly to the President for review and transmittal to Congress, after reasonable opportunity for comment, but without change, by the Secretary of Health and Human Services and the Advisory Council on Alzheimer’s Research, Care, and Services, an annual budget estimate (including an estimate of the number and type of personnel needs for the Institutes) for the initiatives of the National Institutes of Health pursuant to the National Alzheimer’s Plan, as required under section 2(d)(2) of Public Law 111–375.

Only two other areas of biomedical research—cancer and HIV/AIDS—have been the subject of such special NIH budget development aimed at speeding discovery. This approach is often referred to as a “bypass budget” because of its direct transmission to the President and to Congress without modification through the traditional Federal budget process.

The FY 2021 Professional Judgment AD/ADRD budget estimate shows $354 million in additional resources needed for new research, with the total resources needed for AD/ADRD research totaling $2.822 billion. In FY 2021, the projected costs of resources needed for new research to enhance investigator-initiated research grants and initiatives to meet the 2025 treatment and prevention goal is $438 million. This estimate will be reduced by $84 million in funding that is

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projected to become available after completion of previously funded AD/ADRD research initiatives. As a result, the additional resources needed for new research in the FY 2021 budget is $354 million.

In FY 2021, the total resources needed for AD/ADRD research is $2.822 billion. The total budget takes the FY 2020 President’s budget funding level of $2.142 billion for Alzheimer’s disease and related dementias research as the baseline estimate, restores $326 million to account for the difference between the FY 2020 President’s budget funding level and the FY 2019 estimated (enacted) funding level for Alzheimer’s disease and related dementias research of $2.468 billion (Consolidated Appropriations Act, 2019, P.L.116 -6), and adds the $354 million in additional resources needed for new research. As a result, the total FY 2021 Professional Judgment Budget is $680 million above the FY 2020 President’s budget.

Overall, the $2.822 billion Professional Judgment Budget is needed to sustain momentum in Alzheimer’s and related dementias research in FY 2021. This estimate continues to be substantial by virtue of the fact that these funds would enable NIH to focus intensively on better understanding the basic biology of underlying dementia; characterizing novel biomarkers and screening tools such as an amyloid blood test; identifying and testing innovative drug targets; supporting clinical trials and infrastructure like the Alzheimer’s Clinical Trials Consortium; and improving the diagnosis, care, and support of those living with dementia.

**How to Navigate This Bypass Budget**

This bypass budget proposal outlines the additional FY 2021 funding needed to advance NIH-supported research on Alzheimer’s disease and related dementias aimed at the goal of the National Plan: to prevent and effectively treat these disorders by 2025. In addition to the dollar estimate, we provide a narrative to highlight several key areas of recent progress on which NIH would build with increased funding. The document also reflects a subset of Alzheimer’s disease and related dementias research milestones that could begin or be accelerated in FY 2020, on which the current bypass budget estimates are based.

Learn more about plans and progress toward the 2025 goal at the [AD+ADRD Research](https://www.nia.nih.gov/research/milestones) [Implementation Milestones](https://www.nia.nih.gov/research/milestones) database.

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**FISCAL YEAR 2021 PROFESSIONAL JUDGMENT BUDGET: ALZHEIMER’S DISEASE AND RELATED DEMENTIAS**

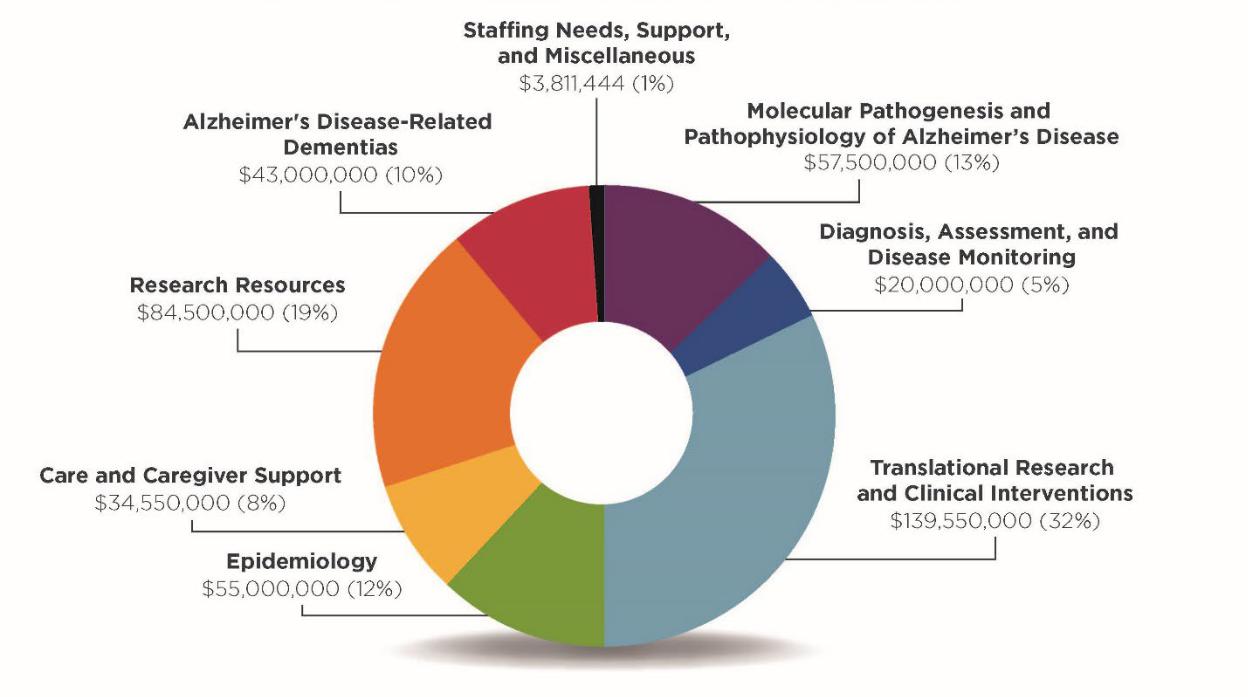
**Baseline Estimate, President’s Budget, Fiscal Year 2020 Alzheimer’s Disease, Including Alzheimer’s Disease-Related**

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| **Dementias (AD/ADRD)1** | | | **$2,142,000,000** | |  |
| **Professional Judgment Budget FY 2021, Projected Costs, and Additional Resources Needed** | | | | | |
|  |  |  |  |  |  |
| **Area of Research** | | |  | **Amount** | |
| Molecular Pathogenesis and Pathophysiology of Alzheimer’s Disease | | |  | $57,500,000 |  |
|  |  |  |  |  |  |
| Diagnosis, Assessment, and Disease Monitoring | | |  | $20,000,000 |  |
| Translational Research and Clinical Interventions | | |  | $139,550,000 |  |
| Epidemiology | | |  | $55,000,000 |  |
| Care and Caregiver Support | | |  | $34,550,000 |  |
| Research Resources | | |  | $84,500,000 |  |
|  |  |  |  |  |  |
| Alzheimer’s Disease-Related Dementias | | |  | $43,000,000 |  |
| Staffing Needs, Support, and Miscellaneous | | |  | $3,811,444 |  |
| **Projected Costs for New AD/ADRD Research** | | |  | **$437,911,444** | |
| Less Funding from Prior Appropriations that is Available for | | |  | ($84,000,000) | |
| New AD/ADRD Research | | |  |
|  |  |  |
|  |  |  |  |  |  |
|  | **Additional FY 2021 Resources Needed for New AD/ADRD Research2** | **$353,911,444** |
|  | | |  |  |  |
| **Professional Judgment Budget FY 2021 Total Resources Needed** | | |  |  |  |
|  |  | |  |  | |
|  | **Factor** | |  | **Amount** | |
|  | FY 2020 President’s Budget Request for AD/ADRD Research (baseline | |  | $2,142,000,000 | |
|  | estimate) | |  |
|  |  |  |  |
|  |  | |  |  |  |
|  | Difference Between FY 2020 President’s Budget Request and FY 2019 | |  | $326,000,000 | |
|  | Appropriation for AD/ADRD Research3 | |  |
|  |  |  |  |
|  | Additional FY 2021 Resources Needed for New AD/ADRD Research | |  | $353,911,444 | |
|  |  | |  |  | |
|  | **TOTAL FY 2021 Resources Needed for AD/ADRD Research** | |  | **$2,821,911,444** | |
|  |  |  |  |  |  |

1. Baseline estimate includes Alzheimer’s disease, frontotemporal dementia, Lewy body dementia, and vascular cognitive impairment/dementia. Individual disease baseline estimates are available on the NIH Categorical Spending website at [https://report.nih.gov/categorical\_spending.aspx.](https://report.nih.gov/categorical_spending.aspx)
2. In FY 2021, the projected costs of resources needed for new research to enhance investigator-initiated research grants and initiatives to meet the 2025 treatment/prevention goal is $438 million. This estimate will be reduced by $84 million in funding that is projected to become available after completion of previously funded AD/ADRD research initiatives. As a result, the additional resources needed for new research in the FY 2021 budget is $354 million.
3. Estimated (enacted) $2.468 billion (AD/ADRD research funding from the Consolidated Appropriations Act, 2019) – estimated $2.142 billion (AD/ADRD research funding from the FY 2020 President’s budget) = $326 million.

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**Distribution of FY 2021 Projected Costs Across Research Areas Total Projected Costs: $437,911,444\* Additional Resources Needed for New Research: $353,911,444**

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\*In FY 2021, the projected costs of resources needed for new research to enhance investigator-initiated research grants and initiatives to meet the 2025 treatment/prevention goal is $438 million. This estimate will be reduced by $84 million in funding that is projected to become available after completion of previously funded AD/ADRD research initiatives. As a result, the additional resources needed for new research in the FY 2021 budget is $354 million.

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**STUDYING POPULATIONS TO IDENTIFY POTENTIAL RISK**

Like many conditions, Alzheimer’s disease and related dementias are believed to be products of our genes and our environment. These influences, to varying degrees, may confer greater risk for disease or offer protection against it. Population and epidemiological studies have pointed to trends in age, lifestyle, and socioeconomic status, for example, that are associated with the chance of developing dementia. Early genetics studies identified a small number of



causal and risk-factor genes involved in these disorders.

Today, the pace of research has markedly accelerated, and there is an explosion of activity to build on what we have already learned. With increased funding, the National Institutes of Health (NIH) has been able to seize on important scientific opportunities, applying technological advances in the study of genetics and expanding the breadth and depth of population and epidemiological research in the search for genetic and nongenetic contributions to disease. Furthermore, biological studies are revealing how these influences manifest themselves at the molecular and cellular level. Across the research spectrum, we are focused on gaining a deeper understanding of increased rates of disease by race, ethnicity, sex, and socioeconomic status, so that disparities can be meaningfully assessed and addressed.

Nowhere is this revolution in research more evident than in the collection, distribution, and rapid analyses of genetic samples and other data from study participants worldwide. Early on, the National Institute on Aging’s (NIA’s) [Alzheimer’s Disease Research Centers,](http://www.nia.nih.gov/research/adc) through the [National Centralized Repository for Alzheimer’s Disease and Related Dementias](http://www.nia.nih.gov/research/resource/national-centralized-repository-alzheimers-disease-and-related-dementias-ncrad) and [National](http://www.nia.nih.gov/research/dn/national-alzheimers-coordinating-center-nacc) [Alzheimer’s Coordinating Center,](http://www.nia.nih.gov/research/dn/national-alzheimers-coordinating-center-nacc) were among the first resources for genetic discoveries. At these Centers, blood and tissue samples from people with Alzheimer’s disease, related dementias, or cognitive impairment could be shared and analyzed, accompanied by well-characterized information on other aspects of study participants’ health and lives. The Centers and early data resources have been expanded as support for Alzheimer’s and related dementias research has increased.

Most recently, scientists have been able to tap into genetic and phenotypic data from studies not primarily focused on Alzheimer’s disease and Alzheimer’s-related dementias (AD/ADRD). Several of these projects include heightened collaboration among NIH institutes. In 2012, for example, NIA and the National Human Genome Research Institute joined to support a next-generation [Alzheimer’s Disease Sequencing Project](http://www.niagads.org/adsp) to access multiethnic genomics data resources and to provide data for analyses. Major studies of disease, health, and aging have been part of the project. They include NIA’s [Health and Retirement Study](http://www.nia.nih.gov/research/resource/health-and-retirement-study-hrs) (HRS) of aging, which started in 1990 as a nationally representative survey of retirement in people 50 and older. Now, HRS investigators also collect DNA samples from a subset of participants, offering to the study

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of Alzheimer’s the ability to link genetics findings with the HRS’s nearly 3 decades of health and socioeconomic data. To address vascular contributions to cognitive impairment/dementia (VCID), institutes across NIH are leveraging more than 30 cohorts in long-term epidemiological studies and clinical trials to clarify risk and protective factors and to harmonize outcome measures. Among the studies supported for VCID data are the Framingham Heart Study, Cardiovascular Health Study, and the Hispanic Community Health Study/Study of Latinos.

In 2016, to organize and target analyses of such genetic and genomic data, NIA established the [Genome Center for Alzheimer’s Disease.](http://www.adgenomics.org/) Today, the Center is searching through data from 19 different Alzheimer’s disease projects to identify variants and underlying genes affected. The Center’s cutting-edge analyses will be provided via the [NIA Genetics of Alzheimer’s Disease](https://www.niagads.org/) [Data Storage Site](https://www.niagads.org/) data- sharing service to investigators who can look at the function of Alzheimer’s-associated genes to discover promising new therapeutic targets.

This massive infrastructure of population studies and consortia collecting and analyzing genetics and tissue data is at the heart of the quest to better identify the genetic and nongenetic underpinnings of dementia. By organizing and analyzing unprecedented volumes of “big data” and sharing that information as quickly and widely as possible, we hope to more clearly predict disease risks for groups and individuals and, for people at risk, to target successful interventions in a precision medicine approach to prevent or slow dementia.

**Identifying Psychosocial and Environmental Factors**

Studies on environmental and lifestyle factors associated with increasing or decreasing one’s risk of dementia continue to reveal social and behavioral influences on disease. Studies reported in 2018 and 2019 revealed the following insights:

**Neighborhoods, sleep quality may influence decline.** Using the 2006 -2008 waves of the HRS,researchers ([Hunter et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29396109)) examined the role of neighborhood socioeconomic status along with sleep quality (as measured by trouble falling asleep, staying asleep, waking too early, and feeling well rested on waking) on dementia risk. Accounting for genetic, demographic, and cardiovascular risk factors, the team found that individuals who lived in neighborhoods of poorer socioeconomic status—characterized by low levels of education, high unemployment, and use of public assistance—and had poor sleep quality experienced the greatest cognitive decline over time. In contrast, people living in high socioeconomic status neighborhoods had the highest cognitive function, regardless of reported sleep quality. While cognitive decline has in the past been linked separately to neighborhood characteristics and sleep quality, these findings are the first to show a combined relationship between the two. This study points to the important role that environment (in this case, neighborhood) may play in relation to other risk factors associated with cognitive decline.

**Evidence builds for the link between education and dementia.** While the number of peoplewith dementia has increased in recent years with the aging of the population, rates of disease appear to be declining in the United States and other developed countries. Two new findings from NIH-supported research bolster the case for recognizing higher levels of educational attainment as a major contributor to this trend:

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* **Longer life expectancy with healthy cognition, especially for people with more education.** This study offers the first estimates of educational differences in prevalence ofcognitive impairment and dementia by age and of changes over time in prevalence of dementia by education levels in the United States. Following a subset of people participating in the HRS from 2000 and 2010, researchers [(Crimmins et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29669097)) found that, in general, life expectancy at age 65 and 85 increased for both men and women in every education group over the decade. For example, women who had completed college and reached age 65 in 2000 could expect to live another 20.9 years, on average. By 2010, this had increased to 22.3 years. The number of years they could expect to live with dementia fell in the same years, from 1.87 to 1.57 years. Longer life has thus meant longer life in good cognitive health for those with more education. For women with less than a high-school education, by contrast, life expectancy at age 65 changed much less during the same decade, from 18.28 to 18.94 years, and for them the expected number of years living with dementia fell only slightly, from 4.16 to 4.12 years. Put another way, the differences in prevalence of dementia associated with different levels of educational attainment, already large in 2000, widened over the following decade.
* **Higher education of younger cohorts explains differences in cognitive impairment.** Analyzing data from the nationally representative Americans’ Changing Lives Study that followed individuals over 25 years, researchers supported by NIH (NIA and the National Institute on Mental Health) and the Department of Veterans Affairs [(Leggett et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/28329815)) offer evidence for the primary role that educational attainment plays in explaining age-group differences in cognitive impairment, above and beyond gender, race, cardiovascular diseases, and other chronic health conditions. The researchers first looked at if and where there were age-group differences in the level and rate of change in cognitive function over years of adulthood, and then examined the extent to which previously confirmed factors—including education, gender, race, and specific health conditions—may have accounted for differences. They found that younger cohorts—those born after 1932—had significantly less cognitive dysfunction over time compared to their pre-1932 counterparts. They then found that the rate of change was stable across the age groups, reflecting what the researchers called “preserved differentiation.” Modeling the effects of education, gender, race, and health conditions, they found that differences in educational attainment wholly explained cohort differences in cognitive dysfunction over time. These findings point to the potential for social and institutional efforts to encourage educational attainment, particularly college degrees, as one way to help reduce the future burden of cognitive impairment for older adults.

**New insights on exercise.** There is enormous interest in how lifestyle interventions, likeexercise and diet, might reduce or increase risk of Alzheimer’s and related dementias. The evidence base from both observational studies and clinical trials linking physical activity to cognitive outcomes is mixed, leading a 2017 [National Academies of Sciences, Engineering, and](https://www.nia.nih.gov/news/national-academies-committee-sees-promising-inconclusive-evidence-interventions-prevent) [Medicine report,](https://www.nia.nih.gov/news/national-academies-committee-sees-promising-inconclusive-evidence-interventions-prevent) sponsored by NIA, to note that interventions that aim to increase physical activity to prevent cognitive decline and dementia are supported by “encouraging although inconclusive evidence.” NIH is pressing to study the effects of lifestyle interventions on cognitive decline and dementia, as subsequent sections of this report describe. At the same time, we continue to strongly support the population and epidemiological studies that can

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examine these factors and help inform policymakers, clinicians, and individuals who are looking for ways now to possibly influence risk of cognitive decline. In 2019, it was reported:

* **Sedentary behavior linked to risk of dementia.** A new report [(Palta et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30321503)) of findings from participants in the Atherosclerosis Risk in Communities study expands the view that sedentary behaviors in middle age may increase risk of dementia in later life. Measuring midlife leisure-time physical activity and later-life cognitive decline and incident dementia among participants at specific points during the study’s median 17-year follow-up period, researchers found that groups with either mid or high levels of physical activity had significantly lower rates of incident dementia when compared with those reporting no physical activity in midlife. Moreover, those in the no-activity group had a more rapid rate of decline in general cognitive ability over 14 years compared with those reporting high levels of midlife physical activity. The strength of the relationship to cognitive decline increased when the analyses included sustained physical activity— meaning the participant reported the same level of physical activity during both the baseline and succeeding visits.

**What’s Behind Disparities in Rates of Dementia?**

A number of NIH-supported studies have explored differences in dementia risk and prevalence in African Americans and other racial groups. The results of these studies may lead to ways to reduce risk in populations in which Alzheimer’s has a disproportionate impact. Recent findings include:

**The role of early-life factors in dementia risk among African Americans.** An NIH-fundedresearch team ([Hendrie et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29669098)) found links between early-life factors and differences in the incidence of dementia in two cohorts of African Americans living in Indianapolis. The study participants, age 70 years and older, were dementia -free when they enrolled in the study in 1992 and 2001 and were followed for 8 or 17 years, respectively, with cognitive evaluations done every 2 to 3 years. Both groups included many people who had grown up in the rural South (primarily Kentucky and Tennessee) and then moved to Indianapolis later in life.

