ALZHEIMER'S DISEASE-RELATED DEMENTIAS SUMMIT 2025

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ADRD Summit 2025 Report

to the National Advisory Neurological Disorders and Stroke Council

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Abstract

This document reports to the National Advisory Neurological Disorders and Stroke (NANDS) Council the results of the Alzheimer's Disease-Related Dementias (ADRD) Summit 2025 that was held virtually on April 29, April 30, and June 2, 2025. The Summit addresses research priorities for ADRD and complements the National Institute on Aging's (NIA) Alzheimer's Disease (AD) Research Summits[1] and National Research Summit on Care, Services, and Supports for Persons with Dementia and Their Care Partners/Caregivers[2]. The National Institute of Neurological Disorders and Stroke (NINDS), in collaboration with the NIA, leads triennial ADRD Summits. The ADRD Summit 2025 follows the ADRD Conference 2013[3], and ADRD Summits held in 2016[4], 2019[5] and 2022[6]. Together, these summits are coordinated planning efforts that respond to the National Plan to Address Alzheimer's Disease ("National Plan")[7] released in 2012 and updated annually. The Summits set national research recommendations with timelines that reflect critical scientific priorities for research on AD and ADRD (AD/ADRD). During each ADRD Summit planning process, the established prioritized recommendations are updated, and developed further, under the leadership of the ADRD Summit Steering Committee, which includes a Working Group of the NANDS Council. The Committee solicits input from nationally and internationally recognized dementia-science experts, as well as interested parties from the public and private organizations. The resulting recommendations guide ADRD research for the next several years. This report, if approved by the NANDS Council, will be delivered to the Department of Health and Human Services (DHHS) National Alzheimer's Project Act (NAPA)[8] Council. The NAPA Council[9] will then consider including the ADRD Summit 2025 recommendations in the next annual update of the National Plan, thus refining, revising, and adding to the previously included ADRD recommendations. The research recommendations reported herein will help guide National Institutes of Health (NIH) investments in ADRD research by informing future AD/ADRD Bypass Budgets[10], the annual professional judgment budget that NIH prepares and submits to the President for review and transmittal to Congress each year.

[1] https://www.nia.nih.gov/2024-alzheimers-summit

[2] https://www.nia.nih.gov/2023-dementia-care-summit

[3] https://www.ninds.nih.gov/sites/default/files/migrate-documents/ADRD_2013_Report-and-Memorandum_508comp_0.pdf

[4] https://www.ninds.nih.gov/news-events/events-proceedings/events/alzheimers-disease-related-dementias-summit-2016

[5] https://www.ninds.nih.gov/news-events/events/alzheimers-disease-related-dementias-summit-2019

[6] https://www.ninds.nih.gov/news-events/events/adrd-summit-2022

[7] https://aspe.hhs.gov/collaborations-committees-advisory-groups/napa/napa-documents/napa-national-plan

[8] https://www.congress.gov/bill/111th-congress/senate-bill/3036

[9] https://aspe.hhs.gov/collaborations-committees-advisory-groups/napa/napa-advisory-council

[10] https://www.nia.nih.gov/about/professional-judgment-budget-proposal

Introduction

Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) represent one of the most pressing public health challenges of our time, affecting millions of individuals across all communities, and carrying a devastating personal, societal, and economic toll. Over 57 million people worldwide live with dementia, including more than 7 million Americans. The burden is growing rapidly, particularly among the oldest and most underserved populations, and the economic costs—already in the hundreds of billions—are expected to rise steeply in coming decades.

The National Alzheimer's Project Act (NAPA), enacted in 2011 and reauthorized in 2024 in the NAPA Reauthorization Act (S. 133 / H.R. 619)[11], established a landmark framework to accelerate progress in addressing this crisis. First released in 2012 and updated annually, the National Plan to Address Alzheimer's Disease[12] ("National Plan") is the federal strategy to overcome AD/ADRD launched by NAPA that coordinates and integrates federal and non-federal (private and state-level) activities, including through research, clinical care, and long-term services and support. The first and most ambitious goal of the National Plan—recently extended beyond its original 2025 target—is to prevent and effectively treat AD/ADRD.

To help achieve Goal 1, and as a federal action specified in the National Plan, summits are held regularly to set and refine AD/ADRD research priorities. At the National Institutes of Health (NIH), the National Institute on Aging (NIA) leads the NIH response to the National Plan, and the Alzheimer's Disease Research Summits and National Research Summits on Care, Services, and Supports. The National Institute of Neurological Disorders and Stroke (NINDS), in close collaboration with NIA, leads overall at NIH for ADRD research and the ADRD Research Summits. The ADRD Research Summits are held every three years and play a critical role in updating national research priorities that inform policy, drive investment, and guide scientific efforts across this research ecosystem. The triennial ADRD Summits began in 2013 and have served as a cornerstone for shaping the U.S. research agenda on frontotemporal dementia (FTD), Lewy body dementia (LBD), vascular contributions to cognitive impairment and dementia (VCID), and multiple etiology dementia (MED). The ADRD field has seen transformative advances across prevention, diagnosis, treatment, and care research since the 2013 Summit, with groundbreaking advances in the last three years. Preventive strategies—based on decades of epidemiologic and intervention research—have matured, with strong evidence for modifiable risk factor reduction. Blood-based and imaging biomarkers have reached new heights in diagnostic utility and accessibility, and new clinical pathways are addressing gaps around diagnosis in primary care. Disease-modifying therapies have emerged—including amyloid-β (Aβ)-targeting monoclonal antibodies—marking a historic milestone, despite their modest efficacy and challenges around eligibility and safety. On the horizon are promising therapies targeting tau, neuroinflammation, and genetic drivers, laying the foundation for precision therapeutics. Meanwhile, innovations in care delivery—such as the Centers for Medicare & Medicaid Services GUIDE model—signal a growing commitment to support individuals and families living with dementia across the continuum of care.

Despite this remarkable progress, a profound translational gap remains. Many individuals at risk for or living with ADRD—particularly those from underserved communities—are not yet benefiting from these advances. A core theme of the 2025 ADRD Summit was ensuring that the breakthroughs in science lead to tangible outcomes for all. The Summit identified critical research priorities, including: advancing discovery and implementation science for multiple etiology dementias (MED), including those involving TDP-43 pathology in common dementia and post-TBI AD/ADRD; developing robust models and biomarkers for mixed pathologies; accelerating therapeutic development across mechanisms including tau, inflammation, and vascular pathways; improving representativeness and equity in research participation and outcomes; and understanding how the exposome—

[11] https://www.congress.gov/bill/118th-congress/house-bill/619

[12] https://aspe.hhs.gov/collaborations-committees-advisory-groups/napa/napa-documents/napa-national-plan

the cumulative environmental exposures across the life course—shapes ADRD risk. These priorities emphasize the need to integrate basic science, clinical trials, health equity, and public health perspectives to create a truly impactful and inclusive research strategy.

Planning and Execution

The ADRD Summit 2025 planning followed successful strategies established in previous ADRD Summits (2013, 2016, 2019, and 2022). Building on the effective virtual format of the 2022 ADRD Summit, the 2025 Summit was held virtually and aimed to prioritize broad engagement by leveraging interactive features in the open microphone sessions and virtual "raise hand" participation. This approach enabled live discussion between the speakers and attendees, while written questions were submitted via email. The Summit was livestreamed and recorded for archival purposes and future viewing on NIH Videocast (links below under "Summit"). There were 230 minutes total of open microphone time across sessions, ensuring transparency and robust input. In keeping with these goals, during the dedicated open microphone time, attendees were asked to raise their virtual hand to be brought onto the virtual stage live with their camera and microphone on to address the speakers and panels directly.

The Summit planning process included regular pre-summit, summit, and post-summit virtual calls to update and further develop draft prioritized research recommendations. These recommendations were presented at the Summit for public input, which informed final deliverables found below under ADRD Summit 2025 Prioritized Recommendations.

The goals of the ADRD Summit 2025 were to:

1) Review and assess progress on research recommendations developed by the ADRD Summits in 2013, 2016, 2019, and 2022.
2) Refine and develop new recommendations based on recent scientific advances.
3) Solicit input from broad range of people interested personally and/or professionally in ADRD.
4) Update priorities and timelines for addressing ADRD.

The 2025 ADRD Summit convened a broad cross-sector representation of parties interested in a "bottom-up approach" to collaboratively assess and manage ADRD research, helping to guide, oversee and coordinate the direction and priorities for ADRD. Individuals with lived AD/ADRD experience were invited to participate in each Summit session subcommittee, spanning pre-Summit, Summit, and post-Summit activities.