Compared to the 1992 cohort, the 2001 cohort had a highly reduced incidence of both dementia and Alzheimer’s disease. The decreased risk of dementia was associated with increased levels of education. However, the researchers found, there was a substantial interaction between education and childhood rural residence for risk of Alzheimer’s. Higher education level was significantly associated with reduced risk in participants with childhood rural residence, but there was no such link in those with an urban upbringing. These results underscore the importance of geographic variation in understanding dementia risk, in combination with other factors associated with geography, such as local economic conditions and resources. Furthermore, the research suggests, early-life context can affect later-life outcomes, even when individuals move elsewhere, highlighting the need for a life-course framework in studying contributions to dementia.

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**Urban, rural differences in dementia remain important.** NIA-supported researchers ([Weden et](https://www.ncbi.nlm.nih.gov/pubmed/29246677)[al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29246677)) used the HRS to look at not only trends in the prevalence of cognitive impairment in the United States, but also to more deeply assess disparities by geography, education, and race/ethnicity. Consistent with other recent studies, the researchers found that between 2000 and 2010, the rate of cognitive impairment in older adults declined. Additionally, the proportion of individuals with dementia and “cognitive impairment not dementia” was significantly higher in rural areas than urban areas in 2000, but not significantly higher in 2010. They attributed the improvements to higher educational attainment in rural areas over that decade.

Still, when the scientists took into account a range of sociodemographic characteristics and health conditions, they found that the relative risk of dementia was still higher in rural than urban areas by 60 percent in 2000 and 80 percent in 2010. For “cognitive impairment not dementia,” the relative risk was higher in rural than urban areas by 44 percent in 2000 and 40 percent in 2010. The persistent disadvantages for rural older adults were particularly disproportionate for minorities, highlighting the importance of public health planning with attention to cognition of rapidly aging rural communities.

**Complex picture of APOE genetics across Latino populations.** Latinos are the largest ethnic-racial minority in the United States, making up nearly 20 percent of the population. However, Latino genetic diversity has been understudied and consequently poorly understood, which has significant implications for understanding disease risk in nearly one-fifth of the U.S. population. Knowing the distribution of APOE genotypes, as well as other risk and protective variants, among this genetically heterogeneous group is important both for understanding the basic biology of Alzheimer’s disease and for public health planning.

An NIH-funded research team ([González et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/30546063)) analyzed APOE genotypes for 10,887 Latino adults of diverse and well-defined ancestral backgrounds, focusing on four major U.S. metropolitan areas: New York (the Bronx), Chicago, Miami, and San Diego. The APOE ε4 allele, a form of the APOE gene linked to increased risk of Alzheimer’s disease, was most frequent among people of Dominican descent (17.4 percent) and lowest among Latinos of Mainland descent (Central Americans, South Americans, and Mexicans; about 11 percent allele frequency). The APOE ε2 allele, which offers protection against Alzheimer’s disease, was least frequent among Mainland Latinos (2.9 to 3.9 percent) but twice as high among Latinos of Caribbean descent (Cubans and Dominicans, 6.5 to 8.6 percent). The distribution of APOE genotypes seen across these groups matched the groups’ known continental ancestry patterns. For example, people of Dominican background have more African ancestry and less Amerindian ancestry than those of Mainland Latino background. They also have higher APOE ε4 and APOE ε2 frequencies, consistent with the relative distributions of those alleles among their ancestral populations.

**Collecting, Storing, Distributing, and Analyzing Genetic Data**

Until 2009, only one genetic variant, APOE ɛ4, had been shown to increase the risk of late-onset Alzheimer’s, the most common form of the disease. However, with the advent of genome-wide association studies (GWAS) and other high-throughput technologies, the list of known genetic

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risk factors grew substantially over the next few years. By 2013, a large GWAS, conducted by the [International Genomics of Alzheimer’s Project,](http://web.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php) or IGAP, a collaborative, international study supported in part by NIH, had identified a total of 11 genetic variants that are associated with increased or decreased risk for late-onset Alzheimer’s disease. Today, there are more than 60 regions (loci) in the genome with variants that are associated with Alzheimer’s. This knowledge has strengthened evidence about the involvement of particular pathways in Alzheimer’s, such as inflammation, lipid metabolism, and amyloid deposition, and also points to entirely new molecular pathways for us to explore. Additional analyses are needed to better understand the exact location of the variant relevant to the gene of interest.

Through discovering these genes and other studies, we have learned that:

* Alzheimer’s is a highly heritable disease.
* Early and late-onset Alzheimer’s are not separate entities, but instead are on a disease continuum.
* Many rare variants contribute to the etiology of the disease.
* Protective variants have been identified in at least three genes to date.
* Advances in understanding genetic characteristics, when analyzed with clinical and pathological information, have shown that Alzheimer’s is not a single entity, but rather has several different complex components.
* Variants across an individual’s genome are being used to calculate a polygenic risk score or genetic risk score that might be used to assess the risk that someone will develop Alzheimer’s over time, which is important both for clinical trials and eventual preventive interventions.
* Clusters of genes in common pathways with similar function contribute to risk. Genetic “hubs” have emerged that point toward common functions that are perturbed in Alzheimer’s. These include the well-known amyloid precursor processing (APP) pathway and the less understood genetic and genomic events associated with cholesterol metabolism, neuroinflammation, cellular immunity, and endocytosis pathways.

Two new reports show how the new genetics databases can bring new insights:

**Analyses of largest sample reveal new risk genes.** A recent analysis of genetic data from morethan 94,000 individuals revealed five new risk-factor loci for Alzheimer’s disease and confirmed 20 known others. The international team of researchers from the IGAP group ([Kunkle et al.,](https://www.ncbi.nlm.nih.gov/pubmed/30820047) [2019](https://www.ncbi.nlm.nih.gov/pubmed/30820047)) also reported for the first time that mutations in genes specific to tau, a hallmark protein of Alzheimer’s disease, may play an earlier role in the development of the disease than originally thought. A genetic analysis to see which cellular pathways might be involved implicated the immune system, lipid metabolism, and APP metabolism. Mutations in the APP gene have been shown to be directly related to early-onset Alzheimer’s, and this study suggests that variants affecting APP and amyloid-beta protein processing may be associated with both autosomal dominant early-onset Alzheimer’s and with late-onset Alzheimer’s.

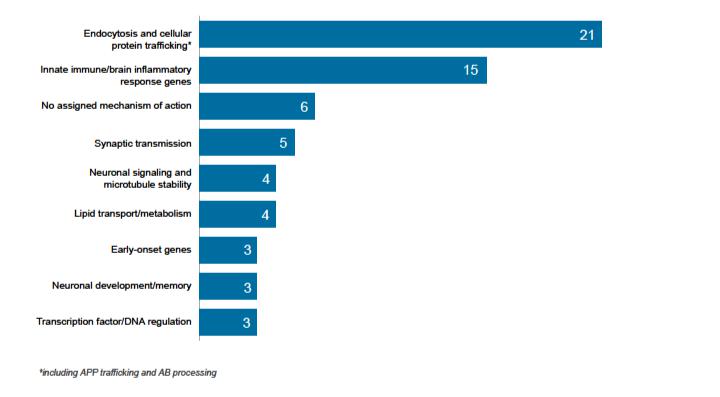
These new findings support developing evidence that groups of genes associated with specific biological processes, such as cell trafficking, lipid transport, inflammation, and the immune response, may be genetic hubs important to the disease process. Once the functions of the five

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loci newly associated with Alzheimer’s—IQCK, ACE, ADAM10, ADAMTS1, and WWOX—are understood and examined in conjunction with the functions of the more than 60 loci in the genome that have variants associated with the disease, researchers will be in a better position to identify where the genetic hubs of Alzheimer’s are clustering. Armed with these findings, they should be able to look more deeply into these genetic hubs to reveal disease mechanisms and potential drug targets. A key to these discoveries was the sample size, the largest to date for this kind of Alzheimer’s study. A large sample is especially important to find rare genes that might be involved with a disease.

**Genetic Regions of Interest in Alzheimer’s Disease**

**Mechanisms of Action**

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This chart shows genetic loci (regions of interest) for Alzheimer’s disease discovered through 2018. The numbers in the bars indicate the number of genetic regions of interest for specific mechanisms of action. There are 21 regions of interest for the mechanism of action called endocytosis and cellular protein trafficking, 15 regions of interest for the mechanism of action innate immune/brain inflammatory response genes, and so on. APP is amyloid precursor protein. Aβ is amyloid-beta.

**Genetic risk variants and amyloid brain changes at stages of disease.** A recent analysis

([Apostolova et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29340569)) examined associations between the top 20 Alzheimer’s genetic risk variants, as well as other variants previously associated with amyloid deposition, and amyloid levels measured by brain imaging. The study of 977 participants (average age, 74 years) from the NIA-supported [Alzheimer’s Disease Neuroimaging Initiative](https://www.nia.nih.gov/research/dn/alzheimers-disease-neuroimaging-initiative-adni) showed that after APOE4, the gene with the strongest association with amyloid deposits was ABCA7, especially in the asymptomatic and early symptomatic disease stages. Studies have previously connected ABCA7 with Alzheimer’s disease processes in the brain; these findings provide further evidence of its role. Research has also shown that African Americans are more likely than whites to have a variant of the ABCA7 gene, with almost double the risk of developing Alzheimer’s. Other

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Alzheimer’s disease risk genes found to be associated with amyloid buildup at different disease stages include FERMT2, which was most pronounced in people with mild cognitive impairment (MCI); SORL1 and EPHA1, which were associated with both the MCI and dementia stages; and CLU, DSG2, and ZCWPWI, which were linked to the dementia stage. Results suggest genetic variants might affect Alzheimer’s disease processes differently across disease stages.

Exploring specific genes, researchers recently reported:

**Genetic factors modify the impact of serum triglycerides on Alzheimer’s risk.** Someepidemiological studies have found links between high plasma lipid levels and greater risk of developing Alzheimer’s, but others have not. According to new findings from NIH-funded research, these inconsistencies might be explained by genetic differences across different study populations [(Peloso et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/30412497)). This latest study looked at the interaction between genetic risk factors and midlife plasma lipid levels (LDL-C, HDL-C, and triglycerides) on Alzheimer’s risk in 150 patients and 2,882 controls in the Framingham Heart study. They found a significant interaction between Genetic Risk Score, calculated based on 20 Alzheimer’s disease single nucleotide polymorphisms (SNPs) plus APOE ε4 genotype, and serum triglyceride levels on the risk of developing clinical Alzheimer’s. They saw no interaction between Genetic Risk Score and LDL-C or HDL-C levels. When the team analyzed individual SNPs, they identified two whose impact on Alzheimer’s risk was significantly modified by serum triglyceride levels: APOE4 and a SNP located near the gene for the sortilin-related receptor (SORL1), a neuronal apolipoprotein E receptor. If confirmed, this information could advance investigation of preventive strategies targeting serum triglyceride levels in individuals at higher genetic risk of developing Alzheimer’s.

**New gene associated with white matter damage/VCID.** White matter hyperintensities (WMH)are bright spots seen on brain magnetic resonance imaging scans that correspond to areas of tissue and cellular damage. WMHs are common among older people, in whom they are associated with cerebral small vessel disease and increased risk of stroke. Susceptibility to developing WMHs has a strong genetic component (55 to 80 percent), but the genes underlying this susceptibility remain largely unknown. To search for such genes, NIH-funded scientists [(Jian](https://www.ncbi.nlm.nih.gov/pubmed/30002152) [et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/30002152) ) analyzed the genotypes of a diverse group of over 20,000 stroke - and dementia - free adults from 13 population-based cohort studies. The scientists analyzed about 250,000 SNPs, most of them located in the protein-encoding regions of genes. The researchers found significant associations between WMH levels and two relatively rare variants of the gene MRPL38. The function of MRPL38 is unknown, but the protein is structurally similar to a family of proteins called PEBPs (phosphatidylethanolamine-binding proteins) that are known to play a role in neural development and that have been implicated in clinical Alzheimer’s disease and brain glial cancers. The scientists also confirmed associations of WMH with common variants in three other genes previously linked to WMH in this population via GWAS analyses: TRIM65, FBF1, and ACOX1. This study shows that both common and rare gene variants influence susceptibility to WMHs and demonstrates the utility of exome chip analysis for discovering rare disease variants.

**Epigenomics of cognitive function.** Environmental factors can influence cognitive function byinducing chemical changes in the genome, called epigenetic modifications or marks, that cause

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heritable alterations in the expression levels of specific genes. An important class of epigenetic marks is DNA methylation, the most common kind of genetic variation in humans. NIH-supported researchers ([Marioni et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29311653)) looked for DNA methylation marks in blood samples from 6,809 older adults who had been tested on seven different measures of cognitive function. The scientists identified two genetic loci whose methylation levels correlated significantly with cognitive measures: a locus on chromosome 12 associated with global cognitive function and one near the INPP5A gene on chromosome 10 associated with verbal fluency. INPP5A and other members of the INPP5 gene family have been linked to neuronal calcium mobilization and neurodegeneration. This study suggests that blood-based DNA methylation signatures can be used to probe the biological mechanisms via which the environment impacts the genome to modulate cognitive function in health and disease.

**First GWAS study of risk genes for dementia with Lewy bodies.** Dementia with Lewy bodies(DLB) is the second most common form of dementia after Alzheimer’s disease. People with DLB typically have both Alzheimer’s disease-like symptoms (dementia) and Parkinson’s disease- like symptoms (motor abnormalities, cognitive fluctuations, and visual hallucinations). Because DLB is relatively rare, its genetics have been difficult to untangle. NIH-funded researchers have now reported on the first large-scale GWAS of DLB [(Guerreiro et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29263008)). The study involved 1,743 people with DLB and 4,454 controls of European ancestry from 22 centers across 10 countries in Europe, North America, and Australia. Researchers analyzed over 8 million SNPs in two separate analyses.

The DNA sequence variants most strongly associated with DLB were in the genes for ApoE, alpha- synuclein (SNCA), and beta -glucocerebrosidase (GBA). ApoE is the strongest genetic risk factor for Alzheimer’s, and SNCA and GBA were previously identified as risk factors for Parkinson’s disease. The SNCA variants associated with DLB were different than those previously associated with Parkinson’s, consistent with the fact that alpha-synuclein pathology affects different brain regions in DLB than it does in Parkinson’s. Variants in a third gene, CNTN1, came close to statistical significance. CNTN1 is a neuronal cell membrane protein with important roles in neural and neuromuscular development and is mutated in a familial form of lethal congenital myopathy.

These results suggest that DLB shares certain biological pathways with Alzheimer’s and Parkinson’s diseases, but also involves unique pathways, additional components of which are likely to be revealed by future genetic studies. This study lays an important foundation for understanding the biological basis of DLB.

**Integrating Epidemiological and Biomarker Studies to Assess Risk, Prevalence**

NIH-funded scientists reported the first-ever estimates of lifetime and 10-year risks of developing Alzheimer’s dementia based on age, gender, and biomarker tests for preclinical disease [(Brookmeyer and Abdalla, 2018](https://www.ncbi.nlm.nih.gov/pubmed/29802030)). Lifetime risk is the probability that an individual will experience a particular clinical condition before death. The team did a mathematical analysis of several longitudinal epidemiological studies in the United States and Europe, which allowed them to model the Alzheimer’s disease process, showing lifetime risks at each age increase by disease state/marker: normal; neurodegeneration alone; amyloidosis (defined by brain amyloid

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identified by positron emission tomography) or amyloid-beta alone; amyloidosis and neurodegeneration; MCI with neurodegeneration; and MCI with amyloidosis and neurodegeneration.

The models showed that the preclinical period of Alzheimer’s disease is very long and variable, and lifetime risks of Alzheimer’s dementia differed considerably by age, gender, and the preclinical or clinical disease state of the individual. For example, the lifetime risks for a female with only amyloidosis were 8.4 percent for a 90-year old and 29.3 percent for a 65- year old. People younger than 85 years with MCI, amyloidosis, and neurodegeneration were shown to have lifetime risks greater than 50 percent.

Overall, the scientists found, most people showing preclinical signs of Alzheimer’s will not develop Alzheimer’s dementia in their lifetimes. The researchers noted that such lifetime risk calculations could be helpful in deciding if an Alzheimer’s biomarker screening would provide clinically useful information for a given patient.

**Looking Ahead: Strengthening the Population, Epidemiological Research of the Future**

Epidemiological research will continue to inform what we know about Alzheimer’s and related dementias on population and subpopulation levels. NIH has funded research programs in this area.

**Taking a U.S., global view to tracking dementia.** The Health and Retirement Study: HarmonizedCognitive Assessment Protocol (HCAP) initiative is an innovative approach to assessing trends in cognitive function and aging in the United States and worldwide. The primary aim of the HRS, funded by NIA and the Social Security Administration, is to collect and distribute multidisciplinary data for research on aging. To provide the research community with new and richer data to study the prevalence, predictors, and outcomes of cognitive impairment and dementia, NIH first supported HCAP during the HRS’ 2016 field period, in which investigators administered a supplemental in-home, 1-hour battery of cognitive tests to about 3,200 randomly selected HRS respondents age 65 and older, along with a 20-minute informant interview. The [data from that 2016 assessment](https://hrs.isr.umich.edu/data-products/cognition-data#hcap) have now been made publicly available to the scientific community, and analyses are underway.

[HCAP 2020,](https://projectreporter.nih.gov/project_info_description.cfm?aid=9618704&icde=42939202) a follow-up to the original, is now being planned. Researchers will readminister the same in-home cognitive assessment and seek an informant report from all surviving members of the original HCAP sample and from a new random sample of those age 65 to 68 in 2020. HCAP 2020 will provide extensive new data to better assess trajectories of cognitive decline among older U.S. adults, including the incidence of new cognitive impairment and dementia.

These data afford an unprecedented opportunity to more clearly describe trends in the incidence and prevalence of dementia around the world. HCAP is also being administered in other developed and developing countries, where HRS-like representative population surveys are conducted, including in China, England, India, Mexico, South Africa, and parts of the

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European Union. In most of these studies, important biomarker data, including DNA for genotyping and future sequencing, is also being collected.

**Understanding the cardiovascular and cerebrovascular risks for dementia.** NIH supports the[Reasons for Geographic and Racial Differences in Stroke](http://www.regardsstudy.org/) (REGARDS) study and the [Northern](http://columbianomas.org/study.html) [Manhattan Study](http://columbianomas.org/study.html) (NOMAS) to improve our understanding of geographic and racial disparities in cardiovascular and cerebrovascular risk factors that lead to cognitive impairment and dementia. Scientists will be able to turn to these studies to address emerging evidence related to the role of midlife cardiovascular and cerebrovascular health in cognitive outcomes, with the research focus of these long-standing cohort studies of black and Hispanic participants recently having been expanded to include investigation of health disparities in risk factors for dementia and how they relate to stroke risk factors.

Learn more about research implementation milestones and progress in this area at [www.nia.nih.gov/research/milestones/focus-area/population-studies-epidemiology-precision-medicine.](http://www.nia.nih.gov/research/milestones/focus-area/population-studies-epidemiology-precision-medicine)

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**BUILDING INFRASTRUCTURE FOR DATA SHARING AND DRUG DISCOVERY**

Much like the U.S. transportation system builds, maintains, and expands infrastructure to move the Nation forward, so, too, does the Alzheimer’s and related dementias research enterprise. Early on, the National Institutes of Health (NIH) recognized that solid, state-of-the-art infrastructure was critical to attain effective interventions for dementia. Those initial projects were innovative ventures that continue to be highly valued resources for Alzheimer’s research.



In 1984, the first NIA [Alzheimer’s Disease Research Centers](http://www.nia.nih.gov/research/adc) (ADRCs) were created to develop the field by training investigators in an integrated, multidisciplinary setting and collecting clinical and biological data on well-characterized research participants. The Centers program pioneered collaborative data collection and sharing for Alzheimer’s research. The [National](http://www.nia.nih.gov/research/dn/national-alzheimers-coordinating-center-nacc) [Alzheimer’s Coordinating Center](http://www.nia.nih.gov/research/dn/national-alzheimers-coordinating-center-nacc) (NACC) was established in 1999 by NIA to facilitate collaborative research across the ADRCs. NACC collects and shares clinical and pathological data in a valuable, cumulative record of people enrolled at the ADRCs from the beginning. In 2005, collection of a Uniform Data Set began across all Centers. Data from thousands of participants across the country has been collected at NACC and is available to qualified researchers. This data is also now connected with genetic, imaging, and neuropathological data for many participants.