Recommendations and National Impact. Upon approval by the NINDS and NAPA Advisory Councils, both revised and new recommendations in this report will be included in the National Plan and inform future AD/ADRD bypass budgets. The AD Summit, ADRD Summit, and the National Research Summit on Care, Services, and Supports for Persons with Dementia and their Caregivers are integral to the NIH response to NAPA. These planning efforts generate recommendations and milestones for the US and international research communities. At the NIH, the recommendations and milestones inform development of the annual NIH AD/ADRD bypass budget proposal[13] mandated in the Consolidated and Further Continuing Appropriations Act of 2015 and reauthorized in 2024 in the Alzheimer's Accountability and Investment Act (S. 134 / H.R. 620)[14]. The annual bypass budget estimates the additional funds – beyond the NIH base – for increased investigator-initiated research and targeted AD/ADRD initiatives needed to achieve the goals of NAPA. The bypass budget is transmitted to Congress separately from the standard federal budget process.

[13] https://www.nia.nih.gov/about/bypass-budget-proposal-archive

[14] https://www.congress.gov/bill/118th-congress/senate-bill/134/text

Recognizing the necessity of addressing AD/ADRD aggressively as the nation ages, since 2015 NIH funding for AD/ADRD research has increased more than six-fold. A significant part of this increase is due to increased AD/ADRD appropriations to NIA and recently also directly to NINDS for AD/ADRD research, and to the NIA's collaborative implementation of research priorities identified through NIH-led planning efforts with NINDS and other NIH institutes. NINDS has advanced ADRD research priorities set in 2013, 2016, 2019, and 2022 by funding ADRD-relevant investigator-initiated research grants within the NINDS pay line, and outside the pay line through a high program priority process, and launching new funding opportunities as detailed in **Appendix 1** and **Appendix 2** of this Report.

A summary of other major activities in advance preparation, the Summit itself, and follow-up, appears below.

Advance Preparation and Session Topics for the 2025 ADRD Summit. Pre-summit efforts began in August of 2024 with discussion between Summit leadership and the overall Scientific Chair to develop an overarching strategy. The Scientific Chair, together with NINDS leadership, NIA leadership, and NINDS staff, selected Scientific Chairs for five session topics designated by NAPA and the National Plan (MED, Health Disparities, VCID, LBD, and FTD) and special focus topics under MED (Figure 1). Reducing AD/ADRD health disparities has been a focus of the ADRD Summits since they began in 2013, and in 2025 was framed as "Research to Improve Outcomes for

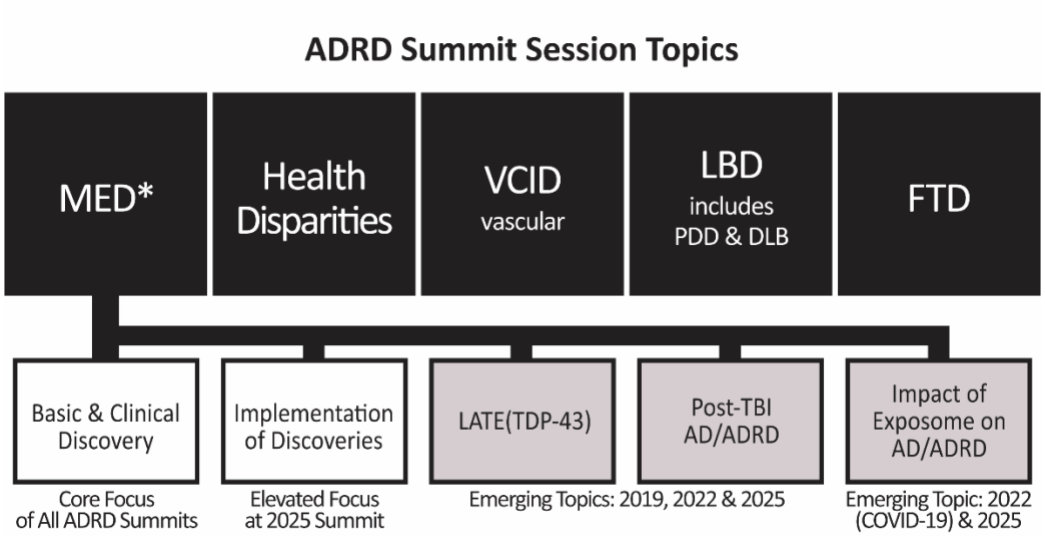

Figure 1. ***Session Topics and Emerging Themes of the 2025 ADRD Summit.***

This diagram summarizes the main session topics and Multiple Etiology dementias (MED) subtopics discussed at the 2025 Alzheimer's disease-related dementia (ADRD) Summit. Five primary sessions (black boxes) represent ADRD research areas in NAPA and the National Plan: MED, Health Disparities, Vascular Contributions to Cognitive Impairment and Dementia (VCID), Frontotemporal Dementias (FTD), and Lewy Body Dementias (LBD). LBD includes Parkinson's disease dementia (PDD) and dementia with Lewy Bodies (DLB). Special topic sessions (gray boxes) are added at each Summit to integrate new discoveries and emerging areas. In 2016, a session focused on Non-Governmental Organizations (not shown). In 2019, sessions on Dementia Nomenclature (not shown) and two emerging topics were introduced (TDP-43 Pathology in Common Dementias; TBI and AD/ADRD Risk), which continued as separate sessions in 2022 and 2025. Since 2022, the TDP-43 session included Limbic predominant Age-related TDP-43 Encephalopathy (LATE) under the expanded topic of TDP-43 in Common, Late-Onset Dementias. In 2025, the session from 2022, "Impact of COVID-19 on AD/ADRD Risk and Outcomes," was incorporated within the broader Exposome session. The asterisk (*) indicates that the MED main session in 2025 was split into two sub sessions (white boxes) to elevate focus on research to translate scientific advances into real-world benefits during the session on MED Research for Implementation of Discoveries into Practice.

Representative Populations at Risk and Living with AD/ADRD." This shift supports NIH's mission[15] and NINDS's vision[16] for accelerated progress and greater hope in AD/ADRD research. The Scientific Chair proposed dividing the MED session into two sessions with 4 recommendations each: "MED Basic and Clinical Discovery Research", a core focus of all ADRD Summits, and another on "MED Research for Implementation of Discoveries into Practice." This implementation session draws on topics from prior MED recommendations but newly elevates and centers the recommendations on research to translate scientific advances into real-world benefits for individuals and society. This proposal was viewed as timely, relevant, and was accepted unanimously. In addition, the leadership decided to maintain two MED subtopic sessions (TDP-43 in Common Dementias and Post-TBI in AD/ADRD) established in the ADRD Summit 2019, and to expand the 2022 subtopic session from the impact of COVID-19 on AD/ADRD risk and outcomes to the "Impact of the Exposome on AD/ADRD Risk and Outcomes."

NIH session leads were selected, and the NINDS established the process as a Working Group of the NINDS Council (for members see Table 1). The session Scientific Chairs, together with NIH session leads, then formed committees by selecting a roster of experts for each topic area. Committees consisted of small groups of members with scientific or lived experience (Tables 2 and 3) tasked with developing recommendations and assessing progress on the current ADRD research milestones then updating, refining, adding to and prioritizing recommendations for formal consideration by the NINDS and NAPA Councils. Each committee met several times via teleconference between October 2024 and the Summit. NIH staff provided the committees with responses to a joint NINDS/NIA Request for Information (NOT-NS-24-132[17]) that solicited public input on updating the ADRD research priorities, as well as an analysis of progress made on existing milestones. Cross-committee coordination occurred through a monthly teleconference of the Summit Steering Committee consisting of the overall Scientific Chair, Session Scientific Chairs, and the Working Group, and select federal officials.

The LBD, FTD, VCID, and Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD session committees considered proposing up to eight recommendations with four levels of priority, such that they could have two #1, #2, #3, and #4 priority recommendations, where the highest priority recommendation has the designation #1. The MED sub-topic sessions each considered proposing up to four recommendations with one recommendation at each priority level. The timelines indicated were determined by each committee estimating the year to complete or fully implement each recommendation if initiated in 2026.