The [National Centralized Repository for Alzheimer’s and Related Dementias,](http://www.nia.nih.gov/research/resource/national-centralized-repository-alzheimers-disease-and-related-dementias-ncrad) begun 28 years ago, is a state-of-the-art biorepository that collects and shares some 220,000 high-quality, curated biological samples (including plasma, serum, cell lines, peripheral blood mononuclear cells, cerebrospinal fluid, fibroblasts, and induced pluripotent stem cells) connected with other clinical data on volunteers from a variety of sources, including people enrolled at ADRCs. This repository serves as a valuable resource to help researchers identify genes and other biomarkers contributing to dementia.

The [Alzheimer’s Disease Neuroimaging Initiative,](http://adni.loni.usc.edu/) launched in 2004, built on that infrastructure as the first public-private partnership of its kind in Alzheimer’s research, to develop biomarkers for tracking Alzheimer’s characteristics in living people. In the behavioral and social realm, NIA’s [Edward R. Roybal Centers for Translational Research in the Behavioral and Social Sciences of](https://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translational-research-behavioral-and-social-sciences-aging) [Aging](https://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translational-research-behavioral-and-social-sciences-aging) and its [Resource Centers for Minority Aging Research](https://www.nia.nih.gov/research/dbsr/resource-centers-minority-aging-research-rcmar) (RCMARs) were established to study aging in diverse communities, and their expertise is now being applied to dementia research.

With a focus on the vascular system’s role in the development of Alzheimer’s disease, NIH in 2016 launched the [Molecular Mechanisms of the Vascular Etiology of Alzheimer’s Disease,](http://www.nia.nih.gov/news/decoding-molecular-ties-between-vascular-disease-and-alzheimers) or

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M2OVE-AD. This team science effort is working to dissect the complex molecular mechanisms by which vascular risk factors influence Alzheimer’s disease and identify new targets for treatment and prevention. About nine projects are underway.

With this remarkable foundation in place, recent growth in federal funding for dementia research has allowed NIH to make additional investments to strengthen the current infrastructure with new, state-of-the- art resources. The ADRCs and the Alzheimer’s Disease Neuroimaging Initiative, for example, are being updated and expanded. NIH is particularly active in supporting new and better ways to promote data sharing and reproducibility, provide research resources, and foster public-private partnerships among a broad range of experts and advocates. Already, investigators can more quickly and effectively work with vast amounts of genetic and molecular data to identify new therapeutic drug and nonpharmacological targets and parlay what they learn into the design and testing of potential therapies. These efforts are already reaping benefits, as described below.

**Sharing Data in New Ways**

**NIA Genetics of Alzheimer’s Disease Data Storage Site (NIAGADS).** In 2012, with a boost infunding from NIH directed to Alzheimer’s research, the Alzheimer’s Disease Sequencing Project (ADSP) was undertaken to sequence and analyze the genomes of large numbers of well-characterized individuals to identify gene variants that increase risk for Alzheimer’s disease or might offer protection against it. At the same time, NIAGADS, an update of an existing genetics repository supported to organize and store data from NIA-funded epidemiological and genetic studies, became the ADSP Data Coordinating Center.

Built as a one-stop access portal for Alzheimer’s disease genetics in anticipation of a large influx of high-throughput sequencing data—vast amounts of genetic data that can be processed quickly with new technologies—NIAGADS now hosts 37 human genetics datasets in addition to ADSP data, covering about 38,000 subjects and 24.5 billion genotypes. In July 2018, NIAGADS announced the release of data generated on 5,000 whole genomes and 11,000 whole exomes from a diverse population of individuals. (Whole genome sequencing determines the order of all 3 billion letters in an individual’s genome; whole exome sequencing is a genomic technique for sequencing all of the protein-coding regions of genes in a genome, known as the exome.) NIAGADS is hosting the harmonized ADSP data; NIH’s Database for Genotypes and Phenotypes hosts the data from the first phase of the project.

Using data from NIAGADS and other repositories, scientists have been able to expand the number of known genetic risk factors for Alzheimer’s disease, and several others are under investigation. The international team that recently identified five new risk factor loci for Alzheimer’s disease and confirmed 20 known others also reported, for the first time, that mutations in genes specific to tau, a hallmark protein of Alzheimer’s disease, may play an earlier role in the development of the disease than originally thought. These new findings support developing evidence that groups of genes associated with specific biological processes, such as cell trafficking, lipid transport, inflammation, and the immune response, are “genetic hubs” that are an important part of the disease process ([Kunkle et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30820047)).

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The [Genome Center for Alzheimer’s Disease](http://www.adgenomics.org/) was funded in 2016 to assemble, check quality control, harmonize, and jointly analyze the genetic and phenotypic data associated with the ADSP. Data are provided to NIAGADS for immediate sharing with the research community.

These efforts include checking for quality and harmonizing data from the [ADSP Follow- Up](https://www.nia.nih.gov/research/dn/alzheimers-disease-sequencing-project-adsp-description-discovery-phase-and-follow-study) [Study,](https://www.nia.nih.gov/research/dn/alzheimers-disease-sequencing-project-adsp-description-discovery-phase-and-follow-study) which contains a wide swath of data, already being sequenced, on up to 20,000 ethnically diverse participants.

**AMP-AD develops new tools, greatly expands access.** The[Accelerating Medicines Partnership–](http://www.nia.nih.gov/research/amp-ad)[Alzheimer’s Disease](http://www.nia.nih.gov/research/amp-ad) (AMP-AD) is a precompetitive public-private effort of government, industry, and nonprofit organizations that focuses on discovering novel therapeutic targets and biomarkers for validating existing and new targets. Established in 2014 to shorten the time for development of new drugs for Alzheimer’s treatment and prevention, this transformative approach integrates analyses of large-scale molecular data from human brain samples with network modeling and experimental validation to generate and test hypotheses for intervention. The Target Discovery Project has generated a wealth of molecular data from over 3,000 human brain and plasma samples collected in several NIA-supported Alzheimer’s disease cohorts and brain banks. The project makes these datasets available to the greater research community through the [AMP-AD Knowledge Portal.](https://ampadportal.org/)

In its first 5 years, beyond building the portal and making rich datasets available to qualified researchers, the AMP-AD Target Discovery Project discovered over 100 genes as potential therapeutic targets. In 2018, these novel target predictions, along with the data and analyses that led to their discovery, were made available via a new AMP-AD data resource, the AGORA platform. This web-based, interactive platform will enable researchers in academia and biotech and pharmaceutical communities to leverage AMP-AD analyses and results to enhance their own work and build on the AMP-AD discoveries. They may, for example, launch independent studies on disease mechanisms or initiate drug discovery for a new set of therapeutic targets. In 2019, an additional 400 AMP-AD candidate target genes will be publicly available, accompanied by results from several new layers of information, including on target “druggability” (the likelihood of a small molecule drug being able to affect a target), developed in collaboration with AMP-AD pharmaceutical industry partners.

In 2018, NIH reinvested in the AMP- AD Target Discovery and Preclinical Validation Project by supporting seven research teams to expand the “big data” infrastructure of the Knowledge Portal and the AGORA platform; use the existing and newly generated molecular data for discovery of additional novel targets and biomarkers and for disease subclassification; and enhance the research capabilities for experimental characterization of the candidate targets to test their utility as potential drug targets for Alzheimer’s treatment and prevention. The next phase of the AMP-AD Target Discovery Project will be a powerful discovery engine fueling new therapy development efforts, extending and expanding the public-private partnership.

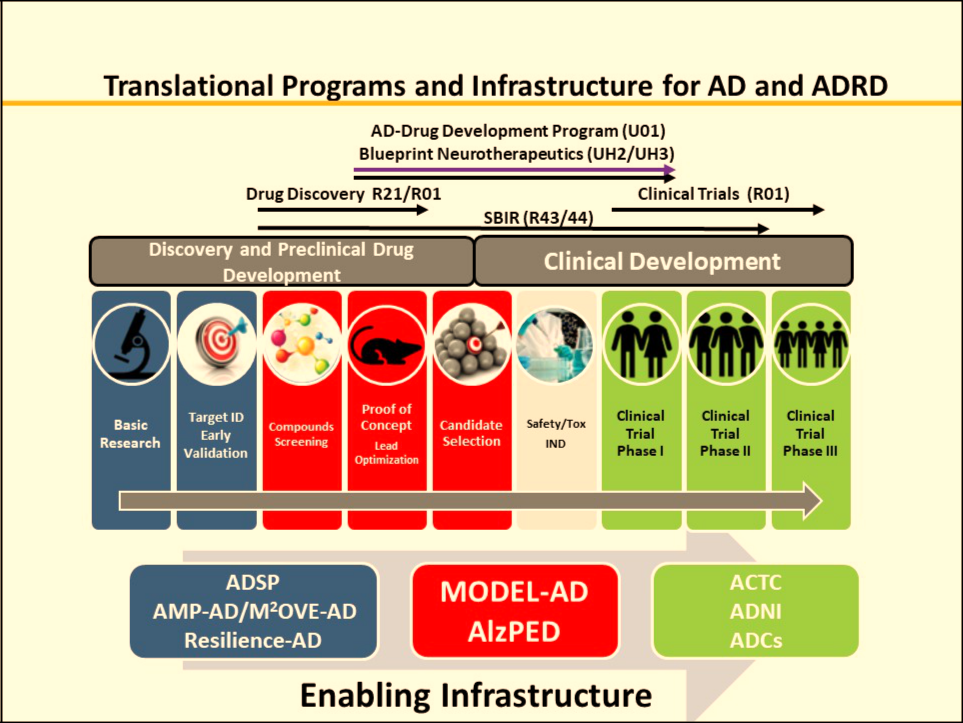
**AMP-AD clinical trials data sharing.** The [AMP-AD Biomarkers Project](https://www.nia.nih.gov/research/dn/amp-ad-biomarkers-project) is a consortium of two NIA-supported Phase II/III secondary prevention trials (Anti-Amyloid Treatment in Asymptomatic Alzheimer’s and Dominantly Inherited Alzheimer’s Network) testing several anti-amyloid therapies. Through the AMP-AD partnership, imaging and fluid biomarker panels already included in these trials will be supplemented with tau positron emission tomography

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imaging to track responsiveness to treatment and/or disease progression. Screening data from the trials will be made broadly available through the [Global Alzheimer’s Association Interactive](http://www.gaain.org/) [Network.](http://www.gaain.org/) Biosamples and data from both the placebo and treatment arms will be made available after trial completion.

**Alzheimer’s Clinical Trials Consortium to prioritize data sharing.** NIA in FY 2018 established amajor new clinical trials network, the [Alzheimer’s Clinical Trials Consortium](https://www.nia.nih.gov/research/dn/alzheimers-clinical-trials-consortium-actc) (ACTC). With a network of 35 U.S. sites, the ACTC will develop, harness, and deploy the best practices and latest methods for the conduct of Alzheimer’s trials. Its infrastructure for multisite trials will centralize functions for imaging, biostatistics, and data management. As studies via the ACTC get underway, the ACTC will share data and biosamples with the research community as quickly and widely as possible.

**Building a clinical research infrastructure for frontotemporal lobar degeneration (FTLD).** The[Advancing Research and Treatment for Frontotemporal Lobar Degeneration](http://www.rarediseasesnetwork.org/cms/artfl) consortium of researchers and patient support organizations is supported by NIH through its [Rare Diseases](http://www.rarediseasesnetwork.org/) [Clinical Research Network.](http://www.rarediseasesnetwork.org/) The collaboration of 14 clinical study sites in the United States and Canada will establish a cohort of patients with a family history of FTLD to discover new biomarkers for disease activity, standardize diagnostic criteria, and identify a large group of potential participants for clinical trials of new therapeutic agents. A subset of patients is participating in a related study, the Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects, which is focusing on participants with known mutations in one of the three genes most commonly linked to FTLD.



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**Translating Data into Prevention, Treatments**

Collecting and sharing data on genetics, population studies, and cellular and animal models are avenues of research critical to the discovery and validation of intervention targets. But what we learn needs to proceed to a logical next step—the design and testing of interventions. NIH is greatly accelerating efforts to move fundamental research into clinical reality. We are investing in the development of new cellular and animal models that better represent dementia in humans, establishment of centers for the discovery of new medicines, and new initiatives aimed at training a next-generation scientific workforce in translational research skills.

**Better Models of Late-Onset Alzheimer’s Disease**

Established in 2016, the [MODEL-AD](https://model-ad.org/) consortium is a key component of the new translational infrastructure for Alzheimer’s and related dementias. The consortium brings together two translational centers to:

* Develop next-generation transgenic mouse models for late-onset Alzheimer’s disease
* Institute a standardized process for characterization of animal models
* Align the pathophysiological features of animal models with corresponding stages of clinical disease using translatable biomarkers
* Establish guidelines for rigorous preclinical testing in animal models
* Ensure rapid availability of animal models, protocols, and data to all researchers for basic research or therapy development

Like the AMP-AD program, the MODEL-AD consortium operates under open-science/open-source principles.

Most transgenic models for Alzheimer’s were based primarily on genetic understanding of what causes the inherited, early-onset form of the disease, which represents only a small fraction of disease cases (less than 5 percent). The MODEL-AD approach centers on the notion that the predictability of candidate-therapeutics testing in animal models might be improved if the models more closely reflect the features of the sporadic, late-onset form of Alzheimer’s, which affects most people with the disease. The thinking behind MODEL-AD was that these new models could be based on recent findings identifying a combination of low-risk forms of genes associated with Alzheimer’s seen in most people with late-onset disease.

In just a little over 2 years, the MODEL-AD consortium has created and made available over a dozen new mouse models. These and additional new models are being characterized across multiple features of disease (molecular, neuropathologic, biochemical, and behavioral) at multiple ages (from young to old age). These rich datasets are offered to researchers through the [AMP-AD Knowledge Portal.](https://ampadportal.org/#/)

**AlzPED: Moving Targets Toward Clinical Testing**

Too often, the public hears reports of positive findings of concepts and interventions based on studies in animal models, only to be disappointed when those findings don’t translate into

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effective interventions for humans. The scientific community shares that sentiment, and important efforts are underway to better understand key factors contributing to this translation gap. NIA and the NIH Library, with the Alzheimer’s Drug Discovery Foundation and the Alzheimer’s Association, have joined forces to create the [Alzheimer’s Disease Preclinical Efficacy](https://alzped.nia.nih.gov/) [Database,](https://alzped.nia.nih.gov/) or AlzPED, an innovative repository of publicly available data for analyses in this area. Currently, the database hosts curated summaries of more than 700 published scientific studies illuminating key elements of study design and results and allows researchers, funding agencies, and the public to survey the scientific rigor of the published work. The database is designed to improve transparency in reporting and increase awareness of the need for greater rigor in study design, aimed at improving the reproducibility and translatability of efficacy testing in animal models. To reduce publication bias in favor of studies reporting positive findings, AlzPED in 2018 became a platform for creating citable reports and preprints of unpublished studies, including studies with negative findings.

**New and Expanded Centers to Catalyze Research**

Established and new centers programs play a key role in providing the knowledge base and research infrastructure on which scientists can build today. Several promising initiatives are underway.

**Alzheimer’s Disease Research Centers reimagined**

The [Alzheimer’s Disease Research Centers](https://www.nia.nih.gov/research/adc) were created to foster and accelerate research, working in communities to develop and share clinical and biological data from well - characterized individuals for basic, translational, and clinical studies in Alzheimer’s and related dementias. As part of its regular strategic planning, NIA in 2016 gathered a wide range of experts in the research community, including industry and nongovernmental organizations, who developed [a set of 166 recommendations](https://www.nia.nih.gov/news/expert-panel-offers-transformative-recommendations-nih-alzheimers-research-centers) for the ADRC program. To begin to address the recommendations, several changes were made in the ADRC program. The next cycle of Requests for Application [started with these grants](https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-19-001.html) and [continued.](https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-20-004.html) Although previously many ADRCs had imaging, genetics, or other biomarker cores, in this cycle, some type of biomarker core is now a requirement. Additionally, in the spirit of making information more available and helping researchers find what they need, NACC collected information from ADRCs about what types of brain tissue might be available for researchers; [this information is now accessible.](https://www.alz.washington.edu/WEB/tissueweb.html)

Last, because brain tissue for AD/ADRD research is so valuable, the ADRC neuropathology core steering committee has partnered with the NIH NeuroBioBank. This partnership will assist both the field and potential donors by 1) increasing options for individuals and families seeking to donate their or their loved ones’ brains in a way that will contribute to research and 2) increasing the diversity (along many dimensions) of a limited supply of brain tissue and other biological samples available to researchers.

**Establishing Alzheimer’s centers for the discovery of new medicines**

In August 2018, NIA announced its intention to establish multidisciplinary Alzheimer’s Centers for the Discovery of New Medicines. The overarching purpose of these translational centers is

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to improve, diversify, and reinvigorate the drug development pipeline by accelerating development of novel therapeutic targets delivered by the AMP-AD program. An important aim is to advance potential therapeutics to the point where pharmaceutical and biotech companies will invest in them, ultimately to ramp up the delivery of new drugs to patients. The new Centers will 1) design, develop, and disseminate open-source research tools for experimental validation of these new targets, such as those from AMP-AD, and 2) initiate early-stage drug discovery campaigns directed at those targets.

The Centers are also focused on reducing the high attrition rate of Alzheimer’s Phase II and Phase III clinical trials. Many studies have centered on the amyloid hypothesis, the development of interventions aimed at disrupting the buildup of protein fragments associated with the hallmark plaques of Alzheimer’s. However, growing evidence suggests that many, highly varied components contribute to the development of clinical Alzheimer’s, caused by multiple genetic and environmental factors affecting molecular networks across a number of biological pathways. This understanding highlights the need for alternative therapeutic approaches that the new Centers are designed to address.

**Focusing on behavioral and social aspects of dementia**

Two ongoing center programs specializing in behavioral and social research will add a specific concentration on Alzheimer’s and related dementias to their portfolios, and a new network will support collaboration in specific areas of high-priority research:

* **New Roybal translational research centers will focus on dementia care.** NIA’s 13 [Edward](https://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translation-research-behavioral-and-social-sciences-aging) [R. Roybal Centers for Translational Research in the Behavioral and Social Sciences of Aging](https://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translation-research-behavioral-and-social-sciences-aging) develop and pilot innovative ideas for moving results of basic behavioral and social research into practice. The Centers were authorized by Congress in 1993 and named for the Chair of the former House Select Committee on Aging, Edward R. Roybal. In 2018, NIA announced it would create new Roybal Centers focused on dementia caregiving. These Roybal Centers for Translational Research on Dementia Care Provider Support will develop behavioral interventions to improve the health, well-being, and/or capacity of both individuals and health care systems providing dementia care. As part of this program, NIA is encouraging the new Centers to make research resources available to the larger scientific community and bring together scientists across academic institutions to promote the adoption of practical care programs.
* **Dementia-focused minority aging centers added to increase attention to diversity and address disparities.** NIA’s established [Resource Centers for Minority Aging Research](https://www.nia.nih.gov/research/dbsr/resource-centers-minority-aging-research-rcmar) (RCMARs) conduct and promote studies in social, behavioral, and economic research on aging, with a focus on health disparities, minority aging, and diversity in the research workforce. NIA in 2018 expanded the RCMARs to include [a new subset of eight Centers](https://www.nia.nih.gov/research/dbsr/resource-centers-minority-aging-research-rcmar) for social and behavioral science related to Alzheimer’s disease and related dementias. These new AD-RCMARs will undertake studies on the epidemiology of dementia, preventive interventions, and formal and informal care challenges, as well as mentoring a research workforce in minority aging issues and dementia research.

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**Creating a new research network for high-priority studies.** A[new NIA initiative](https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-19-016.html)announcedin2018 will create a support system to advance behavioral and social research for Alzheimer’s disease and related dementias. This network infrastructure will not conduct standard research projects beyond small-scale pilots, but it will facilitate the generation of ideas for research through meetings and conferences, intensive workshops, visiting scholar programs, and information sharing. Among the network’s first priorities will be efforts to catalyze care and services research and the coordination of international studies incorporating the Harmonized Cognitive Assessment Protocol to leverage investments in longitudinal studies of aging that use this protocol.