Summit

The primary goal of the 2025 ADRD Summit was to solicit a wide range of input and feedback on the draft recommendations and timelines that had been prepared in advance. The Summit was advertised broadly to the scientific community, government agencies, and non-governmental organizations (NGO). There were 2558 individuals registered for the virtual meeting, with 400-900 attending most sessions. The Summit was recorded and made available for archival viewing on the NIH VideoCast:

- Day 1, April 29, 2025, https://videocast.nih.gov/watch=56742
- Day 2, April 30, 2025, https://videocast.nih.gov/watch=56748
- Day 3, June 2, 2025, https://videocast.nih.gov/watch=56749

A wide range of participants – including academic, clinical, government, industry, non-profit and public – registered for and participated in the virtual Summit. The Summit was structured over three days, featuring nine scientific sessions with 125 non-federal panelists, 33 federal panelists, and 45 individual talks. Each session began with a topic overview, followed by the session's chairs and committee members presenting a summary of

[15] https://www.nih.gov/about-nih/mission-goals

[16] https://www.nih.gov/about-nih/nih-almanac/national-institute-neurological-disorders-stroke-ninds

[17] https://www.grants.nih.gov/grants/guide/notice-files/NOT-NS-24-132.html

scientific progress that had occurred since 2022 and proposing updates and refinements to draft research recommendations for public feedback. On Day 1, Linde Jacobs delivered a perspective talk titled "The Patient Behind the Priorities," underscoring the disease burden on patients with AD/ADRD and their caregivers and stressing the importance of including individuals with lived AD/ADRD experience in the Summit. Day 2 opened with a perspective talk by Dr. Nilüfer Ertekin Taner providing an overview of the recently completed study commissioned by NIA and NINDS and conducted by the National Academies of Sciences, Engineering, and Medicine. The study, published[18] in December 2024, assessed the current state of research broadly on AD/ADRD and identified research priorities on preventing and treating dementia (National Academies of Sciences, Engineering, and Medicine. 2025. *Preventing and Treating Dementia: Research Priorities to Accelerate Progress*. Washington, DC: The National Academies Press. https://doi.org/10.17226/28588). Throughout the Summit, there was strong and active participation from patients and caregivers, ensuring robust public input. The public portion concluded on June 2 with a review of all suggested additions and revisions, providing a final opportunity for input from all participants. Immediately following the public sessions, NINDS led a closed session with the session chairs, NIH and other federal officials, Working Group members, and the Scientific Chair to review proposed revisions, edit the draft recommendations as agreed upon by the Steering Committee, and assign duties for finalizing the recommendations.

Post-Summit Follow-Up. Post-summit efforts included a Steering Committee teleconference and meetings among the session committees to further refine ADRD research recommendations content, prioritization, and proposed timelines and timeframes based on the active input received during the Summit and immediately thereafter. These activities resulted in sign off by the Working Group of Council on the ADRD Summit 2025 Prioritized Recommendations that we submit for approval in this Report. Upon acceptance by the NINDS Council and the NAPA Council, the research recommendations become ADRD milestones that will be included as part of the National Plan.

Organizing Participants. Full membership of the 2025 ADRD Summit session committees appears in Tables 1-3 of this report. In addition to federal representation from the NINDS, NIA participation included Drs. Stephanie L. Courchesne-Schlink, Tong Li, Damali Martin, Elizabeth Newman, Lisa Opanashuk, Alessandra Rovescalli, Nina Silverberg, Indira Turney, Keenan Walker, and Michael Ward. The National Heart, Lung and Blood Institute (NHLBI) participation included Drs. Marishka Brown, Selenia Catania, Jue Chen, and George Sopko. Also participating from the U.S. Department of Veterans Affairs, Dr. Stuart Hoffman, U.S. Department of Defense, Dr. Sarah Fontaine, and from the Centers for Medicare & Medicaid Services, Drs. Shari Ling and Lenise Cummings-Vaughn. The Department of Health and Human Services Assistant Secretary for Planning and Evaluation (ASPE) was represented by Dr. Helen Lamont.

Session Highlights and Cross-Cutting Themes. At the 2025 ADRD Summit, there was broad consensus that substantial scientific progress has been made since the 2022 Summit—including important advances in biomarker development, therapeutic options, and models of care. But alongside optimism, there was also a clear recognition of urgency: urgent need to accelerate clinical translation, expand inclusivity, and deliver meaningful benefits to individuals and families affected by ADRD. Across the nine summit sessions, several cross-cutting themes for where work is most needed emerged that transcend disease subtype and scientific discipline. These include:

a) Accelerating implementation science to bridge discovery and delivery, recognizing that even the most promising interventions have limited public health impact without strategies to support adoption, scale, and sustainability.

[18] https://www.nationalacademies.org/news/2024/12/report-identifies-research-priorities-for-alzheimers-disease-and-related-dementias-more-innovative-and-integrative-research-approaches-needed-to-speed-progress

b) Maintaining a focus on real-world impact for patients and families, ensuring that research priorities are guided by the lived experience of those affected and the urgent need for timely diagnosis, care, and treatment.

c) Embracing complexity in ADRD, recognizing that multiple etiologies, comorbidities, and life-course factors often interact to shape cognitive decline—requiring flexible models, multidimensional biomarkers, and integrative science.

d) Collaborative approaches at every level, from interdisciplinary research teams to cross-sector partnerships with government, industry, and community organizations, to scale innovation and foster implementation.

e) Harnessing digital innovation and artificial intelligence (AI) to transform diagnosis, monitoring, and care, with tools such as AI-powered diagnostic algorithms, digital cognitive assessments, remote monitoring technologies, and electronic health record integration.

f) Advancing biomarker development and application, including fluid- and imaging-based biomarkers and digital tools, with an emphasis on identifying preclinical disease, monitoring treatment response, and enabling precision medicine.

g) Ensuring that research is inclusive and access to care is equitable, by designing studies that reflect the diversity of the aging population and investing in outreach, workforce development, and culturally competent care delivery.

These themes reflect a maturing research landscape that is more connected, more patient-centered, and increasingly positioned to deliver on the original—and still essential—goal of preventing and effectively treating Alzheimer's disease and related dementias. Realizing that goal will require sustained investment, strategic prioritization, and a shared commitment to moving discoveries from bench to bedside, while never losing sight of the people at the center of this work.

As the field has advanced and matured since the ADRD Summits first began in 2013, it has become increasingly clear that many high priority areas of research cut across disease categories. Having one pathology in the brain is

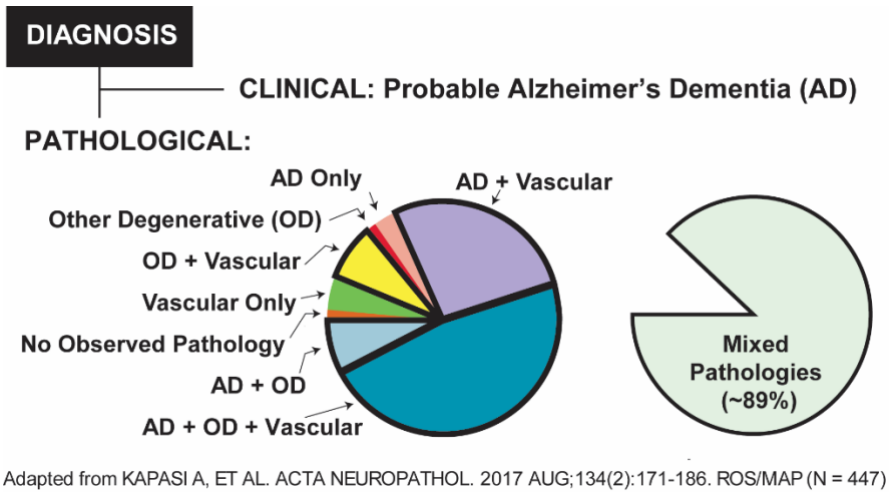

Figure 2 ***Complexity of Brain Pathologies in Clinical Dementia Diagnosis***

The figure illustrates that mixed pathologies are far more common than pure AD, and thus effective treatment plans must account for this complexity. The combinations of pathologies found in individuals clinically diagnosed with Alzheimer's dementia based on data from the ROS/MAP cohort (N=447; Kapasi et al., Acta Neuropathol, 2017) include Alzheimer's disease (AD) alone, other degenerative diseases (OD; included Lewy bodies, TDP-43, and hippocampal sclerosis), vascular pathologies, mixed combinations, and cases with no pathology observed. The largest group represents individuals with AD, OD, and vascular pathologies combined.

the exception and not the rule (Figure 2)[19], and many important areas of research investigation are relevant across pathologies. Future Summits may consider re-organizing some sessions or the recommendations around disease agnostic topics such as biomarkers, modern clinical trial design, and shared mechanisms.

The following summarizes key takeaways from the recommendation presentations and discussions held throughout the Summit.

Session 1: Multiple Etiology Dementias (MED) – Research for Implementation of Discoveries into Practice (Chair: Katherine Possin)

This session elevated implementation research at the 2025 Summit, reflecting both the substantial scientific progress achieved in recent years and the urgent need to translate those advances into real-world benefits for individuals, families, healthcare providers, and health systems. This session was particularly timely given that 2025 marks the original target year for Goal 1 of the National Alzheimer's Plan—to prevent and effectively treat AD/ADRD—making implementation science a critical focus for the field. The session highlighted that while the past decade has yielded breakthroughs in early detection, biomarker testing, prevention, and care models, many individuals—especially those in underserved communities—are still not benefiting from these innovations. Research on topics not yet ready for widespread implementation fall under the MED-Clinical and Basic Research Committee's purview. The committee's *Priority 1 recommendation calls for research to implement and disseminate evidence-based interventions to improve detection and diagnosis in primary healthcare settings, including how results are communicated to patients and families and how patients are linked to quality care.* Additional recommendations focused on developing artificial intelligence (AI)-powered clinical decision tools, improving access to preventive interventions and diagnostics, and strengthening collaborative care models throughout the disease course—including for individuals living alone or lacking care partners. Collectively, these recommendations aim to ensure that scientific advances reach those most affected by dementia and deliver meaningful improvements in prevention, diagnosis, treatment, and quality of life.

Session 2: Frontotemporal Dementias (FTD) (Chairs: David Irwin and Celeste Karch)

The session on Frontotemporal Dementias (FTD) addressed the urgent need for precision diagnostics, targeted therapies, and inclusive clinical research for this diverse and often misdiagnosed group of neurodegenerative disorders. FTDs typically strike earlier in life than Alzheimer's disease, and their clinical, pathological, and genetic heterogeneity presents substantial challenges for diagnosis and treatment. The committee emphasized the importance of building clinical trial infrastructure and regulatory pathways that reflect this complexity. The session had *two Priority 1 recommendations. The first is to accelerate the evaluation of novel FTD treatments by capitalizing on existing resources and developing new FTD-specific clinical trial platforms,* including pragmatic and decentralized approaches that expand inclusion and reduce burden on participants and caregivers. *The second is to advance development of standardized biomarkers and digital health technologies* for early and accurate molecular diagnosis, disease monitoring, and stratification in clinical trials—particularly for underrepresented populations and those with limited access to specialty care. Other key priorities included developing targeted experimental models of FTD, understanding disease-modifying genetic and environmental factors, and addressing longstanding gaps in FTD epidemiology, particularly in diverse populations. The committee also emphasized the need for novel mechanistic studies of selective vulnerability and non-neuronal contributions to pathology, and strategies to translate pathogenic pathway insights into disease-modifying and symptomatic treatments. Taken together, the recommendations reflect a comprehensive research roadmap to

[19] Kapasi, A., DeCarli, C. & Schneider, J.A. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol* **134**, 171–186 (2017). https://doi.org/10.1007/s00401-017-1717-7

meet the unique scientific and clinical challenges posed by FTD and deliver meaningful advances for those affected by the disease.

Session 3: MED – Post-Traumatic Brain Injury (TBI) AD/ADRD (Chair: Kristen Dams-O'Connor)

Traumatic brain injury (TBI) is a significant yet often underrecognized risk factor for later-life cognitive decline and dementia. This session spotlighted TBI as a critical contributor to AD/ADRD and emphasized the urgent need to understand the distinct clinical trajectories and biological mechanisms that underlie post-TBI neurodegeneration. The committee's *Priority 1 recommendation is aimed at clarifying the heterogeneous clinical presentations and clinicopathologic relationships that follow heterogeneous TBI exposure patterns.* Recommendations also included validating exposure metrics and diagnostic criteria for post-traumatic neurodegeneration, identifying post-TBI–specific biomarkers, and determining how head trauma alters biomarker performance and response to ADRD therapies. The session called for strong interdisciplinary collaboration between TBI and dementia researchers, harmonization of data across studies, and representative inclusion of TBI survivors in AD/ADRD research. Additional priorities focused on developing and validating experimental models of post-TBI ADRD pathology, understanding vulnerability and resilience factors, and ensuring that scientific advances are translated into real-world diagnostics, treatments, and education for patients, care partners, and communities. Collectively, these recommendations reflect the field's momentum in characterizing post-TBI ADRDs and the need to address this important, often overlooked, contributor to dementia risk.

Session 4: MED – LATE (TDP-43 in Common Late-Onset Dementias) (Chair: David Wolk)

This session focused on LATE (Limbic-predominant Age-related TDP-43 Encephalopathy), a common and under-recognized contributor to cognitive impairment in older adults. Building on momentum from recent discoveries, the working group emphasized the need to elevate LATE within the broader AD/ADRD research and clinical frameworks, especially as anti-amyloid therapies become more widely available and clinicians encounter cases where patients have limited or no amyloid pathology. The committee's *Priority 1 recommendation is to develop and expand multi-modality cohorts with post-mortem data to evaluate the distinct and shared features of LATE with FTLD-TDP and when LATE co-occurs with other pathologies in mixed etiology dementias,* with the aim of improving diagnosis, advancing therapeutic strategies, leveraging knowledge across TDP-43 neurodegenerative conditions, and increasing awareness among clinicians, researchers, and patients. Other key recommendations included developing validated in-vivo biomarkers for TDP-43 pathology; supporting experimental and mechanistic models to identify therapeutic targets; and enhancing understanding of hippocampal sclerosis of aging (HS-A), which frequently co-occurs with LATE and may involve shared inflammatory, vascular, and senescence-related mechanisms. The committee also emphasized the importance of education for clinicians and researchers, the integration of LATE into biomarker and therapeutic training, and building accessible educational tools for patients and families. Together, these recommendations reflect an urgent call to bring LATE to the forefront of dementia science and care, closing longstanding knowledge and treatment gaps for this common, but often overlooked pathology.

Session 5: MED – Basic and Clinical Discovery Research (Chairs: Cynthia Carlsson and Costantino Iadecola)

This session addressed the scientific foundations needed to understand and ultimately intervene in the complex, overlapping biological pathways that characterize multiple etiology dementias. As aging populations increasingly present with mixed pathologies, the committee emphasized the need for integrated, multimodal research strategies to unravel how diverse mechanisms interact to drive cognitive decline. The session's Priority 1 recommendation calls for research to conduct new and leverage existing longitudinal studies across broad populations and across sexes—integrating cognition, neuroimaging, biofluid, omics, neurophysiological, and post-mortem data—to identify and validate predictive MED phenotypes, risk factors, and responses to therapy.

Other high-priority recommendations included advancing experimental models that reflect polypathology, using cutting-edge technologies to identify shared and unique molecular drivers, and developing new strategies to accelerate target validation and clinical translation. The group also highlighted the importance of harmonizing data across basic, translational, and clinical research platforms through open science and public-private partnerships, and ensuring that MED is appropriately coded in electronic medical records to support real-world research. Finally, the session underscored the urgent need for expanded education and workforce development to equip researchers and clinicians with the tools and understanding needed to address the biological complexity of MED. Together, these recommendations lay the foundation for a next generation of discovery research designed to support precision diagnostics and treatment strategies for individuals with mixed dementia etiologies.

Session 6: Lewy Body Dementias (LBD) (Chairs: James Galvin and Kathleen Poston)

The LBD session addressed the complex scientific and clinical challenges posed by Lewy body dementias, including dementia with Lewy bodies and Parkinson's disease dementia. These disorders are marked by considerable heterogeneity in presentation and progression, as well as pathological overlap with other neurodegenerative conditions. The session emphasized the need for research strategies that span discovery, diagnosis, and care. The committee put forward *two Priority 1 recommendations*. The first is to *expand LBD clinical trial infrastructure and perform trials to slow progression, delay or prevent symptom onset, and alleviate clinical symptoms*, including both novel and repurposed therapies informed by biomarkers and mechanistic understanding. The second Priority 1 recommendation is to *develop and validate experimental models to understand the pathogenesis, toxicity, and normal function of α-synuclein*. This includes in vitro and in vivo systems that reflect key clinical and pathological aspects of LBD, with particular attention to non-motor symptoms like cognitive decline, and to diverse α-synuclein strains that may underlie different clinical trajectories. The committee stressed the importance of investigating mechanisms of α-synuclein aggregation, transmission, and clearance, and of identifying therapeutic targets validated in human tissues. Other recommendations included advancing α-synuclein biomarkers, leveraging digital and wearable technologies, integrating functional genomics, and ensuring engagement and inclusive research design. Collectively, the session's roadmap aims to enable mechanism-based interventions and deliver transformative progress for individuals living with LBD.