The programs and activities featured in this section are just a sample of data-sharing and collaborative science vital to accelerated progress on Alzheimer’s and related dementias research. Working together in unprecedented ways will move research results more quickly and confidently into therapies and interventions that benefit people with dementia, families, and clinicians.

Learn more about research implementation milestones and progress in this area at [www.nia.nih.gov/research/milestones/focus-area/enabling-infrastructure.](http://www.nia.nih.gov/research/milestones/focus-area/enabling-infrastructure)

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**DELVING INTO DISEASE MECHANISMS AT THE MOLECULAR, CELLULAR, AND TISSUE LEVEL**

Population studies point to an array of factors that may increase or decrease risk for dementia. From reports based on measures of a few dozen individuals to DNA and clinical “big data” amassed from tens of thousands of people, we now have many clues about genetic and environmental influences on Alzheimer’s and related dementias.



But how do these factors affect us? What happens at the molecular, cellular, and

tissue levels in our bodies and brains that turns healthy cognition into the devastation of Alzheimer’s and related dementias? How, where, and when do these changes happen?

For answers, we turn to basic biological studies. The National Institutes of Health (NIH) has long recognized that basic research into the mechanisms of dementia must continue to explore as many avenues as possible. Breakthroughs in our understanding of the biology of dementia are critical to describing specific processes that might be interrupted or encouraged as promising targets for possible new therapies.

NIH has important progress to report in this area of Alzheimer’s and related dementias research. Recent findings, some highlighted here, provide new insights about genetics, as scientists elucidate how various forms of the ApoE gene affect the brain, how peripheral systems involving the microbiome and cardiovascular disease may affect Alzheimer’s and related dementias risk, how sleep impacts normal and degenerative brain function, and how resilience and aging affect biological processes related to dementia. The findings reported here reflect just a few of the completed studies, as well as initiatives and new investments in research now underway, to elucidate the mechanisms of dementia and neurodegenerative disease to reveal new, promising targets for intervention.

**Linking Risk Factors to Biological Mechanisms**

Efforts to discover the biological underpinnings of behavioral and neuropsychiatric factors involved in dementia are illustrative. Recent scientific reports explore personality and post-traumatic stress disorder (PTSD):

**Personality as a risk factor for Alzheimer’s.** Changes in personality and behavior are clinicalcriteria for diagnosis of dementia. Little is known, however, about whether changes in personality are a response to increasing neuropathology in the brain in the preclinical phase or whether personality is an independent risk factor. NIH-funded scientists [(Terracciano et al.,](https://www.ncbi.nlm.nih.gov/pubmed/28975188) [2017](https://www.ncbi.nlm.nih.gov/pubmed/28975188)) looked at the personality and clinical assessments conducted between 1980 and 2016 in

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over 2,000 community-dwelling older volunteers in the Baltimore Longitudinal Study of Aging. They found significant differences in several traits associated with impairment and dementia. People who developed dementia scored higher on neuroticism and lower on conscientiousness, openness, and extraversion. However, change in personality was not significantly different when nonimpaired participants were compared with those with Alzheimer’s disease or mild cognitive impairment. The researchers concluded that personality traits like higher neuroticism and lower conscientiousness and extraversion may be independent risk factors for development of dementia.

**PTSD as a risk factor for dementia in civilians.** Research has shown that PTSD greatly increasesthe risk of dementia in male veterans. Although PTSD is common among civilians as well, impacting twice as many women as men, until recently there has been no investigation into how PTSD affects dementia risk in U.S. civilians. In the first study of its kind, NIH-funded scientists ([Flatt et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/28627380)) analyzed the incidence of PTSD and dementia in 13 years of medical records data from a diverse population of almost 500,000 older adult members of Kaiser Permanente Northern California. Compared to those without PTSD, men with PTSD had a two-fold increase and women with PTSD had a 60 percent increase in their risk for developing dementia. Depression is a common symptom in people with PSTD, and the study found that participants who had both PTSD and depression had more than twice the risk of developing dementia than those with no PTSD or depression.

NIH has stepped up efforts to find out how such behavioral and neuropsychiatric conditions and symptoms relate to dementia. It will be important to know if managing or mitigating them, in addition to providing relief from difficult symptoms that affect quality of life, might modify or delay the onset of dementia. People diagnosed with Alzheimer’s disease often suffer from a range of neuropsychiatric symptoms, including depression, anxiety, apathy, delusions, hallucinations, sleep disturbance, agitation, and aggression. These common symptoms are seen at all stages of the disease but may play a different role, depending on when they appear. For example, some neuropsychiatric symptoms are known to be midlife risk factors associated with late-life dementia.

Recent advances in genetics, epigenetics/epigenomics, and systems and network biology provide an opportunity to gain deep mechanistic insights into the dynamic relationship between the neuropsychiatric symptoms and underlying molecular mechanisms of Alzheimer’s disease. In 2018, the National Institute on Aging (NIA), the National Institute of Neurological Disorders and Stroke, and the National Institute of Mental Health [alerted the](https://grants.nih.gov/grants/guide/notice-files/NOT-AG-18-001.html) [research community](https://grants.nih.gov/grants/guide/notice-files/NOT-AG-18-001.html) that this is a high-priority research area. Additional outreach in 2019 by the National Institute of Mental Health, in collaboration with NIA, invited scientists to investigate the [biological mechanisms of neuropsychiatric symptoms](https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-19-510.html) and [emotional regulation](https://grants.nih.gov/grants/guide/pa-files/pa-19-095.html) [and aging, including Alzheimer’s.](https://grants.nih.gov/grants/guide/pa-files/pa-19-095.html)

**Exploring How Changes in Peripheral Systems Influence the Brain**

It is commonly believed that Alzheimer’s disease is an abnormality of the aging brain. However, a growing body of research supports the notion that it is a systemic disease with significant interaction between peripheral systems—immune, metabolic, microbiome, and inflammatory

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pathways—and the brain. It would make sense, then, to approach dementia as a multifactorial health condition, with damage in multiple physiological systems leading to pathological cognitive decline. Recent reports offer new insights into the influences of the microbiome, cerebrovascular contributions, and sleep:

**Effects of Change in the Microbiome**

There is increasing recognition of the role of the gut microbiome in human disease. In recent years, scientists have turned their attention to the “gut-brain axis,” where communication occurs among the gut, its microbiota, and the brain. Although not fully understood, this axis is thought to have a major role in the onset and severity of many neurological and neuropsychiatric disorders.

The NIA-supported [Alzheimer’s Disease Metabolomics Consortium](https://sites.duke.edu/adnimetab/) brings together over 100 researchers from around the world to create a comprehensive metabolomics database map of the metabolic failures across the trajectory of Alzheimer’s disease. Many Alzheimer’s risk genes identified to date are involved in cholesterol production or transport. It is thought that bile acids, products of cholesterol metabolism and clearance produced in the liver and further metabolized by gut bacteria, may become dysregulated in Alzheimer’s disease. Two NIH-funded studies by consortium researchers in collaboration with scientists from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) have linked alterations in serum bile-acids signatures to Alzheimer’s disease. Together, these results reveal critical connections among gut and liver cholesterol metabolism, immune function, and cognitive health:

**Specific bile acids found linked to impairment, dementia.** An international research team

([MahmoudianDehkordi et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30337151)) measured the levels of 15 primary and secondary bile acids (produced by the liver and gut microbiome, respectively) in blood samples from 1,464 participants in ADNI who were either cognitively healthy or who had mild cognitive impairment or Alzheimer’s disease. Compared to people with normal cognition, those with Alzheimer’s had reduced levels of one primary bile acid and increased levels of several secondary bile acids. Higher ratios of secondary, gut-produced bile acids, which are known to be cytotoxic, were also associated with worse cognitive performance in the group as a whole, a finding replicated in samples collected in two other NIH-supported cohorts, Rush University’s Religious Orders Study and Memory and Aging Project.

**Abnormal bile acid signatures linked with biomarkers of dementia.** Another analysis [(Nho et](https://www.ncbi.nlm.nih.gov/pubmed/30337152) [al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30337152)) examined the relationship between the blood levels of 20 different bile acids from 1,562 ADNI participants and an array of cerebrospinal fluid (CSF) and imaging biomarkers of Alzheimer’s disease. The study identified abnormal bile acid signatures that were associated with abnormal CSF levels of beta- amyloid 42, tau, or phosphorylated tau, and/or with brain atrophy or reduced brain glucose metabolism.

**Cerebrovascular Contributions to Dementia**

Cerebrovascular dysfunction has been implicated in Alzheimer’s disease and predicts cognitive decline independently of amyloid plaque accumulation. Scientists are interested in how

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vascular damage works to cause neuroinflammation and cognitive decline. Two recent studies of Alzheimer’s disease-associated vascular changes focused on breakdowns in the blood-brain barrier (BBB) and reductions in brain blood flow:

**Protecting the integrity of the blood-brain barrier.** The integrity of the BBB is critical to brainhealth, as it prevents toxic substances in the bloodstream from leaking into the brain. NIH-funded scientists found that leakage into the brain of one blood protein, the clotting factor fibrinogen, set off a series of cellular events leading to synapse loss and cognitive impairment ([Merlini et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30737131)). Studying the brains of people who died with Alzheimer’s disease, the scientists found fibrinogen deposits scattered throughout the cortex, both alone and in association with amyloid plaques. The brains of Alzheimer’s model mice also contained fibrinogen deposits, and the mice as they aged showed a progressive loss of synapses around these deposits.

To better understand why this was happening, the scientists introduced fibrinogen directly into the brains of healthy mice. The synapses started disappearing from around the injection site within 3 days. The fibrinogen also triggered local microglial cells to become activated and release neurotoxic reactive oxygen species. Microglia are the major immune cells of the brain and are involved in seeking out, destroying, and digesting foreign cells and proteins. When the scientists knocked out a specific receptor (CD11b, by which fibrinogen binds to and activates microglia) in Alzheimer’s model mice, the mice showed less synaptic loss and improved cognition.

**Blood-brain barrier breakdown as a biomarker of disease.** In one study searching for earlybiomarkers of cognitive decline, a team [(Nation et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30643288)) supported by NIH examined two markers involved in the breakdown of the BBB. In more than 160 people with and without cognitive impairment, researchers measured levels of the soluble form of a protein called platelet-derived growth factor receptor beta (PDGFRβ). The protein is found in the capillaries that maintain the BBB’s integrity, and levels of the soluble form rise in CSF when the BBB is compromised. The team also tracked the integrity of the BBB in 73 participants using an imaging technique they'd previously developed.

Compared with those without cognitive impairment, participants with cognitive impairment had higher levels of soluble PDGFRβ and a greater breakdown in the BBB of certain brain regions. Notably, both measures were independent of beta-amyloid and tau protein levels. The findings show that individuals with early cognitive dysfunction develop brain capillary damage and BBB breakdown in the hippocampus irrespective of Alzheimer’s-related beta-amyloid and/or tau biomarker changes. This suggests that BBB breakdown may be an early biomarker of human cognitive dysfunction and a possible new target for disease prevention.

**Maintaining brain blood flow.** Brain blood flow is also compromised early in Alzheimer’sdisease. Reductions of about 25 percent are seen in both humans and mouse models. In a study that for the first time has identified a cause of reduced cerebral blood flow, NIH-supported researchers ([Cruz Hernández et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30742116)) found this problem can result from white blood cells (immune cells) clogging up capillaries. Capillaries are the smallest blood vessels of the brain, so tiny that blood cells squeeze through them single file and can become stuck. The scientists

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imaged the brains of Alzheimer’s model mice and saw that about 2 percent of their brain capillaries were blocked, or four times more than in healthy mice. Most of the blockages lasted less than 5 minutes, although even brief blockages of brain blood flow can impair cognition. One-third of the blockages lasted for more than 15 minutes.

With further study, the researchers discovered that capillary blood flow was stalled by neutrophils, the most common type of white blood cell, sticking to capillary walls. Neutrophils can be identified based on their expression of a cell- surface protein LyG6. When the scientists treated Alzheimer’s model mice with an antibody to LyG6, their capillaries unclogged within minutes, and blood flow to their brains increased by 30 percent. Just one dose of the antibody also improved the mice’s spatial and working memory within 3 hours.

This work suggests a possible new contributing mechanism for Alzheimer’s disease, representing a potential new target for early therapeutic intervention, bolstered by findings that the antibody treatment improved learning and memory in animal models.

**Can Better Sleep Help Reduce Risk of Dementia?**

Sleep disturbances are known to be an early symptom of Alzheimer’s disease, indicative of a faulty circadian system. But it is unknown whether circadian dysfunction is a result of neurodegeneration or plays a causative role in the development of Alzheimer’s disease.

**The circadian clock influences amyloid deposition.** In mammals, the circadian system isorganized in a hierarchy, with a central “master” circadian clock and peripheral clocks distributed throughout the brain and body to coordinate physiology and behavior rhythms over 24 hours. Levels of soluble amyloid-beta have been shown in mice to fluctuate daily in phase with known circadian rhythms. In this study, researchers [(Kress et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29382695)) supported in part by NIH disrupted the circadian clock function in an amyloid-beta mouse model by deleting a core clock gene, Bmal1. They found that loss of the critical gene from the central locus of the circadian system resulted in a disruption of amyloid-beta oscillations in the interstitial fluid of the mouse brain. Loss of Bmal1 elsewhere in the brain outside the central clock did not have the same effect on amyloid-beta oscillations but did lead to an increase in the expression of the Alzheimer’s disease risk gene APOE and accelerated the accumulation of amyloid plaques.

The study results demonstrate how the circadian system, both the central clock and peripheral local clocks, could control both the daily oscillations of soluble amyloid-beta and the local accumulation of amyloid-beta plaques. It suggests a mechanism by which dysfunction in the circadian system may be a contributing factor to the development of Alzheimer’s disease, and that treating circadian dysfunction could be a potential target of early intervention.

**Sleep affects levels of tau pathology.** Studies from researchers [(Holth et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30679382); [Lucey et al.,](https://www.ncbi.nlm.nih.gov/pubmed/30626715) [2019](https://www.ncbi.nlm.nih.gov/pubmed/30626715)) supported by NIH also have established that sleep and circadian rhythms affect the development of Alzheimer’s. They centered on the tau protein, which accumulates in abnormal tangles in the brains of people with Alzheimer’s. While beta-amyloid is an early sign of Alzheimer’s disease, tau deposits track more directly with disease progression and cognitive

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decline. In the healthy brain, active neurons naturally release some tau during waking hours, but it normally gets cleared away during sleep.

The new reports suggest that sleep deprivation upsets this balance, allowing more tau to be released, accumulate, and spread in toxic tangles in brain areas important for memory. In one study, the team set out to explore whether tau levels in the brain naturally are tied to the sleep-wake cycle. They measured tau in brain fluid collected from mice during their normal waking and sleeping hours. The researchers found that tau levels in brain fluid nearly doubled when the animals were awake—and that sleep deprivation caused those levels to double yet again. Further, the researchers reexamined CSF in people from an earlier study of healthy adults who stayed awake all night and found that tau levels were elevated, on average, by about 50 percent.

Tau is also known to spread from one area to the next as it accumulates in the brain, prompting the team to wonder whether a lack of sleep over longer periods also might encourage this spread. They tracked tau in model mice with human tau fibrils in their brains, who got less and reduced quality sleep over several weeks. While less sleep did not change the original deposition of tau in the brain, it did lead to a significant increase in tau’s spread in the same areas affected in people with Alzheimer’s disease. In a second paper by the same group, researchers showed that older people who had more tau tangles in their brains, as shown by PET scans, had less slow-wave, deep sleep.

Sleep disturbances are pervasive in Alzheimer’s disease, and sleep quality generally worsens with aging. Abnormal sleep may be a biomarker for Alzheimer’s disease and other dementias, as all are associated with sleep disorders to one degree or another. These studies suggest that improving or stabilizing sleep may be therapeutic as well.

NIA has designated peripheral systems and their influence on Alzheimer’s and related dementias an important area of research, along with more closely examining dementia in the context of aging. Toward that end, NIA in 2017 through late 2019 let the research community know that it is seeking [proposals for research projects](https://grants.nih.gov/grants/guide/pa-files/PAR-17-029.html) on the role of aging-related changes in systemic, peripheral, and/or nonneuronal factors—individually or in combination—to the pathogenesis, presentation, and/or progression of Alzheimer’s disease. Successful studies may identify critical processes and pathophysiological pathways for novel approaches to slowing or preventing disease. A number of important projects have been funded.

**Resilience as a New Pathway to Disease Prevention, Treatment**

For the most part, studies about Alzheimer’s have focused on people with the disease, typically comparing characteristics of those with the disease to those without it. More and more, that approach is being turned on its head—we now want to learn more about individuals who have managed to escape dementia. What makes them resilient to developing disease or not experiencing symptoms? What are the genomic, epigenomic, biological, environmental, social, and behavioral factors that promote wellness and protect against cognitive decline? Understanding such mechanisms might allow interventions to target enhanced wellness as well as disease avoidance to help preserve cognition.

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**Genetic Contributions to Resilience and Risk**

Humans carry three different forms, or alleles, of the apolipoprotein, or APOE, gene: APOE ɛ2, APOE ɛ3, and APOE ɛ4. The ɛ4 allele, carried by 14 percent of the population, is associated with increased risk of Alzheimer’s disease. The ɛ2 allele, carried by 7 percent of the population, is protective against Alzheimer’s disease. The ɛ3 allele, the most prevalent allele, is considered neutral with respect to Alzheimer’s disease risk. How these alleles confer Alzheimer’s disease risk or resilience is not clear.

One NIH-supported team ([Wu et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29967007)) found that the APOE alleles have different effects on the brain’s ability to take up and process glucose, a key source of fuel for the brain’s high-energy demands. In laboratory mice expressing the human versions of the APOE ɛ2, APOE ɛ3, and APOE ɛ4 genes, scientists analyzed cortical tissues for the expression of 43 genes involved in glucose uptake and metabolism. The brains of the APOE ɛ2 mice showed the highest expression of those genes, while brains of the APOE ɛ4 mice showed the lowest. When the scientists looked at cultured mouse neural cells expressing the three ApoE forms, they found that APOE ɛ2-expressing cells were the most efficient in converting glucose to energy, and the APOE ɛ4-expressing cells were the least.

Deficits in brain glucose uptake and metabolism are one of the earliest signs of incipient Alzheimer’s disease. This study suggests that approaches aimed at boosting the brain’s capacity for converting glucose to cellular energy could be investigated for staving off Alzheimer’s disease in people with the APOE ɛ4 allele.

NIA continues to support research on ApoE2. In a [notice to the research community for](https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-17-056.html) [proposals to study ApoE2, the brain, and aging,](https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-17-056.html) we want to learn more about ApoE2’s functional effects on healthy aging of the brain and other tissues. New mechanistic insights could help identify potential predictive and diagnostic markers and therapeutic targets for Alzheimer’s and other age-related cognitive disorders.

**Building a Research Focus on Resilience**

Beyond ApoE2, there is a growing focus generally on resilience for both healthy aging overall and cognitive well -being. NIA in 2017 launched its [Resilience in Aging](http://www.nia.nih.gov/resilienceandaging) program, which consists of several funding initiatives addressing resilience across organ systems and diseases of aging, including Alzheimer’s disease, adding to a strong foundation of research on resilience in the behavioral sciences.

In Alzheimer’s specifically, NIA seeks to learn more about the [complex biology of cognitive](https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-18-029.html) [resilience in individuals with high risk of disease.](https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-18-029.html) Through this funding initiative, NIA established

1. new research program, the Resilience-Alzheimer’s Disease Consortium, which complements and expands NIA’s existing open-science programs (AMP-AD and M2OVE-AD). The consortium is already at work building predictive molecular models for novel target and biomarker discovery in dementia. Scientists across 10 interdisciplinary teams are generating molecular data using biosamples from people who resist Alzheimer’s despite having high genetic risk (including those who have the ApoE4 risk gene or Down syndrome), people who remain dementia-free despite

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very old age (90-plus and centenarians), and people who remain cognitively normal despite the presence of biomarkers seen in neuroimaging or pathology after death. They are also using advanced systems and network biology approaches to build maps of resilience and test predictions of resilience from human data, with a variety of cell-based and animal models.