Session 7: Vascular Contributions to Cognitive Impairment and Dementia (VCID) (Chairs: Silvia Fossati and Hanzhang Lu)

The VCID session emphasized the foundational role of vascular pathology in age-related cognitive decline and dementia, underscoring its high prevalence and complex interactions with neurodegenerative processes such as amyloid and tau accumulation. The session's first *Priority 1 recommendation is to understand mechanisms of vascular disease onset and progression in specific cell types and their interactions, in the context of cognitive decline.* This includes dissecting the roles of endothelial cells, pericytes, astrocytes, and microglia, among others, in blood-brain barrier integrity, neurovascular coupling, and clearance pathways. The *second Priority 1 recommendation calls for advancing biomarkers of VCID through instrumental and clinical validation for defined use cases*, with the goal of achieving regulatory readiness. This includes refining candidate biomarkers across imaging, fluid, omic, digital, and AI-enhanced domains, while integrating measures of daily function and quality of life. Additional recommendations included developing experimental models that mimic complex human VCID conditions, characterizing cerebral small vessel disease, and testing preventive strategies in high-risk populations. The group emphasized the importance of translational alignment across model systems and human studies, and of addressing sex, age, and comorbidity effects. Together, these priorities aim to bridge mechanistic understanding with real-world tools for diagnosis, prevention, and treatment of vascular brain injury across diverse populations.

Session 8: Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD (Chairs: M. Maria Glymour and Katie Deters)

This session focused on improving outcomes for individuals and communities who are disproportionately affected by AD/ADRD by addressing gaps in research participation, access to care, and quality of life. Though AD/ADRD affects all populations, current evidence suggests substantial differences in the incidence and prognosis after diagnosis of AD/ADRD by educational attainment, geography including rural populations, sex, race, and ethnicity, among other dimensions. The session highlighted the need for research strategies that more accurately reflect the full diversity of the population and that lead to improvements in diagnosis, treatment, and care. The committee presented *two Priority 1 recommendations. The first is to advance community-driven AD/ADRD research to improve representative sampling and retention of populations disproportionately affected,* including through better engagement practices, expanded inclusion criteria, and improved data on recruitment and retention. The second is to *prioritize infrastructure and policy research to understand individual, community, and societal drivers of care costs and access to treatments and care,* with the goal of identifying approaches that improve quality of life and health outcomes. Additional recommendations included supporting a strong workforce across biomedical, behavioral, and social sciences to advance research in high-risk populations; improving cognitive and biomarker assessments and analytic methods to enhance generalizability of scientific findings; and identifying life course and multi-level mechanisms to inform prevention. The committee also recommended expanding access to research training and improving monitoring of AD/ADRD trends and disparities using new and existing surveillance methods. Several of the recommendations emphasize community-engaged research, which means including the voices of individuals affected by AD/ADRD or representing the disproportionately impacted groups in the planning, implementation, or interpretation of research results. Together, these priorities aim to improve scientific understanding and care for all populations affected by AD/ADRD.

Session 9: MED – Impact of Exposome on AD/ADRD Risk & Outcomes (Chairs: Farah Lubin and Jonathan Kipnis)

This session explored how a broad range of environmental exposures across the lifespan—collectively referred to as the exposome—may influence the risk, onset, progression, and outcomes of AD/ADRD. The group highlighted the need for a new research paradigm that systematically investigates how factors such as microbes, infections, pollution, toxicants, diet, and social conditions interact with genetic susceptibility and biological systems to shape cognitive aging. The *Priority 1 recommendation is to investigate the interplay between the exposome and the human body in influencing AD/ADRD, with a particular focus on microbes and infectious diseases.* This includes characterizing differences in the microbiome, infection burden, immune responses, and sleep/circadian rhythms across disease stages, and studying how these factors influence AD/ADRD pathology and clinical manifestations in both animal models and humans. Additional recommendations include advancing mechanistic studies of exposome-related pathways (e.g., neuroinflammation, oxidative stress, autophagy); establishing research infrastructure and biobanks to support exposome studies; and identifying diagnostic criteria for neurocognitive impairment associated with environmental exposures. The group also emphasized the importance of prioritizing clinical, epidemiological, and basic research in populations disproportionately exposed to environmental and social risk factors, and of developing preventive and therapeutic interventions informed by a mechanistic understanding of beneficial and harmful exposures. Together, these recommendations reflect a major effort to incorporate environmental context into the understanding and treatment of dementia.

Recommendations

The recommendations in this Report, which have been approved by the NANDS Working Group of Council, represent national research priorities that will inform future NIH AD/ADRD Bypass Budgets and, as congressionally appropriated funds become available, guide the corresponding funding of AD/ADRD research

activities. Each recommendation included in this report represents a top priority within its respective field and reflects the consensus of the session committees.

Each session committee was required to assign rank priorities to its recommendations, and only those deemed highest priority were included here. Bullet points beneath each recommendation provide context and elaboration based on the committee discussions and supporting evidence. Estimated completion times are when the recommended work could be accomplished if initiated in 2026. The ordering of sessions within this report does not reflect any hierarchy or prioritization—each session topic represents a critical and equally high priority for advancing the national research agenda.

As Scientific Chair of the ADRD Summit 2025, I respectfully submit this Report to the NINDS Council on behalf of all committee co-chairs and members. We remain committed to translating these recommendations into action to improve the lives of individuals at risk for or living with AD/ADRD and their families.

Sincerely,

Katherine L. Possin, PhD
John Douglas French Foundation Endowed Professorship
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ADRD Summit 2025

PRIORITIZED RECOMMENDATIONS

Session 1: Multiple Etiology Dementias (MED) – Research for Implementation of Discoveries into Practice

Recommendation 1 - Priority 1. Conduct implementation and dissemination research on evidence-based interventions to detect and diagnose cognitive, behavioral, or functional impairments associated with AD/ADRD, communicate results to patients and care partners, and link them to quality care in primary healthcare settings. (2031)

- Research should optimize and evaluate the interventions for improving timely, accurate, compassionate, and actionable detection and diagnosis in a way that reduces health disparities and that is accessible, scalable, and sustainable.
- Interventions should be designed to improve primary care provider comfort level with diagnosis and management.
- Research should prioritize evaluation of patients with elevated risk for AD/ADRD, especially patients about whom the patient, care partner, or clinician reports cognitive, behavioral or functional changes. To better identify at-risk patients, research should advance the use of initial screening questions that elicit concerns and other risk identification approaches that could trigger an evaluation.
- Interventions should include person-centered approaches for communicating the purpose and the results of the assessment to patients and care partners that consider stage of cognitive impairment, cultural context, and individual preferences.
- Develop and evaluate EMR-integrated clinical decision support tools that leverage patient data to deliver actionable recommendations. These tools may incorporate artificial intelligence, including large language models, to enhance clinical reasoning and decision-making.

Recommendation 2 - Priority 2. Evaluate the implementation and effectiveness of interventions that promote brain health and mitigate the risk of cognitive decline in primary care and community settings, with a strong focus on populations experiencing disproportionate AD/ADRD burden. (2031)

- Develop and implement scalable tools to identify high-risk individuals for intervention.
- Primary and secondary prevention interventions should focus on intervenable factors that promote brain health and reduce the risk of cognitive decline, such as addressing cardiovascular or metabolic risks at mid and late life, addressing sleep quality and disturbances, as well as others such as hearing and vision loss, social isolation, depression and the use of medications with risks to brain health.
- Interventions may include guidance for primary care on personalizing intervention strategies based on patients' risk profiles.

Recommendation 3 - Priority 3. Implement and evaluate strategies to improve access for patients and care partners to high-quality AD/ADRD care, including diagnostic evaluations and biomarker testing, pharmacologic and non-pharmacologic treatments, home and community-based services, and palliative or hospice care, as well as opportunities to participate in brain health research. (2031)

- Conduct implementation studies of promising approaches to identify and navigate people to quality care, with a focus on populations experiencing health disparities, people without care partners or who live alone, and people living in rural areas.
- Interventions should take a systems perspective, include primary care or acute care settings, and improve health system – community linkages.
- Approaches should incorporate education and training for providers to reduce disparities in access and how to link patients with care that is right for them.
- Examine ethical issues and evaluate pathways, including their clinical appropriateness, in connecting patients with AD/ADRD biomarkers, including plasma, in everyday clinical practice. This should include research on helping providers to understand, interpret, and communicate biomarker results, including their limitations, in a way that prioritizes patient/care partner agency and reduces harm.

Recommendation 4 - Priority 4. Conduct research to enhance the efficiency and effectiveness of evidence-based and evidence-informed collaborative care models that support the needs of patient and care partners at key points in the AD/ADRD care journey, from diagnosis to end-of-life, including populations most at risk for poor outcomes. (2031)

- Adapt, implement, and test collaborative care models to address vulnerable points in the care journey, including during the process of diagnosis, screening for and delivery of disease modifying therapies, discharge from acute care settings, management of neuropsychiatric symptoms or comorbid conditions, and end of life and bereavement.
- Advance research on collaborative care models that meet the needs of individuals in the demographically heterogeneous AD/ADRD population including persons living with dementia who live alone or do not have care partners.
- Incorporate decision support tools and generative AI approaches to drive efficiencies and adherence to best practices.
- Conduct pragmatic investigations to identify the core components of collaborative care that drive effectiveness and their mechanisms in real world practice, and what components are less effective or not necessary.
- Advance work on the availability of common data elements for evaluation of collaborative care models in real world settings, including measures of well-being.

Session 2: Frontotemporal Dementias (FTD)

Recommendation 1 – Priority 1. Accelerate the evaluation of novel and clinically impactful FTD treatments by both capitalizing on existing evidence, infrastructure, and resources and on the development of new clinical trial resources and FTD-specific designs, including conducting new prevention and treatment trials in cohorts representative of the US population. (2030)

- Given the variety of pathways leading to FTD, the heterogeneity even within FTD subtypes, and the rarity of FTD in general, new tools and clinical trial approaches are needed to efficiently and effectively test investigational therapies. There is increasing support from regulatory agencies for innovative approaches to clinical trials in FTD. For example, travel requirements for standard clinical research designs are burdensome and often restrict participation to those in proximity to specialist sites or with financial resources, comfort level, and physical fitness for long-distance travel. Public-private partnerships are an essential mechanism to address these unique aspects of trial design in FTD.
- Advance novel clinical trial designs for FTD to increase power, reduce placebo exposure, increase inclusion of patient populations more representative of the US, reduce sample size and/or trial duration to accelerate decision making, and enable more efficient testing of multiple therapeutic approaches.
- Encourage entry of early stage FTD therapeutics, as well as therapeutic targets being developed for biologically related disorders (e.g. ALS, LATE-NC, tau-directed therapies in AD), into human proof of concept studies through master protocols and other approaches.
- Build infrastructure to support early stage, as well as pivotal global clinical trials, especially in rare genetic FTD syndromes where global efforts will be necessary to perform adequately powered studies.
- Develop and validate tools to advance decentralized clinical research study designs and measure endpoints remotely.
- Develop and use new clinical trial endpoints that incorporate caregiver burden and FTD specific definitions of clinical meaningfulness based on patient and caregiver reports from representative populations with distinct linguistic, social, and cultural backgrounds.
- Conduct pragmatic clinical trials in sporadic FTD syndromes to understand current treatment practices and identify potentially beneficial approaches.
- Conduct interventional studies of non-pharmacological therapies for FTD including rehabilitation strategies and caregiver support, which can be implemented at both early and late stages of the disease.
- In addition to pursuing disease-modifying approaches, symptomatic therapies should also be pursued including, but not limited to, electro/magnetic neurostimulation, rehabilitation approaches, and leverage symptomatic therapeutics approved for neuropsychiatric symptoms in related neurodegenerative or psychiatric disorders.
- Symptomatic therapeutic approaches should leverage patient/caregiver experience and input on FTD specific symptoms and functional impact. Patient/caregiver centric approaches to non-pharmacological interventions should be prioritized.

Recommendation 2 – Priority 1. Advance development of an array of standardized biomarkers and digital health technologies for screening, early in vivo molecular diagnosis and differentiation from other ADRDs, phenoconversion prediction, disease monitoring, and clinical-trial based patient stratification and target engagement for FTD-associated pathologies. (2029)

- Early and accurate diagnosis of underlying FTD-associated pathologies is a critical unmet need for clinical care, epidemiology, natural history studies, and therapeutic trials. This need is amplified for underserved/geographically isolated US populations, who may not have access to specialized expertise

and diagnostic tools, necessitating low-cost screening tools to identify individuals with/at risk for underlying FTD-pathology.

- Patients with early-stage disease can be difficult to distinguish from patients with non-neurodegenerative mimics of FTD, including psychiatric disease. Moreover, well-documented delays in an FTD diagnosis and subsequent supportive care cause considerable personal and societal costs that could be alleviated, in part, by development and validation of biological markers for clinical use to aid in early and accurate diagnosis.
- The heterogeneity and poor-predictive value of most FTD clinical syndromes for a specific underlying neuropathology is a barrier to clinical identification and differentiation of pathological forms of FTD-related pathologies (i.e. tauopathies, TDP-43 proteinopathies, FET proteinopathies: fused in sarcoma (FUS), Ewing's sarcoma protein (EWS) and TATA-binding protein-associated factor 15 (TAF15)). Thus, diagnostic biomarkers that can identify and differentiate FTD-associated molecular pathologies from each other, as well as from other forms of ADRD and non-neurodegenerative mimics early in the disease, is a high priority.
- Autopsy-based validation is critical to test disease specificity and biomarker performance in the setting of mixed pathologies. An emphasis on digital methods and other advanced postmortem imaging will enhance biological characterization of candidate markers.
- Biomarker strategies for patient stratification based on target engagement, disease stage, prediction of disease progression, and surrogate measures of clinical benefit are critical for effective and efficient clinical trials, including both symptomatic and disease-mechanistic approaches.
- Autopsy-based studies find a higher prevalence of FTD-associated pathologies than previously reported using clinical criteria alone, suggesting FTD is underdiagnosed. FTD-specific biomarkers are needed to screen at-risk populations to improve epidemiological assessments of FTD and enhance natural history studies of clinically defined cohorts with biological characterization to elucidate causes of disease heterogeneity.
- Non-invasive and low-cost digital health technologies that can be implemented in a range of environments, including at-home remote assessments, are prioritized to quantify various cognitive, emotional/behavioral, motor and autonomic functions in FTD that limit the functional and emotional burden of trial design for caregivers and persons with lived experience.
- Biomarkers that can improve the precision of predicted timing for onset of phenoconversion in asymptomatic individuals at risk for familial FTD are urgently needed to inform clinical care and trial design.
- PET and other imaging modalities that can visualize tau, TDP-43 and FET protein-associated neurodegeneration are needed to quantify the severity and topographic distribution of neurodegeneration in FTD to guide prognosis and disease progression models, as well as target engagement in treatment trials. Once autopsy-validated and standardized for widespread use, FTD-specific PET tracers can also accelerate the validation of other lower-cost, less-invasive biomarker modalities.
- Blood-based biomarkers are a high priority, particularly for use in screening populations at risk for FTD to improve early diagnosis.
- Observational studies that compare biomarker values in cross-sectional cohorts of FTD subtypes, investigate changes over time, as well as test predictive value in longitudinal cohorts are needed. Specific investigations on the influences of mixed pathologies and pathologic/genetic subgroups of FTD associated pathologies are a priority.
- Develop and standardize machine learning, AI and other data-driven approaches that use and integrate existing biomarker datasets to develop prediction algorithms or other tools that facilitate FTD diagnosis,

disease progression modelling, and treatment response/clinical trial simulation. There is a need for infrastructure to allow harmonization and open access to the datasets and codes for reproducibility.
- Discovery and validation of FTD specific biomarkers will necessitate optimization of nomenclature and alignment of the existing frameworks for biomarker classification of other ADRDs.

Recommendation 3 – Priority 2. Establish and validate pre-clinical and translational models and resources that foster mechanistic studies and the identification of novel therapeutic approaches in FTD. (2030)

- Generate new models of familial as well as sporadic FTD that accurately recapitulate molecular, pathological, and behavioral aspects of disease. It is crucial that newly developed models mimic key pathophysiological hallmarks of FTD (specifically those found in humans with disease) to maximize predictive validity in translational studies of potential therapeutics.
- Capitalize on model systems for developing molecular maps of disease pathogenesis, identifying disease modifiers, and predicting disease progression and/or response to potential interventions.
- Collect and catalogue multi-omic datasets (genetic, transcriptomic, epigenetic/epitranscriptomic, proteomic, metabolomic, lipidomic, single-cell and spatial transcriptomics, and more) obtained from individuals with FTD as well as pre-clinical FTD models. These complex datasets should be integrated with associated detailed clinical, cognitive, neuroimaging, and biomarker data. These datasets should also be compared with similar datasets for other ADRDs and related disorder such as ALS.
- Increase resources to expand and broaden the identification and collection of genetic and clinical information from FTD cohorts across all populations, stages, and clinical presentations of FTD.
- Establish public-private partnerships for storing, managing, harmonizing, and maintaining access to multi-dimensional datasets for researchers world-wide.
- Clarify potential contributions of artificial intelligence (AI) for the analysis of multi-dimensional data, emphasizing applications in therapeutic target identification, as well as the development of novel biomarkers for diagnosis, stratification, prognostication and target engagement.
- Create and support biosample repositories housing fluid, cells, and post-mortem tissue obtained from well-characterized FTD cohorts, linked with individualized ante-mortem clinical, cognitive and neuroimaging data.
- Advertise, distribute, and monitor use of biosamples from newly-established FTD repositories through collaborative multi-center partnerships dedicated to data sharing and resource accessibility.