**A Better Mouse Model for Resilience, Vulnerability**

One team from the Resilience-Alzheimer’s Disease Consortium ([Neuner et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30595332)) became the first to show that many of the molecular, genetic, and clinical features of Alzheimer’s disease can be replicated in a genetically diverse mouse model. This is critically important to improving the predictive power of animal models and increasing their usability for precision medicine research.

In this study, scientists combined a well-established model of inherited Alzheimer’s with a genetically diverse set of mice. A detailed analysis of the new panel of mice, referred to as AD-BXD, showed a high degree of overlap with the genetic, molecular, pathologic, and cognitive features of Alzheimer’s in humans. The team also discovered that one mouse strain commonly used to generate Alzheimer’s transgenic mouse models harbored resilience factors protecting against the disease. This feature lessened the impact of Alzheimer’s risk-factor genes, interfering with that model’s suitability for testing novel therapeutic agents. The researchers noted this finding may help explain the poor predictive power of drug screening studies using current Alzheimer’s transgenic mouse models.

The new, genetically diverse model incorporates the protective genes and allows their mechanisms to be identified, while at the same time letting scientists better account for the heterogeneous nature of normal aging and Alzheimer’s and more precisely describe molecular factors that lead to resilience and vulnerabilities to genetic and environmental disease risk factors.

An infrastructure and new analytics tools support studies in cognitive reserve and resilience. After seeking ideas for a new [Collaboratory on Research Definitions for Cognitive Reserve and](https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-18-024.html) [Resilience to Alzheimer's Disease,](https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-18-024.html) [an award to establish the collaboratory](https://projectreporter.nih.gov/project_info_description.cfm?aid=9654946&icde=44220141&ddparam=&ddvalue=&ddsub=&cr=4&csb=default&cs=ASC&pball=) was made in 2018 to help define and clarify the concepts of cognitive reserve and resilience more uniformly for research.

The NIA has also [invited small businesses](https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-19-025.html) to join these efforts, seeking to develop [new](https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-19-026.html) [analytical tools, such as assays,](https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-19-026.html) that can measure resiliencies at the cellular level.

**Understanding the Intersection of Aging and Neurodegeneration**

NIH’s expanded efforts to learn more about the basic biology of dementia freshly focus on implications of the most fundamental fact about Alzheimer’s disease and related dementias: Most are diseases of aging.

The scientific community studying aging and age-related diseases has conceptualized the notion of geroscience, a field of research that aims to understand, at the cellular and molecular level,

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the connections between aging, disease, and disability. It focuses on understanding the mechanisms by which aging contributes as the major risk factor for most chronic diseases. Geroscience posits that affecting the aging process will simultaneously delay the appearance or severity of multiple chronic diseases because these diseases share aging as an underlying major risk factor. Supporting this theory are data from NIA-supported programs and initiatives, through which researchers have identified behavioral, genetic, and pharmacological approaches to extend lifespan in a variety of model systems. Importantly, interventions that extend lifespan often result in significant delays in the appearance of pathology and frailty. Conversely, when lifespan is shortened, diseases and frailty occur earlier.

In 2015, NIA initiated a program to understand Alzheimer’s disease in the context of the aging brain. [These efforts](https://grants.nih.gov/grants/guide/notice-files/NOT-AG-18-051.html) have continued, along with new opportunities for more targeted research. In 2019, NIA [invited research teams to investigate](https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-20-013.html) how established approaches to manipulate the rate of aging in model systems could advance understanding of the effect of aging on development of dementia. It asked scientists, too, to propose how they would [examine the role](https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-20-014.html) [played by known mechanisms of aging:](https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-20-014.html) cell senescence, systemic inflammation, proteostasis (the complex pathway that maintains proteins within and around a cell), and others. These types of studies will help us articulate how aging and other biological processes may make us vulnerable or resistant to the development of dementia.

Highlighted here are a few recent findings focused on how the forms of the APOE gene, the best-known genetic risk factor for late-onset Alzheimer’s disease, influences aging; the maintenance of proteostasis in Alzheimer’s; and mechanistic links between TDP-43 proteinopathy and ApoE4. We continue to explore possible known, and new, targets for intervention:

**Preserving proteostasis: Allowing cellular proteins to maintain proper function clearing senescent cells to preserve cognition.** Geroscience approaches are already opening newavenues for translational research. Last year, investigators supported by NIA [(Bussian et al.,](https://www.ncbi.nlm.nih.gov/pubmed/30232451) [2018](https://www.ncbi.nlm.nih.gov/pubmed/30232451)) found in a mouse model that senescent cells, which are alive but no longer divide or function normally, played a role in the neurodegeneration associated with Alzheimer’s and related dementias. The analysis showed a causal link between the accumulation of senescent glial cells and neuronal loss associated with cognition. Additionally, the researchers found that eliminating senescent cells before they cause damage to neurons appeared to preserve cognition. Further study could investigate whether these findings apply to other mouse models of disease and ultimately to humans, and whether treatments to destroy or inhibit senescent cells can reverse cognitive damage that has already occurred.

**Beta-amyloid provokes tau formation, spread.** Alzheimer’s disease is characterized by beta-amyloid plaques outside cells and clumps of tau inside cells. To better understand the mechanistic link between these two pathologies, NIH-funded researchers [(He et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29200205)) studied the brains of a strain of transgenic mice that develop beta-amyloid but normally not tau pathology as they age. After the mice had developed amyloid plaques, the scientists introduced pathological tau isolated from post mortem Alzheimer’s brain tissue. The mice subsequently developed all three forms of tau pathology seen in human Alzheimer’s disease. The researchers

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also could track the spread of tau, first in neurites surrounding amyloid plaques, which in turn seeded the formation of neurofibrillary tangles and neuropil threads.

This study has demonstrated for the first time how beta-amyloid plaques create an environment that accelerates the formation and spread of tau pathology in the brain. It is also the first mouse model with beta-amyloid plaques, as well as the three major forms of pathological tau. With this new model, scientists will be able to further investigate the link between beta-amyloid plaques and tau pathology and the progression of Alzheimer’s disease, making it a more useful resource for studying and testing potential therapies.

Better understanding of the dynamics of amyloid in Alzheimer’s remains an important research question, as its accumulation into plaques is one of the hallmarks of the disease. Alzheimer’s is one of a large class of diseases known as protein conformational disorders, in which the formation and accumulation of certain protein aggregates, or groupings, is one of the most common features. Our understanding of the molecular structures of protein aggregates associated with these diseases has advanced considerably. Scientists have learned that not all amyloid structures in Alzheimer’s are the same. There appear to be at least five and maybe 10 beta-amyloid fibril polymorphs (or conformers), with this type of polymorphism shown in other protein aggregates associated with disease, such as alpha-synuclein and tau. There also is evidence that these structural variations could correlate with different stages and subtypes of Alzheimer’s disease.

With the identification of many different types of tau and beta-amyloid strains, a next step is finding out what regulates the initial assembly and spread of these protein conformers. NIA has [called for proposals](https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-18-025.html) in this area. [One award was recently made](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9674854) for research that aims to analyze the different strains of beta-amyloid that occur both within and between individual mouse models, and what characteristics and factors may play a role in that variation.

**Pursuing a shared drug target for aging and dementia.** Because Alzheimer’s is a disease ofaging, scientists have been interested in targeting aging as a therapeutic strategy for dementia. But the relationship has not been well understood at the molecular level. In an ongoing study, scientists ([Goldberg et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29316249)) funded by NIH reported a novel molecular link through identification of a drug candidate, J147. The compound was developed to address disease toxicities in the aging brain and shown to have a positive effect against dementia in various mouse models. Further study identified mitochondrial ATP synthase, an enzyme that powers cellular activities, as the compound’s target, with its regulation of mitochondrial processes found in animal models to prevent age-related adverse effects in the hippocampus and plasma metabolome and to extend life. By linking aging and age-associated dementia through the ATP synthase, the researchers believe that there is an unexpectedly close relationship between the two, which offers a novel molecular drug target to investigate for both.

**TDP-43: Learning More About an Important Protein in Dementia**

**ApoE4 increases TDP-43 pathology.** TDP-43 (transactive response DNA-binding protein of 43kDa) proteinopathy first came into the scientific spotlight when it was discovered to be the primary aggregated protein in amyotrophic lateral sclerosis (ALS) and in the most common form

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of frontotemporal dementia (FTD). More recently, studies are pointing to TDP-43 pathology as a feature of clinical Alzheimer’s disease. In 2018, scientists supported by NIH found a strong association of APOE ɛ4, the leading genetic risk factor for late-onset Alzheimer’s disease, with TDP-43 pathology ([Yang et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/30093249)). The team analyzed genetic and autopsy data from 1,044 older adults in the Rush Religious Orders Study and the Rush Memory and Aging Project. In those who had died with a diagnosis of Alzheimer’s, there was a clear association between APOE ɛ4 and brain TDP-43 pathology, stronger than any seen previously. The link remained even after accounting for levels of beta -amyloid and other neurodegenerative proteins. The study further showed that LATE (limbic predominant age- related TDP disease), a late-onset amnestic syndrome with TDP-43 that often co-exists with the clinical syndrome of Alzheimer’s, is also associated with APOE ɛ4.

This research adds important insights into the relationships among Alzheimer’s disease, TDP-43 proteinopathy, and hippocampal sclerosis through a shared risk factor, ApoE4. It implies a further mechanistic link between Alzheimer’s disease and TDP-43 proteinopathy. TDP-43 proteinopathy, the investigators suggested, should be considered an integral component of ApoE-related neurodegeneration and assessed in future translational research and clinical trials.

**TDP-43 may disrupt nuclear traffic in ALS, FTD.** TDP-43 is normally found in the cell nucleus,where it is thought to regulate RNA processing and transport. In several neurodegenerative diseases, however, including ALS, FTD, and Alzheimer’s, TDP -43 forms abnormal aggregates inside the cell. In a recent study, scientists supported by the National Institute of Neurological Disorders and Stroke and NIA ([Chou et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29311743) ), examined the composition of these abnormal aggregates by engineering cultured neural cells to express a form of TDP-43 linked to an enzyme that tags all proteins lying in close proximity to it. Prominent among the tagged proteins were components of the nuclear pore and other proteins involved in shuttling molecules across the nuclear membrane (the membrane that separates the nucleus from the cytoplasm).

When the scientists introduced a disease-causing form of the TDP-43 gene into the cultured mouse cortical neurons or into human skin cells, they discovered abnormalities in the structure of the nucleus and nuclear membrane, together with disruptions of protein and RNA transport between the nucleus and cytoplasm. These appeared similar to the structural damage seen in people with both familial and sporadic forms of ALS and suggest that TDP-43- mediated disruptions of traffic between the nucleus and cytoplasm are a major disease mechanism in both ALS and FTD.

Additional funds for Alzheimer’s and related dementias research in FY 2018 allowed NIH to support several new research projects in this area. A focus on the [structural biology of related](https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-18-015.html) [dementias proteinopathies](https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-18-015.html) is supporting three projects that leverage recent advances in cryo-electron microscopy to investigate structural differences in proteins such as tau, alpha-synuclein, and TDP-43. The consortium on these projects will connect with another research team working on biomarkers for related dementias to integrate structural biology efforts with the development of PET radioligands for related dementias. [Another program](https://grants.nih.gov/grants/guide/pa-files/par-18-661.html) supports use of

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enhanced bioinformatics for large-scale data analysis and disease modeling to discover and validate new pathways, targets, and potential biomarkers.

**Identifying Risk Factors for Alzheimer’s Disease and Related Dementias**

Because we now know that Alzheimer’s is a multifactorial disorder with a long incubation period, we focus on the contributions of many risks over time and how they work together in the development of disease. Some of the influences emerging from research reported over the past year point to high salt in the diet, viral species, and previously unknown effects of APOE ɛ2 on tauopathy:

**Mechanisms linking dietary salt to vascular contributions to cognitive impairment and dementia.** High- salt diets have been linked to increased risk of cerebrovascular disease anddementia, but it has been unclear how salt harms the brain. NIH-supported researchers [(Faraco](https://www.ncbi.nlm.nih.gov/pubmed/29335605) [et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29335605)) found that mice fed a high-salt diet for 3 months had reduced blood flow to their brains and performed worse on learning and memory tests than mice fed normal chow. The deficit in brain blood flow turned out not to be due to high blood pressure, but rather to impaired production of nitric oxide (NO), a key regulator of blood vessel diameter, by the endothelial cells lining brain blood vessels.

Following from recent research showing that a high-salt diet causes immune changes in the gut, the scientists investigated further. After zeroing in on the mechanisms involved, the team found that in mice fed a high-salt diet, the enzyme responsible for producing NO in endothelial cells (endothelial nitric oxide synthase, or eNOS) was suppressed due to actions of another enzyme, Rho-kinase. Treating high-salt-fed mice with Rho-kinase inhibitors normalized their NO production and memory performance, suggesting that drugs boosting NO production might be studied further for their potential in treating age-related cognitive impairment. While these findings have not yet proved true in humans, it provides one more reason, potentially, for people to avoid excess salt.

**Emerging evidence on the role of viral species in Alzheimer’s disease biology.** A recent analysis([Readhead et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29937276)) of large datasets from brain samples after death of people with and without Alzheimer's disease revealed new evidence that viral species, particularly herpesviruses, may have a role in Alzheimer's biology. Researchers funded by NIH made the discovery thanks to the availability of rich genomic datasets from brain banks and cohort studies, generated by the research teams participating in the [Accelerating Medicines](https://www.nia.nih.gov/research/amp-ad) [Partnership–Alzheimer’s Disease](https://www.nia.nih.gov/research/amp-ad) consortium. While the hypothesis that viruses play a part in brain disease is not new, the findings were the first to provide strong evidence based on unbiased approaches and large datasets.

In 2018, a second analysis showed for the first time how viral infections could trigger the deposition of amyloid-beta, the protein involved in forming Alzheimer’s plaques, and provides insights on the mechanistic link by which pathogenic infections could be involved in the disease. This study [(Eimer et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/30001512)) found that introduction of the herpes simplex virus 1 in a mouse model provoked what appeared to be an immune response. Within 48 hours, beta- amyloid plaques appeared surrounding the viral particles in the Alzheimer’s mice but not in the control

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mice, and the Alzheimer’s mice survived significantly longer than the control mice. To understand how beta-amyloid protects cells from viral infection, the scientists studied an “Alzheimer’s in a dish” model, three-dimensional cultures of neural cells expressing beta-amyloid with a familial Alzheimer’s mutation. Infection with herpes simplex virus 1 or two other common human herpes viruses triggered rapid increases in the neural cells’ beta-amyloid production. Microscopic observations showed that the beta-amyloid bound to the viral particles and formed nets of fibrils, which entrapped the virus and prevented it from entering the neural cells.

The research tested the investigators’ hypothesis that in Alzheimer’s disease, the normally protective antimicrobial pathway via amyloid-beta is overactivated, and the continual deposition of amyloid-beta leads to neuroinflammation and neuronal death. This “antimicrobial protection hypothesis of Alzheimer’s disease,” the researchers noted, suggests that antiviral drugs might be explored for their potential in helping to prevent the disease.

**APOE ɛ2 may increase risk of tauopathies.** The APOEɛ2 allele is associated with reduced risk ofdeveloping Alzheimer’s disease. But new research in animal and cellular models suggests that it may increase the risk of “primary” tauopathies, such as progressive supranuclear palsy and corticobasal degeneration. To find out more, NIH-funded scientists [(Zhao et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/30348994)) examined 6-month-old transgenic mice carrying the human APOE ɛ2, ɛ3, and ɛ4 alleles whose brains contained a mutant tau gene. Compared to the brains of APOE ɛ3 and APOE ɛ4 mice, those of APOE ɛ2 mice had significantly higher levels of abnormal (hyperphosphorylated) tau, tau deposits, and proliferation of astrocytes (the star-shaped form of glial cells that support neurons and help maintain synaptic function). The APOE ɛ2 mice also showed synaptic deficits and behavioral abnormalities similar to those seen in human tauopathies, including increased signs of anxiety, abnormal exploratory behavior, and impairment on certain memory tests. The scientists then studied brain tissue after death of patients with progressive supranuclear palsy and saw increased tau pathology in those bearing at least one copy of the APOE ɛ2 allele. They also found a significant association between possession of two copies of the APOE ɛ2 allele and increased risk of tauopathy in two series of post mortem brain samples from patients with progressive supranuclear palsy or corticobasal degeneration. These results suggest that the APOE ɛ2 allele increases the risk of developing neurodegenerative diseases in which there is tau pathology but no amyloid pathology.

Learn more about research implementation milestones and progress in this area at [www.nia.nih.gov/research/milestones/focus-area/disease-mechanisms.](http://www.nia.nih.gov/research/milestones/focus-area/disease-mechanisms)

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**FINDING BIOMARKERS TO DETECT, DIAGNOSE, AND TREAT DEMENTIA**

As mechanisms of disease are revealed, we have made enormous strides in the identification and use of biomarkers to detect disease and track progress. Clinical, imaging, genetic, and biochemical measures are being tested and validated, primarily in a research context, although they are sometimes used to aid clinically in differential diagnoses of a dementia. This important work has focused on ways to define Alzheimer’s and related dementias biologically, particularly in the preclinical phase of the disease, before outward signs of cognitive change may appear. The goal is to find ways to determine who is most at risk for cognitive decline due to dementia and to see if biomarkers can follow disease progression and help show the effectiveness of potential treatments.



In 2019, we celebrate the 15th anniversary of the groundbreaking Alzheimer’s Disease Neuroimaging Initiative (ADNI). The first major public-private partnership in Alzheimer’s research, it fostered much of our early success in early detection and monitoring through brain imaging and biomarkers and continues to innovate. ADNI researchers were at the forefront of developing the ability to detect the signature proteins and brain changes associated with Alzheimer’s in images of the living brain and in cerebrospinal fluid (CSF). Its data-access policy continues to pioneer: To date, more than 53 million data downloads from ADNI servers have been executed by investigators worldwide.

In 2018, ongoing work by ADNI investigators and others led to the NIA-Alzheimer’s Association Research Framework: Toward a Biological Definition of Alzheimer’s Disease. The framework aims to facilitate better understanding of the disease process and the sequence of events that leads to cognitive impairment and dementia ([Jack et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29653606)). Focusing on biological or physical targets, the Framework team reasoned, would lead to a more precise and faster approach to testing drug and other interventions. Its common language regarding how different stages of the disease are measured should allow studies to be compared more easily and to be presented more clearly to the medical field and public. Ultimately, several of these measures may be useful for diagnosing pathological Alzheimer’s disease during life—much like cholesterol, for example, is a marker for heart disease.

Capturing the earliest clinical signs of Alzheimer’s and related dementias is also a priority. The National Institutes of Health (NIH) is launching a number of programs and projects to develop and validate more sensitive neuropsychological and behavioral assessments, including the extension of ongoing research on social and emotional functioning and decision-making in normal aging, mild cognitive impairment (MCI), and Alzheimer’s disease to identify early behavioral markers of disease. These domains of functioning may also be candidates for assessment using “digital” biomarkers. There are also efforts underway to explore whether

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accelerated aging processes in peripheral systems may be an early warning sign of Alzheimer’s risk.

**Discerning Differences in Biomarkers in Diverse Populations**

It is critically important that efforts to discover and validate biomarkers pay greater attention to their application in diverse populations. For NIH, addressing diversity is a high priority. With growing evidence of different biological mechanisms when considering race and Alzheimer’s, for example, research is intensifying in this area. A new effort was recently launched to recruit and retain a diverse group of scientists and study participants for future research.

In one recent report ([Morris et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30615028)), scientists funded by NIH found differences in some biological markers underlying Alzheimer’s disease in African Americans and non-Hispanic whites. Using the largest set of fluid biomarker data from African Americans to date, investigators looked at biomarker data in people enrolled in studies in which two-thirds of both African American and white participants had normal cognition, and the rest were mildly impaired. All had undergone at least one Alzheimer’s biomarker test, including brain scans to measure brain shrinkage and harmful forms of the amyloid protein, as well as lumbar punctures to collect CSF, which reveals levels of amyloid and another protein, tau, indicating the disease processes.