Recommendation 4 – Priority2. Define genetic and molecular modifiers of inherited and sporadic FTD (including in cohorts representative of the US populations) along with their molecular and cellular mechanisms of action. (2031)

- Some of the most common autosomal dominant causes of inherited FTD have been identified, but rare genetic causes remain undefined and have the potential to reveal novel insights into disease mechanisms.
- It is a priority to understand the genetic architecture of FTD in understudied populations and determine how rare or common variants impact disease risk across populations. There remains a need to determine how genetic variants confer risk or resilience within specific populations, and to determine if the penetrance/effect size of pathogenic or risk variants differ in specific populations as these differences have the potential point to novel therapeutic targets.
- Identify and functionally annotate risk/resilience loci in Mendelian and sporadic forms of FTD and within FTD subtypes. This includes leveraging functional genomics to map variants and their effects on specific genes within given loci. Single-cell sequencing and spatial transcriptomics approaches will be important to define the cell-type(s) in which variants confer risk/resilience is critical to understanding the disease mechanism and possible therapeutic approaches.

- Define and functionally characterize the genetic factors that influence onset age and pace of progression in Mendelian and sporadic forms of the disease.
- Elucidate how genetic background and environment are linked to the patient's clinico-pathological syndrome. This should be studied in clinical cohorts and modeled in vitro and in vivo.
- Continue to build core services for FTD genotyping and DNA banking where any researcher can send samples, receive genotype information, or request data/samples from large cohorts. Some of these samples could also include fibroblast/stem cell models.
- Pursue a focused effort to find additional genetic causes and risk factors for FTD through deep sequencing and epigenetic approaches, initially in small families and expanding into large cohorts of unrelated FTD patients to confirm pathogenicity.

Recommendation 5 – Priority 3. Understand FTD epidemiology in representative populations and how disease-modifying factors including genetic ancestry, environmental heterogeneity, sex, and the exposome affect disease risk, clinical manifestations, and the unique aspects of the lived experience of FTD. (2030)

- Conduct studies to determine the prevalence, incidence, risk, and resilience factors for FTD in understudied populations in North America, as well as other populations worldwide. Given the complexity and multiple subgroups within each population, oversampling for data collection should be employed.
- Studies of international cohorts suggest that FTD genetics in these populations are significantly different from those documented in current U.S. and European Union cohorts. Little is known about FTD in other populations. It is possible that the incidence, prevalence, range of clinical phenotypes, and types of symptoms may be different in various populations which may discover new factors that modulate FTD risk in the US.
- Develop culturally tailored and linguistically appropriate education and outreach tools to both support studies in populations representative of the US and to promote access to diagnosis among all populations. Such tools should be deliverable via online, mobile device, print, and in-person interactions. Clinicians/scientists from populations representative of the US should be engaged in these efforts.
- Deploy new biomarkers that can be collected remotely and assessed in geographically remote, resource-limited facilities to study representative populations.
- Understand the role of socioeconomic, environmental, psychological factors, social determinants of health, and comorbidities in the etiology of FTD syndromes.
- Develop educational tools and infrastructure to encourage and support brain and biosample donations from populations underrepresented in research but reflective of the US population. Encourage community outreach programs and partnerships with primary care and community health clinics.
- Train researchers from communities representative of the US to facilitate inclusion of underrepresented populations to better understand FTD as well as bring new perspectives into FTD research, for example, in clinical assessments, cognitive testing, etc.
- Unlike AD, FTD is a rare disease with a much lower prevalence, earlier age of onset, and initial symptoms that may be less likely to be recognized as part of a neurodegenerative disease. FTD may also be disproportionately diagnosed in populations with greater resources. For these reasons, traditional approaches to improving representation among populations missing from AD/ADRD research may not be applicable to FTD, and new approaches for recruitment and clinical research of underrepresented population are needed specifically for FTD.
- A priority for epidemiological studies of the exposome and lived experience of FTD should focus on unique aspects of the disease, including the “mid-life” age at onset, which poses significant challenges to caregivers and patients who are often in the workforce and have dependent-aged children at time of diagnosis.

- Comparative work in clinical and biological subgroups of FTD for environmental and lived experience risk factors identified for dementias and other ADRDs, as well as ALS, are a priority to determine shared and distinct risk factors for biological subgroups of FTD and ADRDs (e.g. FTLD-TDP and LATE-NC).

Recommendation 6 – Priority 3. Elucidate cell-autonomous and non-autonomous mechanisms underlying neurodegeneration in FTD, with the goal of understanding selective vulnerabilities and thereby identifying new targets for therapeutic development. (2031)

- The brain regions and cell-types that are selectively vulnerable in FTD are distinct from AD and other ADRDs, particularly early in disease. A greater understanding of fundamental mechanisms underlying selective cellular vulnerability across disease stages has the potential to reveal unique and novel therapeutic targets. Additional effort should also be placed on recapitulating cell-type vulnerability in FTD in in vitro and in vivo models, including development of new approaches to model cell types that lack correlates in rodents.
- While previous efforts have been primarily placed on mechanisms underlying degeneration of neurons among FTDs, roles for various glial, endothelial, and immune cell types are increasingly being identified as a central feature of these disorders. Additional work is required to elucidate how and to what extent dysfunction in non-neuronal cell-types or systems impacts FTD pathology and cellular toxicity.
- Our understanding of the cellular mechanisms whereby pathogenic proteins that accumulate in FTDs drive neurotoxicity has grown in recent years and has led to new strategies for therapeutic development. There is a need for a deeper mechanistic understanding in this area, including identifying and characterizing cell-autonomous processes that go awry in neurons, such as how protein gain and/or loss of function, dysregulated proteostasis and lipid metabolism, epigenetic changes, and deficits in RNA metabolism led to neuronal dysfunction and death in FTD.
- The brain is a complex system in which many cell types interact dynamically. A greater understanding of non-cell autonomous mechanisms driving disease progression in FTD, including but not limited to neuroinflammation, senescence, intercellular spreading of toxic proteins, and vascular dysfunction, is needed to appreciate how dysfunction of discrete cell types affects their brain microenvironment. Use of new approaches and tools that enable the study of a variety of cell types will reveal how their interactions shape neurodegeneration in FTD. It is also important to understand the mechanisms whereby general physiological processes, such as aging, stress and sleep dysfunction, contribute to cellular vulnerability in FTD.

Recommendation 7 – Priority 4. Identify shared and disparate mechanisms underlying the clinical and molecular subtypes of FTD, inclusive of co-pathologies, at the molecular, cellular, circuit, and tissue levels. (2030)

- The vast heterogeneity of FTD, from both a clinical and pathological perspective, poses significant obstacles in terms of nomenclature, classification, and emerging mechanistic treatment strategies. Notably, there is both clinicopathologic convergence of multiple different FTD associated pathologies (i.e. tauopathies, TDP-43 proteinopathies, FET proteinopathies) and other ADRDs (e.g. frontal-variant AD) presenting with similar clinical FTD syndromes (e.g. behavioral-variant FTD) and divergence of clinical expression into different FTD and non-FTD (e.g. amyotrophic lateral sclerosis) syndromes between individuals within each molecular subtype of FTD-associated proteinopathy. Thus, elucidating the neural substrates and modulating factors that determine clinicopathological heterogeneity in FTD is a high priority.
- FTD clinical symptoms and human behavior/cognition are derived from complex connectivity and higher order structure of the human brain (i.e. the connectome). Mechanistic and clinical studies examining clinical and pathological heterogeneity within the context of human brain cytoarchitecture and

connectivity at multiple levels of resolution are needed to identify shared and disparate patterns of neurodegeneration between and within FTD molecular subtypes.