Although there were no differences between African Americans and whites on some measures, including amyloid levels in the brain and CSF, other test results showed African Americans with a family history of dementia had a smaller hippocampus, a brain structure important for learning and memory, and that they had significantly lower levels of tau in CSF than whites when both had the APOE ɛ4 gene form, a genetic risk factor for Alzheimer’s. Generally, lower tau—which forms damaging tangles inside neurons—means a person is less likely to be cognitively impaired, but African Americans were just as impaired as whites. The researchers suggested it was possible that CSF tau levels found to be abnormal in whites are not abnormal in African Americans because APOE ɛ4 exerts a weaker effect in African Americans. The authors concluded that racial differences in Alzheimer’s biomarkers suggest possible race-dependent biological mechanisms that contribute to expression of disease.

The research team and an accompanying editorial [(Barnes, 2019](https://www.ncbi.nlm.nih.gov/pubmed/30615027)) pointed to future considerations for studies in this area. They suggested considering the influence of other diseases and social factors, such as discrimination and education. They also noted a need to combine data from several centers and projects to generate larger samples because there are relatively few lumbar puncture results for CSF from African Americans, who are underrepresented in research.

**Brain Changes Seen Through Imaging May Be Early Biomarkers for Disease**

**Measuring synaptic loss to track disease**. One of the critical steps in the Alzheimer’s diseaseprocess is loss of synaptic terminals, which affects communication between cells. But there has never been a method for demonstrating this loss in living humans. In 2018, for the first time, NIA-supported researchers ([Chen et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/30014145)) used imaging to measure synaptic loss in the

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brains of living people. The team, at one of NIA’s Alzheimer’s Disease Research Centers, used positron emission tomography (PET) to measure a specific protein, SV2A, found in synaptic terminals. Neurotransmitter chemicals released from synaptic terminals of one brain neuron cross a narrow gap (the synapse) and cause the adjacent neuron to turn on or off. The scientists theorized that levels of SV2A protein should reflect the density of synapses; however, until this work, measurements of SV2A or synaptic density were only possible in brains of people after they died.

The exploratory study involved a small number of participants with either MCI or mild Alzheimer’s disease who were compared with participants who were cognitively unimpaired (average age, 73). PET scans showed that people with MCI or mild Alzheimer’s had significantly less SV2A binding in the hippocampus, indicating a decrease in synaptic density compared to cognitively normal participants. The hippocampus is part of the brain essential in forming memories and the location of early damage associated with Alzheimer’s disease. The PET scan results also correlated with test scores of episodic memory (memories of recent events), as well as scores on a cognitive test for Alzheimer’s disease.

In comparison, some other brain imaging measures, though they detect proteins related to Alzheimer’s disease, do not correlate directly with cognitive function. Researchers believe that a reliable measure of synaptic density in living people could provide both a better measure of disease progression and could help objectively evaluate treatment response in clinical trials of disease-modifying drugs. The method might prove useful not only in Alzheimer’s disease, but also other neurodegenerative and psychiatric diseases. NIH is seeking additional research in synaptic imaging.

**Preclinical predictors of neurodegeneration.** NIA researchers ([Armstrong et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30580127))examined data from participants in the Baltimore Longitudinal Study of Aging (BLSA) to look at the effects of Alzheimer’s disease risk factors on brain-volume changes to see if they might partly explain what happens during preclinical Alzheimer’s in people who become cognitively impaired. The study looked at magnetic resonance imaging data from 688 volunteers in the BLSA, as well as a number of Alzheimer’s risk factors, including age, APOE ɛ4 carrier status, diabetes, hypertension, obesity, current smoking, and having low LDL cholesterol.

Older age, the APOE ɛ4 allele, hypertension, and low HDL cholesterol were associated with greater brain volume loss across the whole group of participants. All participants had normal cognition at all assessments in the study. But when the participants were divided into those who developed cognitive impairment in the future and those who did not, differences in risk factor susceptibility became evident. Hypertension, obesity, and APOE ɛ4 carrier status were associated with greater neurodegeneration over time only in those who later developed cognitive impairment. The most striking differences in brain tissue loss between the people who became cognitively impaired and those who did not were seen in the hippocampus and other areas of the medial temporal lobe of the brain that are critical for memory.

These findings demonstrate that potentially modifiable predictors of brain volume loss and neurodegeneration influence brain changes later on, and that those in the earliest stages of

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Alzheimer’s disease are vulnerable to risk factors that have little or no effect in people who remain cognitively normal.

**Peripheral Biomarkers May Be Easier, Cheaper Tools to Detection, Monitoring**

While imaging and CSF analysis looking for proteins and other markers of disease have become a staple of research, the samples are cumbersome and expensive to obtain and analyze, with challenges for patients as well as researchers. NIH-supported researchers are on the hunt for markers found in blood and plasma, such as detecting levels of amyloid-beta, a pathological hallmark of Alzheimer’s, and other related entities. We are making excellent progress in developing and testing these peripheral biomarkers and are encouraging expanded efforts.

**Looking to metabolites to measure Alzheimer’s pathology.** It has been difficult to connectmarkers in the blood to those in the brain, as scientists have been trying to learn more about the long timeline between the start of Alzheimer’s brain pathology and the development of clinical symptoms. In 2018, a team of researchers ([Varma et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29370177) ), led by scientists from the NIA Intramural Research Program, tried a novel approach, examining brain metabolites associated with Alzheimer’s pathology to see if they could also be detected in blood and were related to progression of the disease. The researchers analyzed brain and blood tissue samples from autopsies of BLSA participants who had Alzheimer’s disease, a normal control group, and a smaller group who had asymptomatic Alzheimer’s disease—significant disease pathology at autopsy but no signs of cognitive impairment during life.

Using a computer system with machine learning techniques, they used algorithms to more rapidly analyze metabolites and find the most likely targets. Data patterns identified a panel of 26 metabolites out of 180 studied that could accurately differentiate Alzheimer’s disease from control brain samples. The researchers then measured these 26 metabolites in about 700 blood samples from ADNI and BLSA, testing for relationships with known signs of Alzheimer’s. Altered blood concentrations of some of the 26 metabolites were consistently associated with brain atrophy on magnetic resonance imaging scans, CSF measures of abnormal proteins linked to Alzheimer’s, cognitive test performance, and risk of Alzheimer’s disease before established symptoms developed. The targeted metabolomics study represents a novel approach for identifying markers of disease progression in Alzheimer’s and potential avenues for therapeutic intervention.

**Driving cessation—what can biomarkers tell us about function?** The decision to stop drivingwith advancing age is difficult for older adults, their families, and clinicians. While safety concerns are paramount, no longer driving is also associated with adverse outcomes such as depression. In what may be the first study to examine the relationship between Alzheimer’s biomarkers and driving cessation, scientists [(Stout et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29328928)) found Alzheimer’s biomarkers linked to driving performance, and that early driving cessation may also be a functional outcome of preclinical Alzheimer’s disease.

In people 55 years and older enrolled in studies at an NIA-supported Alzheimer’s Disease Research Center, researchers examined the time from baseline to driving cessation as a function of Alzheimer’s CSF biomarker ratios in 559 participants and [Clinical Dementia Rating](https://www.sciencedirect.com/topics/medicine-and-dentistry/clinical-dementia-rating)

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(CDR) scores in 1,795 participants, over a period of up to 24 years. They found that individuals with higher baseline CDR scores would stop driving earlier, and that CSF biomarkers would predict time to driving cessation independent of CDR scores. Participants with very mild or mild dementia at the beginning of the study stopped driving at higher rates (3.5 times and more than 5 times, respectively) than those without dementia. Those with abnormal CSF biomarker levels (tau/Aβ42 and ptau/Aβ42 ratios) stopped driving at about twice the rate per year compared to those with normal CSF biomarker levels at all levels of cognition. Education and race did not appear to play a role in time to driving cessation, and there was no difference between men and women.

The study results suggest that individuals may have discernible functional limitations well before cognitive symptoms are apparent. It is possible that earlier driving cessation is a function of changes in sensory, motor, visuomotor, and navigational abilities that occur in individuals with preclinical disease. Future research will be needed to better understand the functional changes that occur in preclinical Alzheimer’s disease, develop driving cessation decision tools, and examine interventions for those most at risk for unsafe driving.

The search for accurate and novel biological biomarkers is an increasingly active area of study. Several studies are underway, including, for example, one involving detection of small-vessel microvascular changes in the eye—the Eye Determinants of Cognition, or EyeDoc, Study—using new technology to examine retinal biomarkers that may signal cerebrovascular changes related to dementia. Researchers are using a novel PET radiotracer, now being tested in an animal model for Parkinson’s disease, for imaging oxidative stress to track neuroinflammation in patients at risk for developing Alzheimer's. Others are working to develop and validate a blood test for Alzheimer’s for primary care settings.

**Digital Technologies Bring New Dimension to Dementia Study, Care**

NIH has long been interested in promoting the development and use of new technologies in dementia study and care. Highlighted here are initiatives in mobile measures of cognitive change, screening in clinical settings, and learning more about how patients and their caregivers react to findings from imaging tests.

**Mobile Measuring of Cognitive Change**

Building on the success of the [NIH Toolbox](http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox/intro-to-nih-toolbox) and its common measures of cognitive and emotional health, NIA in 2017 sought to expand and update technology to help assess cognitive change through mobile monitoring. In 2018, two projects began:

**Ambulatory methods for measuring cognitive change** ([U2CAG060408, PI Martin Sliwinski](https://projectreporter.nih.gov/project_info_description.cfm?aid=9593254&icde=42940188&ddparam=&ddvalue=&ddsub=&cr=4&csb=default&cs=ASC&pball=)). Inthis study, scientists are developing infrastructure to provide the research community with validated open, flexible, and usable mobile application tools for sensitive and accurate measurement of cognitive change. The tools aim to detect subtle cognitive changes years before the onset of discernable cognitive symptoms by developing innovative ambulatory methods that rely on mobile and sensor technology to measure the cognitive and behavioral function of people in their everyday lives. These methods may improve measurements of early

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signs of cognitive impairment and set the stage for a next generation of early intervention and prevention studies.

**MobileToolbox for monitoring cognitive function** ([U2CAG060426, PI Richard Gershon](https://projectreporter.nih.gov/project_info_description.cfm?aid=9593880&icde=43011920&ddparam=&ddvalue=&ddsub=&cr=2&csb=default&cs=ASC&pball=)).Researchers are developing and validating tests from the NIH Toolbox for use on mobile platforms. A set of harmonized, app-based cognitive assessment tools will seek to discern normal from abnormal cognitive change in adults age 20 to 85. This mobile version would be used where in-person administration of the NIH Toolbox assessments would be too expensive. Once developed and validated, the assessments in the MobileToolbox platform can be used in treatment trials and, ultimately, in the clinical environment.

**Improving Clinicians’ Assessment Capabilities**

There is considerable evidence that early signs of cognitive impairment are not being detected in the medical system. This failure is occurring despite demonstrated benefits that early knowledge offers important opportunities for individuals and families, such as participation in a clinical trial or study, intervention on potentially modifiable risk factors, compliance with treatments for comorbid conditions, and the chance to prepare for progressing disease. Research is underway to better understand many aspects of screening and diagnostic instruments for clinical and community settings, including not only their validity, sensitivity, and specificity, but also how they work in diverse populations, how they relate to biomarkers, and the balance of potential harm from false positives with potential benefit from early and accurate diagnosis. An ongoing effort, [DetectCID](https://www.detectcid.org/)—the Consortium for Detecting Cognitive Impairment, Including Dementia—is a collaborative network supported by NIH to develop and validate approaches to detect cognitive impairment in primary care and other everyday clinical settings.

NIH continues to look for improved and practical screening capabilities. In a recent report ([Galvin et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29963365)), a team of researchers supported by NIH evaluated performance and informant-based assessments, as well as the usefulness of patient self-reports of subjective cognitive impairment. They developed an algorithm combining these measures for screening for dementia in a variety of clinical settings. The approach may help to inform providers about the presence or absence of a cognitive disorder, stage the extent of the disorder, and develop a differential diagnosis and management plan. The research team has received support to develop and test their approach in a multicultural community.

**Assessing the Impact of Biomarker, Imaging Tests on Patients and Caregivers**

How people living with dementia and their caregivers are impacted by news about brain scans and biomarkers is an important element in care. The Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) Study, supported by the Alzheimer’s Association and the American College of Radiology in collaboration with the Centers for Medicare and Medicaid Services, examines how amyloid PET scans guide doctors in diagnosing Alzheimer’s disease and other dementias early in disease progression, where a differential diagnosis is needed. To add the perspective of people with dementia and caregivers to this practice, NIA supported a supplemental CARE IDEAS Study on decision making, preferences, and emotional well-being of people with dementia, families,

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and caregivers in reaction to diagnostic results from a brain scan. The study has received support to conduct a 2-year, follow-up data collection, aimed at filling a gap in understanding the patient/caregiver dynamic in these situations. Specifically, researchers will look at care-seeking behavior and health care utilization, future planning, emotional well-being, and economic security, as influenced by the results of amyloid PET scans. The update will provide the research community with a longitudinal data resource that includes survey data, Medicare claims data, and IDEAS study amyloid PET scans to help determine the value people with dementia and their care partners place on getting a diagnosis confirmed by imaging, and whether diagnosis affects the pursuit of additional diagnostic certainty.

Learn more about research implementation milestones and progress in this area at [www.nia.nih.gov/research/milestones/focus-area/biomarkers-diagnosis.](http://www.nia.nih.gov/research/milestones/focus-area/biomarkers-diagnosis)

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**DRUG DISCOVERY, DEVELOPMENT, AND TESTING: ZEROING IN ON NEW TARGETS**

The translation of basic findings into effective treatments has traditionally been a slow process, for any disease. In recent years, spurred by a boost in funding, the National Institutes of Health (NIH) has been able to accelerate that process significantly for Alzheimer’s disease and related dementias, building strategically on basic science and the capabilities of an expanded, foundational infrastructure for discovery.



Negative reports from a few recently completed trials of Alzheimer’s drugs have been disappointing. These studies, based on early knowledge, mostly sought to interfere with processes involved in forming and/or clearing beta-amyloid plaques in the brain. Despite these setbacks, scientists continue to be interested in amyloid, as basic and mechanistic studies further describe its role. It may be that these initial trials intervened too late in the disease process, and an anti-amyloid line of attack still may have the potential to make a difference at an early presymptomatic stage. It is important that studies continue to investigate amyloid, as both negative and positive findings help refine the research approach to all dementias.

**Aiming at a Multitude of Therapeutic Targets**

As we continue to investigate amyloid, it appears likely that a variety of targets and combined therapies may be the ultimate approach to treat dementia. We are undertaking a next-generation program, seeking to treat and prevent neurodegenerative disease at the earliest possible stage while continuing to seek relief for patients and families already affected. Breakthroughs in biomedical imaging and detection of promising biomarkers, coupled with new understanding of disease genetics and mechanisms, have opened exciting windows of opportunity to affect and even reverse underlying pathology. The search for pharmaceutical and nondrug interventions is energized as never before.

The pipeline for developing novel drug candidates for Alzheimer’s treatment and prevention is diverse and expanding. Over the last 12 years, NIH has invested in a robust translational research program to develop and diversify therapeutic targets and candidate drugs for dementia. Today, more than 30 novel therapeutic candidates for more than a dozen non-amyloid/non-tau targets are at different stages of preclinical drug development, including several funded under NIH small-business programs. Some 40 compounds are further along the pipeline, under study for the prevention and treatment of Alzheimer’s and related dementias, mild cognitive impairment, and age-related cognitive decline. And approximately 200 clinical trials, both pilot and large-scale studies, of a wide range of interventions are underway. Not only drugs are being tested. Several trials are examining nonpharmacological interventions, including diet, exercise, and cognitive training.

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Crucial to these discoveries are massive datasets containing detailed, deidentified information on millions of individuals. By analyzing data across such large groups of people, scientists can look at common influences on dementia and pinpoint what may put subgroups and types of individuals at risk. This strategy will inform the ultimate goal of developing a precision medicine approach to treatment and prevention.

In Alzheimer’s genetics, discoveries pointing to targets for treatment and prevention are supported through a highly interconnected network of programs that collect, store, disseminate, and analyze genetic and related clinical data. These and other findings support emerging evidence that groups of genes associated with specific biological processes, such as cell trafficking, lipid transport, inflammation, and immune response, are “genetic hubs” that may play an important role in the disease process, and that interventions aimed at these processes—or multiple processes—affected by a gene might help identify highly targeted therapeutic approaches.

To model and predict how large sets of genes interact and lead to clinical and pathologic traits, NIH has employed “big data” in several innovative ways. In Alzheimer’s, the flagship NIH drug and biomarker discovery initiative is the [Accelerating Medicines Partnership–Alzheimer’s](https://www.nia.nih.gov/research/amp-ad) [Disease](https://www.nia.nih.gov/research/amp-ad) (AMP-AD), a precompetitive public-private collaboration of government, industry, and nonprofits. AMP-AD’s use of powerful molecular profiling and advanced information technologies, along with an infrastructure for rapid, broad sharing of datasets and analyses, has transformed the way new therapeutic targets and biomarkers are discovered.

The Target Discovery component of AMP-AD is already producing results. Since its inception in 2014, the AMP-AD Target Discovery research teams have established a centralized data resource/infrastructure, the [AMP-AD Knowledge Portal,](https://www.synapse.org/#!Synapse:syn2580853/wiki/409840) for rapid, broad data sharing. They have also generated human data from over 2,000 brains and over 1,000 plasma samples (across all stages of Alzheimer’s) and made them widely available to researchers; developed network models of disease pathways/targets; and in July 2018 nominated over 100 novel candidate targets. The newly nominated targets and associated data and analyses are available through a new [AGORA](https://agora.ampadportal.org/genes) web-based interactive platform. This groundbreaking program was renewed in 2018.

To further drive translational studies, in 2019 NIA plans to launch two new Alzheimer’s Disease Centers for Discovery of New Medicines. The Centers’ multidisciplinary translational projects are designed to move findings of targets from AMP-AD and other initiatives along the drug discovery pipeline. An important aim is to advance potential therapeutics to a point where pharmaceutical and biotech companies will invest in them, ramping up the delivery of new drugs to patients. The new centers will focus on reducing the high attrition rate of treatments in Alzheimer’s Phase II and Phase III clinical trials.

Accelerated basic discoveries have brought an unprecedented and exciting diversity to NIH’s Alzheimer’s disease and related dementias translational research portfolio. Investments to move these discoveries forward are highlighted here. They describe, at various stages in the translational pipeline, how investigators are pursuing many promising avenues—both novel and

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existing targets, alone or in combination therapies, with brand new drugs and repurposed medications that have been used for other diseases and conditions.

**Promising Therapies in Preclinical Drug Development**

NIA continues to support its long-standing [Alzheimer’s Drug Development Program](https://grants.nih.gov/grants/guide/pa-files/par-18-820.html) (ADDP) to foster new therapeutics for symptoms and root causes of disease, at multiple stages. The ADDP has funded 14 preclinical drug development projects since 2013, in various stages of testing. Projects in its pipeline now include development of small molecule, immune, regenerative, and gene therapies.

**Stem cells to target multiple disease mechanisms.** Studies have shown the benefit of cell-based therapies in Alzheimer’s models and that their effectiveness can be enhanced when delivered with trophic factors, naturally occurring substances important for regulating a variety of cellular functions. [One group of researchers](https://projectreporter.nih.gov/project_info_description.cfm?aid=9520552&icde=44013095) is developing a unique line of human cortex-derived neural stem cells as a potential Alzheimer’s therapeutic. The efficacy of the stem cells, which produce neuroprotective growth factors, will be tested in two mouse models of disease, followed by studies in nonhuman primates. The project is aimed at delivering a disease-modifying therapy targeting multiple disease mechanisms.

**A novel approach to inflammation.** There is a growing body of evidence across genetic,experimental, and clinical research pointing to a connection between inflammation and neurodegeneration. [One research team](https://projectreporter.nih.gov/project_info_description.cfm?aid=9525788&icde=44030592&ddparam=&ddvalue=&ddsub=&cr=2&csb=default&cs=ASC&pball=) is developing a novel anti-inflammatory therapeutic targeting the prostanoid receptor, EP2. This therapeutic approach, to be tested in a mouse model, was designed to alleviate inflammation-driven neurodegeneration while avoiding undesirable side effects typical for many anti-inflammatory drugs.

**Regulating glutamate for synaptic communications.** Glutamate, an importantneurotransmitter in the brain, plays a key role in learning and memory by helping to support synaptic plasticity. It is particularly involved in long-term potentiation, a form of plasticity maintained over time for signaling between neurons. Two newly funded studies will select and test compounds targeting glutamate for effective communication between neurons to help preserve cognition:

* [In one study,](https://projectreporter.nih.gov/project_info_description.cfm?aid=9519769&icde=44030776&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=) scientists will select a novel small molecule from among candidate compounds to increase expression of a glutamate transporter protein called EAAT2. Studies have shown that loss of the EAAT2 protein and function are common in Alzheimer’s disease and that the loss occurs early in the disease process. Previous work by this team in a mouse model was able to restore the function of EAAT2 through a novel small molecule that could penetrate the brain and improve cognitive function and synaptic integrity. The new project will move the research forward to selection of a specific drug candidate, through various phases of preclinical testing for safety and efficacy.
* [Another research group](https://projectreporter.nih.gov/project_info_description.cfm?aid=9594565&icde=44030966&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=) will try to halt disease development by inhibiting the activity of the mGluR5 glutamate receptor. With access to an exclusive chemical collection of

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mGluR5-directed compounds licensed from pharmaceutical companies, the scientists have identified a drug candidate which, in preliminary studies in Alzheimer’s model mice, helped recover synapse density, restore long-term potentiation, and return memory performance. As a next step, the team will identify a lead compound it will further develop for human trials.

**From Mice to Men and Women: Advancing Promising Therapeutic Candidates into Human Trials**

New challenges arise when a compound is ready to move from animal into human testing. Basic researchers may lack the resources or know- how to move promising compounds or other types of interventions into clinical trials. For drugs, biotechnology and pharmaceutical companies may be reluctant to invest in development because there are few clinically validated targets or strategies, there is a long track record of failure, and many nervous system disorders affect relatively small populations. NIH programs for supporting pilot and early-stage clinical trials, with drug discovery and development, seek to break those barriers. Among the innovative projects are:

**Novel anti-inflammatory Phase I trials.** NIH’s translational research portfolio for Alzheimer’sdisease has several promising anti-inflammatory therapeutics. Two research teams—based at the [University of Kentucky](https://projectreporter.nih.gov/project_info_description.cfm?aid=9673257&icde=44032263) and [Immunochem Therapeutics](https://projectreporter.nih.gov/project_info_description.cfm?aid=9621847&icde=42152260)—are conducting first -in-human Phase I clinical trials to test the safety and establish optimal dosing of MW151, a novel small molecule that targets dysregulated inflammation in the brain. This brain penetrant compound is aimed at suppressing proinflammatory cytokine overproduction, known to be a key contributor to synaptic dysfunction, neurodegeneration, and cognitive decline in Alzheimer’s and other neurodegenerative diseases. These studies follow on successful animal model research supported through NIA’s ADDP. The human trials are supported by the [NIH Small Business](https://sbir.nih.gov/) [funding initiative](https://sbir.nih.gov/) and [NIH’s early-stage clinical trials program for Alzheimer’s disease and](https://grants.nih.gov/grants/guide/pa-files/par-18-175.html) [related dementias.](https://grants.nih.gov/grants/guide/pa-files/par-18-175.html)

**Generating new neurons to stave off cognitive impairment.** Neurogenesis is at the heart of thebrain’s ability to recover from various types of injuries, a natural restorative capacity that is diminished in aging and in Alzheimer’s disease. In a small business effort, [researchers](https://projectreporter.nih.gov/project_info_description.cfm?aid=9590459&icde=42152260&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=) have developed a neurogenic compound, NNI-362, as a small molecule therapeutic candidate. The compound has been shown to stimulate neurogenesis in animal models and recently received a green light from the U.S. Food and Drug Administration to enter human trials. With continued support from NIA, the compound will be tested in healthy older volunteers for safety and to determine the optimal dose. This research is funded under a [program to support pilot clinical](https://grants.nih.gov/grants/guide/pa-files/PAR-16-365.html) [trials for age-related cognitive decline and across the Alzheimer’s disease spectrum.](https://grants.nih.gov/grants/guide/pa-files/PAR-16-365.html)

**Repurposing Medications Used to Treat Other Diseases for Dementia**

What we learn about disease mechanisms is not only relevant to the development of novel therapies, but also to discovering whether drugs that are on the market to treat other conditions can be used to treat Alzheimer’s disease and related dementias. Repurposing a drug

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has advantages over the development of new compounds and has been done successfully for a number of diseases and conditions.

**Investigating antiviral therapies.** Multiple lines of evidence have suggested a connectionbetween herpes virus and Alzheimer’s disease. In the first-ever trial to directly test whether an antiviral drug may be an effective treatment for Alzheimer’s disease, researchers supported by NIA’s early-stage clinical trial program will evaluate valacylovir, used for treating herpes virus infections, for its ability to slow cognitive decline and reduce amyloid accumulation in the brain. [This Phase II trial](https://projectreporter.nih.gov/project_info_description.cfm?aid=9565371&icde=42152260) will be conducted in people with mild Alzheimer’s disease who test positive for herpes simplex virus 1 or 2.

**Anti-seizure drug moves into Phase III testing.** Several studies have established a link betweenneural overactivity in the hippocampus and development of tau pathology in Alzheimer’s disease. In 2018, NIA’s late-stage clinical trials program supported launch of a pivotal Phase III trial to test the effectiveness of AGB101, a low-dose, once-a-day form of the generic drug levetiracetam to halt the progression of mild cognitive impairment due to Alzheimer’s disease. Higher doses of levetiracetam are being used to treat epilepsy. [The Phase III trial](https://projectreporter.nih.gov/project_info_description.cfm?aid=9642036&icde=44153471&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=) will include 830 participants randomly assigned to the therapy or a placebo for 78 weeks. During the trial and at its conclusion, their dementia status will be assessed. Through a public-private partnership, NIA is supporting a substudy of 160 participants, who will undergo tau positron emission tomography imaging to assess the effect of AGB101 on the spread of tau pathology.

**Making better bets for drug repurposing.** Drug repurposing for Alzheimer’s and relateddementias has proved to be quite challenging. To accelerate identification of drugs that can be repurposed for the treatment and prevention of Alzheimer’s disease and related dementias and to increase the odds of their success, NIH is trying a new approach. As we learn about the enormous complexity of pathology and comorbid conditions associated with these dementias, drug repurposing and the development of combination therapies must be preceded by data-driven, systems-based approaches to align possible disease mechanisms with potential drugs targeting those mechanisms.

In 2017, NIA launched [a new funding initiative](https://grants.nih.gov/grants/guide/pa-files/PAR-17-032.html) that invited applications from the scientific community to use such translational bioinformatics approaches to advance drug repurposing and combination therapy development for Alzheimer’s disease. Since then, NIA has supported 13 projects that bring together data scientists working in the fields of cancer, diabetes, and other complex diseases and Alzheimer’s disease researchers with expertise in biology, translational, and clinical research. These cross-disciplinary teams are using myriad computational approaches to mine and analyze publicly available data, from electronic medical health records to genomic data and data on all approved drugs. Based on this analytical dragnet, they are developing predictions about which existing drugs (for diabetes, cancer, irritable bowel syndrome, etc.) may be effective in slowing the progression of Alzheimer’s or addressing cognitive and behavioral symptoms. The research teams funded through this program also seek to identify combinations of approved drugs that can be used to treat Alzheimer’s more effectively and with less toxicity.

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In a separate translational bioinformatics project, a team from NIA’s Intramural Research Program is investigating whether several U.S. Food and Drug Administration-approved drugs prescribed for non-Alzheimer’s indications may also target the abnormal pathways involved in dementia and offer protection. They have started the DREAM—Drug Repurposing for Effective Alzheimer’s Medicines—Study and have nominated about 20 drugs as candidates. Next, the team will analyze “chemi-informatics” databases of known drugs and their targets to hone in on compounds aimed at abnormal metabolic pathways the team has identified. From these databases, the researchers can scan compounds in common use for non-Alzheimer’s conditions and test whether prior exposure to these drugs in older people protected against dementia. The researchers also have access to large prescription datasets representing more than 30 million individuals internationally, which provide information on both exposure to these drugs and subsequent diagnoses of Alzheimer’s. Their analyses should reveal drugs of promise, providing a strong rationale for targeted study in randomized clinical trials.

**Learning from failure.** Computational analyses of the data from failed clinical trials inAlzheimer’s can identify whether a drug that failed to show a positive effect for trial participants as a whole may have been effective for individual trial participants with certain genetic or biomarker characteristics. For example, one study looking at data from a previous, negative trial of a statin drug for its effect on Alzheimer’s found in an analysis of subgroups that the use of statins still may warrant further study, particularly for long-term statin users and people with the ApoE4 risk allele [(Geifman et al., 2017](https://www.ncbi.nlm.nih.gov/pubmed/28212683)).

**Joining Forces in the Fight Against Dementia**

The studies highlighted above illustrate NIH’s key role in translating basic research discoveries to the clinic. The output of these translational programs is the basis for follow-on, private-sector investment. For example, BPN14770, a novel inhibitor of the Phosphodiesterase 4D enzyme involved in learning and memory, is being developed as a treatment for cognitive deficits in early-stage Alzheimer’s disease. This therapeutic program was initiated by a biotech team at Tetra Discovery Partners, which developed the compound through the NIH [Blueprint](https://neuroscienceblueprint.nih.gov/neurotherapeutics/blueprint-neurotherapeutics-bpn-network) [Neurotherapeutics Network](https://neuroscienceblueprint.nih.gov/neurotherapeutics/blueprint-neurotherapeutics-bpn-network) and the NIA Small Business program through Phase I human testing. The [Phase I research](https://projectreporter.nih.gov/project_info_details.cfm?aid=9199688&icde=0) suggested a cognitive benefit in working memory in healthy older volunteers.

In December 2018, Tetra entered into a collaboration with Shionogi & Co., Ltd. for further clinical development and commercialization. The company in May 2019 announced the start of

1. Phase II trial, [PICASSO AD,](https://clinicaltrials.gov/ct2/show/NCT03817684) a 3-month randomized, double-blind, placebo-controlled trial that will be conducted at up to 60 sites in the United States, testing varying doses of the drug against placebo in people with a clinical diagnosis of early Alzheimer’s disease.

Learn more about research implementation milestones and progress in this area at [www.nia.nih.gov/research/milestones/focus-area/translational-clinical-research-pharmacological.](http://www.nia.nih.gov/research/milestones/focus-area/translational-clinical-research-pharmacological)

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**MANAGING HEALTH TO PREVENT AND TREAT DEMENTIA**

Beyond drugs designed to attack the mechanisms of Alzheimer’s and related dementias, managing overall health and well-being in a variety of ways may make a difference as well. Population and observational studies point to chronic conditions and to lifestyle, social, or behavioral factors that can harm or protect us when it comes to dementia. Among these factors are high blood pressure, heart disease, diabetes, and depression, as well as exercise (or



lack thereof), diet, and cognitive training. Of course, paying attention to some of these factors has proven to improve health with age in many ways. But can it also contribute directly to preventing or slowing down neurodegeneration?

With the infusion of additional funds in the past 5 years, the National Institutes of Health (NIH) is now able to more vigorously pursue a strong translational research agenda to develop and test both pharmaceutical and nondrug interventions. Today, approximately 200 trials are underway. More than 80 of them are nonpharmacological investigations, while another 60 are aimed at care and caregiving for people with dementia.

**Managing High Blood Pressure, Diabetes**

Across NIH, institutes and centers with missions to prevent and cure different diseases and conditions often join forces to pursue important scientific opportunities. Alzheimer’s disease and related dementias have long been a focus of collaboration among neuroscience institutes. In recent years, as interest has increased in the potential connection between, for example, heart disease and diabetes with dementia, there is a broader effort to learn more and build on each other’s research, with major trials being leveraged:

**A Benefit from Lowering Blood Pressure**

High blood pressure, or hypertension, is very common in people over age 50. It is a leading risk factor for heart disease, stroke, and kidney failure, and a growing body of research suggests that it may increase risk for dementia later in life. In 2019, secondary results from the Systolic Blood Pressure Intervention Trial–Memory and Cognition in Decreased Hypertension (SPRINT-MIND) were the first to show beneficial effects of intensive lowering of high blood pressure for reducing risk of mild cognitive impairment (MCI), a known precursor for dementia ([SPRINT-MIND Investigators et al., 2019](https://www.ncbi.nlm.nih.gov/pubmed/30688979)). The findings, however, did not show significantly reduced dementia, its primary outcome measure.

SPRINT-MIND was an integral aspect of the initial design for [SPRINT,](https://www.nhlbi.nih.gov/science/systolic-blood-pressure-intervention-trial-sprint-study) a randomized clinical trial that tested the effects of intensive blood pressure lowering on cardiovascular and renal disease

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in 9,300 participants who were 50 years and older and at high risk for cardiovascular disease. The trial showed that intensive blood pressure control (systolic blood pressure of less than 120 mmHg), compared to a standard target of less than 140 mmHg, reduced cardiovascular events and overall mortality. In August 2015, the SPRINT trial was stopped after 3.3 years of treatment when the major beneficial effects of intensive blood pressure management on mortality and cardiovascular disease became evident and warranted early publication of the results. Assessment for development of dementia and MCI continued for the full 5 years.

The NIH-supported [SPRINT Alzheimer’s, Seniors, and Kidney (SPRINT-ASK) Study,](https://projectreporter.nih.gov/project_info_description.cfm?aid=9288712&icde=36839619&ddparam=&ddvalue=&ddsub=&cr=10&csb=default&cs=ASC&pball) which tracked SPRINT -MIND participants 1 year later for effects on cognitive outcomes and measures of kidney safety, will obtain longer-term data. Through SPRINT-ASK, the participants were assessed for the full 5 years for development of dementia and MCI. While the primary results for SPRINT -MIND found no statistically significant difference between standard and intensive treatment in the proportion of participants who were diagnosed with dementia, they did show fewer cases of dementia than expected. The researchers pointed out that because the study intervention was stopped and participants were treated for a shorter time than originally planned, it was difficult to determine the role of intensive blood pressure control on dementia.

**Weight Loss for Diabetes in Reducing Risk of Alzheimer’s**

The Action for Health in Diabetes (Look AHEAD) study, sponsored by NIH, is a long-term randomized clinical trial of lifestyle interventions in obese and overweight people with type 2 diabetes. To find out more about the definitive impact of these interventions on cognitive impairment and dementia, NIH in 2018 funded a follow-up assessment, the Action for Health in Diabetes, Alzheimer’s Disease, and Related Dementias Study (Look AHEAD-MIND). Researchers will examine whether interventions designed to induce and sustain long-term weight loss lead to cognitive benefit or harm, determining the role that baseline weight may play. They will repeat the cognitive assessments conducted in the original study in 3,500 participants and compare the results with data from the well-characterized Look-AHEAD cohort. The team will also develop public-use databases to promote research on cognitive health in older people who are overweight or obese and have type 2 diabetes, an understudied population.

**Taking Direct Aim at Dementia with Lifestyle, Cognitive Training**

A recent clinical trial ([Rovner et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/30208380)) provides one example of how an innovative approach to lifestyle and behavioral interventions for preventing cognitive decline can succeed. The study found that older African Americans with MCI who got help setting goals to be more socially, physically, or cognitively active had slower memory decline than those who did not receive such help. While studies have suggested that a more active lifestyle may help prevent cognitive decline, African Americans are significantly underrepresented in those efforts.

In this study, African Americans with MCI (average age, 76) were randomly assigned to one of two interventions. One group received “behavioral activation,” in which community health workers helped them choose goals to be more active, then develop step-by-step action plans. The control group received “supportive therapy,” conversations with community health workers that did not involve setting goals. After 2 years, the behavioral-activation group

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participated in significantly more cognitive activities, the researchers found, even though there were no differences in physical or social activity levels. Both groups had memory decline, but the behavioral-activation group declined by 1.2 percent, compared with 9.3 percent for the control group. The study provides evidence that a behavioral intervention can slow memory decline in older African Americans at risk for dementia. It is possible that planning a more active lifestyle can help reduce the disparity in dementia risk between African Americans and whites.

This study also shows how the scientific community is following up on evidence that links risk of cognitive health or dementia, as well as ameliorating that risk, to everyday health practices and policies. A robust and creative research program seeks to find out which interventions—at which dose, at what age, and for which groups of people by gender and race—will be most effective in preventing or slowing cognitive decline and dementia. Ongoing projects are either fully or partly funded by NIH:

**A pilot multi-domain study.** Investigators in a new[Multi-Domain Alzheimer’s Risk Reduction](https://projectreporter.nih.gov/project_info_description.cfm?aid=9564038&icde=42152866)[Study](https://projectreporter.nih.gov/project_info_description.cfm?aid=9564038&icde=42152866) (MARRS) will first undertake an effort to help determine whether risk reduction can slow cognitive decline or prevent Alzheimer’s in higher-risk people age 70 and older. The pilot study will randomize higher-risk people within a single health care delivery site to receive either an intervention designed to reduce their Alzheimer’s risk factors or health education.

In the MARRS intervention group, researchers will work with participants to develop a personalized action plan to reduce risks, including cardiovascular risk management; smoking cessation; physical, mental, and social activity; healthy diet; improved sleep quality; and medication management. The study will compare the 2-year rate of decline in the intervention group and the control group. Researchers will also compare changes in Alzheimer’s modifiable risk factors and gather preliminary data on the effects of the intervention versus health education on other health-related outcomes. The team will also compare strategies for identifying higher-risk patients for their own and future studies.

**Exercise to prevent dementia.** In some short-term clinical trials, exercise is associated withreduced risk for cognitive decline. The [Exercise in Adults with Mild Memory Problems Study](https://www.nia.nih.gov/alzheimers/clinical-trials/exercise-adults-mild-memory-problems-exert) (EXERT) is supported by NIH to test the direct effects of physical exercise on cognition, functional status, brain atrophy, blood flow, and cerebrospinal fluid biomarkers of Alzheimer's disease in adults with a mild memory impairment. Half of the participants are participating in a stretching-balance-range of motion exercise program, while the other half are participating in a moderate- to high-intensity aerobic training program. Participants exercise at participating local YMCAs under the partial supervision of a personal trainer for the first year, then complete their assigned exercise program unsupervised for the final 6 months.

**Cognitive training to prevent Alzheimer’s.** NIH is interested in continuing research on cognitivetraining as one way to maintain cognitive function with age. That effort continues with funding in 2018 of the proposed [Preventing Alzheimer’s Disease with Cognitive Training (PACT) Trial,](https://projectreporter.nih.gov/project_info_description.cfm?aid=9784931&icde=42893624) designed to determine the efficacy of computerized cognitive training to reduce the incidence of MCI and dementia. Findings from the NIH-supported Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial demonstrated that computerized speed-of-processing training (SPT) improved cognition, and that benefits transferred to instrumental

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activities of daily living. An unanswered question is whether SPT can decrease incidence of MCI or dementia, as the ACTIVE trial and follow-up did not include clinical measures of dementia.

The 7-year PACT Trial will try to answer those questions. A large population of cognitively normal older adults will be randomized to SPT or an active control group receiving cognitive stimulation (computer games). Progression to MCI or dementia will be clinically assessed over time. Genetic data and information from amyloid positron emission tomography scans will also be part of the study, and the team will try to quantify the effects of SPT on subsequent health care costs and utilization.

**Strategic training for attention, working memory.** Developing and refining new interventionstrategies for Alzheimer’s disease remains a focus for NIA. [This award](https://projectreporter.nih.gov/project_info_description.cfm?aid=9781086&icde=42893624) will allow researchers to collect additional preliminary data on the effects of a specially designed, simulated computer game designed to enhance the ability of at-risk older adults to respond to the kinds of unpredictable events that present significant challenges in daily life. The team anticipates that this kind of training could also improve cognition in older adults and have a positive impact on brain structures that often decline with aging.

Learn more about research implementation milestones and progress in this area at [www.nia.nih.gov/research/milestones/focus-area/translational-clinical-research-non-pharmacological.](http://www.nia.nih.gov/research/milestones/focus-area/translational-clinical-research-non-pharmacological)

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**MAKING CLINICAL TRIALS MORE EFFICIENT AND INCLUSIVE**

Basic biological and translational findings must move out of the laboratory and into therapies that make a difference for people with Alzheimer’s disease and related dementias. Determining whether an intervention is promising requires casting a wide net. We want to slow progression of disease and relieve behavioral symptoms in people who are diagnosed with mild cognitive impairment, Alzheimer’s disease, or an Alzheimer’s-related dementia. At the same time, we seek to prevent dementia in at-risk people without symptoms and healthy older adults. Trials also look at various approaches to caregiving to



determine which ones might work best for both caregivers and care recipients in informal and formal care settings. Optimizing medical care for dementia patients involves interventions at the level of single practitioners as well as large health care systems.

The National Institutes of Health (NIH) currently supports about 200 clinical trials on Alzheimer’s and related dementias, from pilot studies to large-scale trials, on a wide range of interventions for diagnosis, treatment, prevention, care, and caregiving. NIH has taken significant steps to modernize and speed up trials to test potential interventions earlier in the disease continuum, examine how therapies can be delivered pragmatically in real-world settings, and foster new partnerships with organizations and individuals in the design and operation of trials. Ensuring greater racial, ethnic, gender, and socioeconomic diversity among participants and researchers in clinical trial design, operation, and participation is central to these efforts. Inclusion is key to understanding and addressing disparities in the incidence and prevalence of disease and identifying unique care needs for diverse populations.

Ongoing initiatives are being updated and new projects added to support more efficient, practical, and inclusive trials.

**Intensified Efforts to Diversify Clinical Trials Participation**

The advances made to date in understanding Alzheimer’s disease and related dementias would not be possible without the participation of tens of thousands of people in clinical trials and studies. We are deeply grateful for their commitment, cooperation, and willingness to be part of research.

But the need for more people to engage as participants has only grown with the recent increases in funding, with a particular need to engage underrepresented communities. Today’s participants in Alzheimer’s and related dementias research are mostly white, non- Hispanic, well-educated, heterosexual, and married, with a spouse study partner. However, studies point

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to significant differences between rates of Alzheimer’s disease in specific populations, for whom factors like diet, culture, genetic influences, geography, and medical conditions may play a role. Broadly diverse participation in both observational and clinical studies must be achieved. It will help us to better define and address racial, ethnic, gender, and other differences so that interventions can be better tailored to communities and individuals.

In 2018 and early 2019, NIH sought to provide research support and resources in new ways, described below.

**NIA Introduces National Strategy for Diverse Participation in Research**

In October 2018, NIA released a national strategy focused on increasing diversity in clinical studies, titled [Together We Make the Difference: National Strategy for Recruitment and](https://www.nia.nih.gov/research/recruitment-strategy) [Participation in Alzheimer’s and Related Dementias Clinical Research.](https://www.nia.nih.gov/research/recruitment-strategy) The National Strategy was the culmination of more than 2 years of dedicated work to outline practical, proactive approaches for study sites to engage more and more diverse volunteers. It was developed with facilitation by the Alzheimer’s Association and the expertise and insights of a collaborative of government, private, academic, and industry stakeholders, including individuals, caregivers, and study participants. The strategy focuses on four overarching themes:

* Increase awareness and engagement at a broad, national level
* Build and improve capacity and infrastructure at the study site level
* Engage local communities and support participants
* Develop an applied science of recruitment

**A New Recruitment Resource for Investigators**

In 2019, NIA launched the [Alzheimer’s and Dementia Outreach, Recruitment, and Engagement](https://www.nia.nih.gov/research/alzheimers-dementia-outreach-recruitment-engagement-resources) [(ADORE) Resources.](https://www.nia.nih.gov/research/alzheimers-dementia-outreach-recruitment-engagement-resources) This new repository offers the research community resources to support recruitment and retention of volunteers into clinical trials and studies. The National Recruitment Strategy for participation in dementia studies called for sharing approaches in recruitment and participation that have proven successful, so that study leaders and stakeholders can see and adapt what has worked for other sites and communities. The repository is curated and updated by NIA with the help of its Alzheimer’s Disease Research Centers and other sources. It contains more than 300 resources about education, awareness, and recruitment. It provides information on working with participants during their time in a study, explaining study procedures and results, and managing research operations.

Learn more about research implementation milestones and progress in this area at [www.nia.nih.gov/research/milestones/focus-area/trial-innovation.](http://www.nia.nih.gov/research/milestones/focus-area/trial-innovation)

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**“Why I Participate in Alzheimer’s Research” Videos**

To help researchers address the burgeoning demand for clinical research volunteers, NIA produced a series of recruitment videos, [Why I Participate in Alzheimer’s Research.](https://www.nia.nih.gov/research/alzheimers-dementia-outreach-recruitment-engagement-resources/why-i-participate-alzheimers) The testimonial-style videos profile the experiences of four participants in Alzheimer’s disease clinical trials, who discuss what motivates them and how research staff support them. Each video features a specific type of participant—African Americans, caregivers, healthy volunteers, and people with a family history of dementia. [The videos are available on the](https://www.nia.nih.gov/alzheimers/alzheimers-scientific-images-and-video) [NIA website.](https://www.nia.nih.gov/alzheimers/alzheimers-scientific-images-and-video) We encourage researchers, community organizations, participants, and anyone interested in helping spread the word about participating in research to download and share them. As one participant says, “I’m just one drop of water in a bucket. But it takes thousands of drops to win the fight against dementia.”

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**RESEARCH ON CARE AND CAREGIVER SUPPORT**

Care and support by family, friends, and health care providers are central to the well-being of people with Alzheimer’s and related dementias. This is particularly true as an individual’s cognitive decline progresses over time. In communities across America, informal and formal caregivers provide varying levels of help, sometimes 24/7. Primary care clinicians and specialists attend to the medical needs of people with cognitive decline, who are among the most complex patients to treat due to multiple comorbidities and special challenges.



The National Institutes of Health (NIH) has supported research on care for many years. Studies continue to focus on optimizing long-term care and support services and informing how clinical care can be best delivered to people living with dementia. Research findings in this area are being examined to see how they might effectively be translated into practice. At the same time, NIH-supported researchers are pursuing completely new avenues of study—for example, testing how state- of-the-art technologies might be used in homes or by health care systems to serve people with Alzheimer’s and their families.

Major efforts in these areas include:

**Supporting crucial evidence reviews.** The National Institute on Aging (NIA) in 2018commissioned a [two-part, evidence-based review](http://www.nationalacademies.org/hmd/Activities/Aging/CareInterventionsforIndividualswithDementiaandTheirCaregivers.aspx) to help identify demonstrated strategies, interventions, and services for people living with dementia and their caregivers. This endeavor is being conducted by the Agency for Healthcare Research and Quality and the National Academies of Sciences, Engineering, and Medicine. Today’s care programs are offered based on varying levels of evidence, and important gaps remain in our understanding of what works best and for whom. This review will take stock of current knowledge and evaluate which care interventions are ready for dissemination and scaling up. The public will be asked to comment at various points in the review and recommendations process.

**Dementia Care Summit helps set research agenda.** A groundbreaking[National Research](https://aspe.hhs.gov/national-research-summit-care-services-and-supports-persons-dementia-and-their-caregivers)[Summit on Care, Services, and Supports for Persons with Dementia and Their Caregivers](https://aspe.hhs.gov/national-research-summit-care-services-and-supports-persons-dementia-and-their-caregivers) took place in October 2017. Hosted by NIH and led by the Office of the Assistant Secretary for Planning and Evaluation of the U.S. Department of Health and Human Services and the Secretary’s Advisory Council on Alzheimer’s Research, Care, and Services, the summit and the months-long outreach leading up it galvanized a deep and ongoing national conversation about dementia care and services.

The [summit community’s final report,](https://aspe.hhs.gov/national-research-summit-care-services-and-supports-persons-dementia-and-their-caregivers-recommendations) issued in April 2018, distilled 694 recommendations into 58 main items in 12 categories, ranging from research methods and models for dementia care to engagement of people living with dementia and their caregivers to help guide and

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participate in research. Stimulated by the summit discussions and recommendations, NIA continues to encourage and fund behavioral and social science research in dementia care and caregiving. Most recently, two notices were posted: Behavioral and Social Science Priority Areas in Dementia Care Research: Programs and Services for Persons with Dementia [(NOT-AG-18-056](https://grants.nih.gov/grants/guide/notice-files/NOT-AG-18-056.html)) and Behavioral and Social Science Priority Areas in Dementia Caregiver Research [(NOT-AG-18-057](https://grants.nih.gov/grants/guide/notice-files/NOT-AG-18-057.html)).

Preparation for the next Dementia Care and Services Summit, to be held in March 2020, is underway, with plans to hold subsequent care summits every 3 years to assess progress and update research directions.

**Emphasizing care research at new centers.** NIH in 2018 expanded efforts through several of itsCenter programs to focus on dementia care. The new Edward R. Roybal Centers for Translational Research on Dementia Care Provider Support are being planned, with the goal of developing behavioral interventions that improve the health, well-being, and capacity of systems or people who provide care for people with Alzheimer’s disease and related dementias. Recently, NIH expanded its Resource Centers for Minority Aging Research program to include a subset of Centers that focus on the behavioral and social science research of Alzheimer’s disease and related dementias. Topics include the epidemiology and prevention of these diseases, as well as the formal and informal care challenges of people with Alzheimer’s and related dementias and their caregivers.

**High-priority behavioral and social research networks.** A funding opportunity announcementreleased in 2018 invited applications to establish research networks that would foster the development of priority areas of behavioral and social research on Alzheimer’s disease and related dementias. These networks would focus on topics such as disparities in quality and access to dementia care; the effectiveness of models and programs of nonresidential and residential care for people with dementia; the impact of a dementia diagnosis on individuals, families, and caregivers; and the coordination of international studies conducting the Harmonized Cognitive Assessment Protocol.

**Expanding Research on Care**

Thanks to increased Federal funding for Alzheimer’s and related dementias, NIH wasted no time in addressing critical research needs highlighted by the 2017 Dementia Care and Services Summit and in other summits, workshops, and venues. New funding opportunities highlighting specific areas of interest have been announced, with projects expeditiously reviewed and funded. In a creative approach to spark research in care and caregiving, NIA is sponsoring a prize competition for the development of technology- based applications to improve dementia care coordination and care navigation (see below). At the same time, NIH remains interested in original proposals submitted independently by investigators.

New or expanded studies supported in 2018 and 2019 will investigate:

**Dementia care pragmatic trials.** NIA in 2018 announced a funding opportunity for projectsestablishing a [Health Care Systems Research Collaboratory](https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-19-009.html) for Alzheimer’s disease and related

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dementias. The effort is directed at improving the quality of clinical and long-term care for people with dementia and their caregivers, who face a lack of continuity of care, late diagnoses of dementia, problems in coordination of care, and burdensome transitions between care settings for people with late-stage dementia.

**National Study of Caregiving (NSOC)**. NSOC and its parent study, the[National Health and Aging](https://projectreporter.nih.gov/project_info_history.cfm?aid=9530573&icde=42937084)[Trends Study,](https://projectreporter.nih.gov/project_info_history.cfm?aid=9530573&icde=42937084) with continued NIA support in fiscal year 2018, are the only national, population-based surveys that provide insights on a well- characterized population of older adults and the informal caregivers who assist them in health and functioning. The database is being made widely available to the research community in easy-to-use longitudinal files. The data allow assessment of care needs and challenges, including comparisons between caregivers of older adults with and without Alzheimer’s disease and related dementias.

**The future availability of family care for Alzheimer’s.** As the NSOC looks at current trends andissues in caregiving, a new NIA-supported initiative attempts to project [future supply and](https://projectreporter.nih.gov/project_info_description.cfm?aid=9469467&icde=43126422) [demand for U.S. family care for Alzheimer’s disease and related dementias.](https://projectreporter.nih.gov/project_info_description.cfm?aid=9469467&icde=43126422) For the first time, data from the nationally representative Health and Retirement Study will be linked to a model of kinship networks to project future availability of family care for dementia and the burden of care to individual family members. The work should provide a better understanding of how current sociodemographic trends—smaller family sizes, increased longevity, and changes in marital patterns—could affect family care for dementia and the burden of care on individual caregivers over the next 50 years, as the Nation plans for future needs.

1. **tablet-based nonpharmacological intervention.** [This study](https://projectreporter.nih.gov/project_info_description.cfm?aid=9747540&icde=43126911)willexamine an interventionprogram, delivered through state-of-the art computer tablet technology, in a group of ethnically/culturally diverse people with Alzheimer’s disease and their family caregivers. By using the technology to augment interventions underway for caregivers and people with dementia, researchers will examine whether the lives of family caregivers and their ability to provide care can be improved, if the well-being of people with Alzheimer’s can be improved, and if disparities in access to services and support can be reduced.

**Breast cancer screening in women with Alzheimer’s and related dementias.** As women age,their risk increases for developing both Alzheimer’s disease and related dementias and breast cancer. Women with their doctors determine how to proceed with breast cancer screening as they age. But with dementia, a woman’s ability to participate in her medical decision making can be significantly impaired, and many dementia caregivers find themselves making decisions for their loved ones they may not have anticipated. They have reported that their new role can be difficult, as the burdens and risks of having a mammogram and undergoing follow-up tests and treatment are significantly greater for older women with Alzheimer’s. The [Decisions About](https://projectreporter.nih.gov/project_info_description.cfm?aid=9567449&icde=43127026) [Cancer Screening in Alzheimer’s Disease](https://projectreporter.nih.gov/project_info_description.cfm?aid=9567449&icde=43127026) study will look at whether an evidence-based decision aid about mammography screening can improve the quality of caregivers’ medical decision making about mammograms for older women.

**Using music to reduce behavioral and psychological symptoms in nursing home residents.**

Research on [music and its impact on people with Alzheimer’s disease](https://projectreporter.nih.gov/project_info_description.cfm?aid=9775655&icde=43637992) is a particular area of

interest. In a clinical trial in four nursing homes, NIH-funded researchers will see if a specific

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music and memory program can be standardized and its impact measured for improving behavioral and psychological symptoms. This type of nonpharmacological approach might be able to reduce symptoms and help avoid use of some antipsychotic medications, which carry significant risks and are not advised for use in older people with dementia.

**iCare-AD/ADRD: A Eureka Prize Competition**

Navigating the complex U.S. health care system can be challenging for people with dementia and their caregivers. The course of care is uncertain, of unknown duration, takes place across different care settings, and involves many different types of care providers and interventions. Models of dementia care have evolved in recent years, with the potential to improve outcomes, such as reducing behavioral and psychological symptoms of dementia and lowering health care costs, by decreasing emergency department visits, inpatient hospitalizations, and some readmissions. But there are barriers to adoption, including workforce limitations, the cost of practice redesign, and limited uptake by insurers and health systems.

The Improving Care for People with Alzheimer’s Disease and Related Dementias Using Technology (iCare-AD/ADRD) Challenge is a Eureka prize competition seeking to use technology to improve coordination and/or navigation of dementia care. NIA, which is sponsoring the prize competition, plans to spur and reward the development of solutions for a technology-based application that can foster connections between relevant stakeholders to use technology or to develop new technology applications. The application can be aimed at people with dementia and their caregivers; health care providers; health care service organizations; and/or community, local, or state governments. NIA is not only seeking ideas, it is also asking entrants to demonstrate that the product would work and to discuss how they would promote its use.

Up to three winners may be selected to claim the total prize purse. The first place winner will receive up to $250,000; second place, up to $100,000; and third place, up to $50,000. The deadline for applications was June 30, and the review of submissions is underway, with the goal of announcing the winning applications in fall 2019.

**Research Advances in Dementia Care and Caregiving**

Caregiving can be deeply rewarding. But it also comes with physical, emotional, and financial demands that intensify with advancing disease. Family caregivers are at risk of disrupted sleep, anxiety, depression, and immune system effects, according to studies. In addition, when caregivers turn to more formal care options, costs can be significant, often unsupported by insurance, and how well that care is managed can affect the health and well-being of both the person receiving care and the caregiver.

Recently reported research findings provide insights into ways that care might be made easier or more efficient for caregivers and for people with dementia, as well as clinicians and health

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care systems. Advances reported over the last year show progress in new approaches, from the advent of simple paper-and-pencil checklists enhancing doctor visits to newer video technologies supporting patient-centered care:

**Use of video decision support tool.** Researchers [(Mitchell et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/29868778) ) conducting the Advance Care Planning trial looked at whether a 12-minute “decision support” video might help establish care preferences. The effects of the video—focused on do-not-hospitalize directives, burdensome treatments, and goals of care—were evaluated for 402 nursing home residents with advanced dementia and their proxies in 64 nursing homes. Results were mixed. There was no difference between the video intervention and a control group on the do-not-hospitalize directives and other preferences, but the study did find that the intervention helped align goals with care in specific areas. For example, residents in the intervention facilities whose proxies preferred comfort care were more likely to have do -not-hospitalize and no-tube-feeding directives compared with those in facilities without the intervention.

**Optimizing clinical, primary care.** Most medical care for people with dementia is provided byprimary care physicians in the community. But time and reimbursement issues, some doctors’ lack of experience with cognitive impairment and appropriate resources, and challenges associated with the presence of family members or caregivers, can hinder the effectiveness and efficiency of an office visit. In the SAME Page Trial, investigators ([Wolff et al., 2018](https://www.ncbi.nlm.nih.gov/pubmed/30022409)) tested a self-administered, agenda-setting checklist. The checklist, which could be completed in the doctor’s office waiting room, was designed to establish expectations and set priorities for the visit. Data from the lists showed that for people with dementia, their priorities for visits tended to focus on memory and mood issues, while caregivers were interested in safety and behavior changes. Tuning into the list of concerns from people with dementia, the researchers found, resulted in significantly more patient-centered communications in visits using the tool. The researchers concluded that patient-family agenda setting may improve communication during primary care visits for people with cognitive impairment.

**Use of health care services in older adults with undiagnosed dementia.** How can the medicalcommunity and health care systems better respond to dementia patients and their caregivers? Scientists ([Lee et al., 2018](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5756157/)) in one study looked at the experience of people who developed dementia in the Adult Changes in Thought study, a prospective cohort study of older adults. An examination of electronic health data and use of health care services for the 2 years prior to a diagnosis of dementia found that people who were undiagnosed during that period were an intermediate group, between people with diagnosed dementia (having the most health care needs) and no dementia (with the least health care needs). Individuals with undiagnosed dementia had a more difficult time remembering medical appointments and had more emergency department visits and hospitalizations than those without dementia, but less than those with dementia. The findings suggest that identifying undiagnosed individuals may allow for support services to remind them and caregivers about appointments, reducing “no shows” and leading to fewer emergency department visits and hospitalizations.

Learn more about research implementation milestones and progress in this area at [www.nia.nih.gov/research/milestones/focus-area/care-caregiver-support.](http://www.nia.nih.gov/research/milestones/focus-area/care-caregiver-support)

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**The Path Forward**

Increased Federal investment as well as expanded collaborations among scientists, patients, caregivers, and advocates have enabled significant advances in Alzheimer’s and related dementias research. Still, in the years to come, these diseases will continue to challenge far too many within our Nation and beyond—individuals and society as a whole—from access to better diagnostics and treatments to care costs. For those already living with AD/ADRD, improved care and services are crucial endeavors that cannot be met soon enough.

As described in the earlier pages of this report and as outlined in our [Research Implementation](https://www.nia.nih.gov/research/milestones) [Milestones](https://www.nia.nih.gov/research/milestones) research framework, NIH support has led to substantial progress and significant gains in understanding the complexities of AD/ADRD. Expanded Federal support will enable continued efforts to:

* Better understand risk and protective factors in individuals and across populations
* Conduct basic science studies in genetics and disease mechanisms
* Develop biomarkers to detect and diagnose disease and treatments
* Discover, develop, and test promising therapies
* Develop comprehensive models of care for people living with dementia
* Leverage emerging digital technologies and “big data” to improve discoveries
* Make clinical trials more efficient, practical, and inclusive

NIH looks forward to supporting more AD/ADRD research to advance understanding of how to better reduce risk, delay onset when it appears inevitable, and effectively treat these conditions when they occur. Together, we must continue to seek manifold solutions to the multiple causes and effects of these devastating diseases.

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