- Comparative studies between FTD and other ADRDs are needed to identify distinct and overlapping pathogenic mechanisms. The focus should include not only common pathogenic factors leading to this array of neurodegenerative disorders and FTD (e.g., tauopathies), but also on genetic, environmental and acquired factors that drive phenotypic expression in susceptible individuals.
- There is an emphasis for the need for postmortem autopsy tissue/data and/or patient derived materials (e.g. IPSCs) in comparative studies of FTD subtypes, including increased access to brain donation for research in geographically isolated areas.
- Familial forms of FTD share neuropathologic and pathophysiologic features with sporadic disease (i.e. MAPT-FTD compared to sporadic tauopathies; C9orf72-FTD, GRN-FTD compared to sporadic TDP-43 proteinopathies); however, it is not entirely clear if mechanisms, modifying factors, and/or treatment strategies (e.g. PGRN augmentation) for familial FTD are relevant to disease pathogenesis of sporadic FTD. Finally, examination of shared mechanisms of familial FTD across other ADRDs, such as variants in GRN for risk of both TDP-43 proteinopathy, LBD and other disorders are also needed.
- Cross-disciplinary multi-disease comparative genetic (including transcriptomic and epigenomic), proteomic, metabolomic and lipidomic analyses of FTD disorders with other neurodegenerative disorders with similar underlying pathology (i.e. FTD-associated TDP-43 proteinopathies with ALS, LATE and other disorders; FTD-associated tauopathies including MAPT carriers, CBD, PSP and others with AD, CTE) are needed to determine common risk factors and mechanisms.
- It is increasingly recognized that mixed pathologies are common in aging and can contribute to clinical expression and variability in biomarker studies of FTD. There is a need for in-depth study of postmortem and in vivo study of mixed ADRD co-pathologies (i.e. vascular, ADNC, LBD) in FTD, as well as FTD associated pathologies (i.e. TDP-43, Annexin-A11, TMEM106b) in the context of other ADRDs.
- Determine whether genetic variants identified in one FTD subset (i.e. TMEM106B) confer risk/resilience across the FTD spectrum, other ADRDs and across populations representative of the US.
- Expand the scope and precision of human neuropathologic and biomarker studies across the FTD spectrum and related neurodegenerative disorders (FTD, ALS, AD, HD, etc.). At present, regions impacted in FTD are not often included in neuropathologic studies of disorders with possible connections to FTD such as AD and HD, and the collection of this additional information will be helpful in elucidating potential convergent and divergent mechanisms.
- Accelerate novel methods of digital pathology and multi-omics studies of human brain tissue and patient/derived materials with integration of antemortem neuroimaging and other clinical data to model and contrast disease progression of FTD and ADRD subtypes for prognostic markers and trial endpoints.

Recommendation 8 – Priority 4. Accelerate pre-clinical disease-modifying therapeutic development in FTD by leveraging known pathogenic pathways or use of mechanism-agnostic approaches such as high-throughput compound screening. (2031)

- The field has made significant progress in identifying several potential pathogenic pathways leading to FTD, yet effective therapeutics are still lacking. Increased emphasis on therapeutic development through leveraging existing areas of knowledge or use of mechanism-agnostic approaches such as high-throughput compound screening should be considered. These efforts should further collect IND-enabling information and pursue validation and clinical testing.
- Identify pathways, cell-type specific effects, and the timing of pathogenic processes relative to pre-symptomatic, prodromal, early, and late symptomatic stages of the disease. Leverage tools to identify drugs/compounds that target these pathways to model and nominate therapeutic strategies.

Session 3: MED Special Topic: Post-TBI AD/ADRD

Recommendation 1 – Priority 1. Support and engage longitudinal studies with deep multimodal clinical phenotyping, and preferably with autopsy endpoints, designed to accelerate our understanding of heterogeneous post-TBI AD/ADRD phenotypes and clinicopathologic relationships following a range of head trauma exposure(s) in populations representative of those living with TBI. (2036)

- Establish and validate quantitative metrics of lifetime head trauma based on standardized measurements to characterize a broad spectrum of clinically relevant exposures (including but not limited to isolated TBI(s), RHI, blast).
- Establish and validate clinical research diagnostic criteria for post-traumatic neurodegeneration (PTND) that distinguish chronic static clinical symptoms from progressive dementia as measured by clinical decline and changes in biofluid and imaging biomarkers that can be accessed at point of care.
- Establish blood and neuroimaging biomarkers to map the temporal progression and regional distribution of PTND, examine clinical significance of biomarker changes, and capture heterogeneity across head trauma exposure patterns and/or clinical subtypes over time.
- Prioritize investigation of chronic TBI survivors as an at-risk group with a "time zero" for comparison of TBI outcomes and post-TBI ADRDs with other ADRDs to help elucidate the earliest biologic signs of dementia risk.
- Validate biomarkers specific to post-TBI ADRD (e.g., psychometric, wearable sensors, imaging, and biofluid) to non-invasively identify post-TBI AD/ADRD endophenotypes during life, predict and monitor disease progression over time, and elucidate pathological substrates of domain-specific clinical decline.
- Determine how diverse patterns of biomechanical loadings to the brain modify the trajectory of late onset AD/ADRD, how this influences the performance of new ADRD diagnostic biomarkers, and whether the exposure patterns influence response to disease-modifying treatment with approved therapies.
- Support collection of consensus-based TBI CDEs in ongoing AD/ADRD studies, and enrich longitudinal TBI studies with AD/ADRD metrics and postmortem TBI CDEs. Optimize overlap of shared data elements across ongoing studies to facilitate cross-study comparisons and data sharing.

Recommendation 2 – Priority 2. Promote national and international interdisciplinary collaboration among TBI and dementia researchers across basic, translational, and clinical science through working groups and consortia, and promote data sharing through data infrastructure and measurement harmonization efforts. (2031)

- Convene a working group of representatives from the TBI and AD/ADRD communities to evaluate the extent to which current knowledge in AD/ADRD can be applied to the study of dementia after TBI, and how TBI contributes to AD/ADRD.
- Develop a forum for post-TBI ADRD knowledge exchange among scientists from all levels of basic, translational, and clinical research to encourage bidirectional communication (e.g., highlight clinical discoveries that reveal gaps with actionable gains from mechanistic studies; highlight basic science discoveries that may inform development of clinically accessible biomarkers and/or interpretation of factors contributing to clinically relevant pathologies).
- Delineate the unique clinical and/or biological signatures of diverse head trauma patterns, etiologies, and contexts (e.g., community/civilian TBI including those in war zones & disaster-hit areas, a range of contact sports, military combat/training, intimate partner violence, etc.) by studying these exposures in the same studies and/or using the same study methods and measurement tools.
- Support efforts to make existing data and newly collected data usable for rigorous and reproducible research. This includes revamping the structure of new or existing federated repositories to support psychometric data harmonization across studies by creating data capture tools for CDEs establishing

study-specific codebooks, supporting usability studies to simplify data collection and sharing, and requiring prospective data collection with standardized CDEs and minimum data elements.
- Foster collaboration and utilize clinical research processes that build toward the goal of regulatory support of assessment methods, patient inclusion/exclusion criteria, and safety/efficacy of therapeutic interventions in clinical trials.

Recommendation 3 – Priority 3. Conduct basic and translational research with human specimens and experimental models to characterize the post-TBI tissue response, identify mechanistic pathways and elucidate therapeutic targets for protection against and/or amelioration of pathologic progression of post-TBI AD/ADRDs. (2032)

- Deploy traditional, quantitative, and/or molecular (omics) approaches using human specimens to deeply characterize post-TBI and post-TBI AD/ADRD neuropathologies, disentangle the complex secondary injury responses and myriad contributing factors, and determine pivotal mechanistic commonalities and distinguishing features from other AD/ADRDs.
- Foster new and existing longitudinal preclinical studies to examine the temporal and regional progression of post-TBI AD/ADRD signatures to identify underlying cell and molecular mechanisms.
- Use clinically-relevant experimental systems that model distinct features of human post-TBI and post-AD/ADRD neuropathologies to identify conserved mechanisms by which head trauma, involving heterogenous early pathologies, can drive and/or contribute to the emergence of late AD/ADRD pathologies, including proteinopathies, vascular and inflammatory processes, and CTE-neuropathologic change.
- Accelerate the development, standardization, and validation of clinically relevant experimental models of aspects of head trauma across the spectrum of injury mechanisms and biomechanics; and accurately reproduce their distinct and interactive acute and chronic neuropathological and behavioral sequelae.
- Support clinical and translational research to disentangle associations and causal pathways of falls and other head trauma etiologies with PTND and other ADRD processes, given the possibility that ADRDs may elevate risk for late-life TBI and TBI in older adults may initiate and/or accelerate ADRD risk and pathogenesis.
- Integrate clinical and experimental research to identify intrinsic (e.g., genetic, proteomic) factors that confer resilience/susceptibility to pathologic and cognitive decline after TBI and during aging, and overlay environmental (e.g. socioeconomic, educational, lifestyle) factors to personalize patient phenotyping and guide care.

Recommendation 4 – Priority 4. Accelerate translation of scientific advances into clinical application, and ensure established and evolving knowledge is shared with people living with TBI and/or post-TBI AD/ADRD and their communities. (2035)

- Support collaboration across federal agencies and between clinicians, researchers, community partners, and implementation scientists to develop and conduct clinically relevant rigorous research that aligns with the needs and priorities of people with lived experience to reduce the burden of post-TBI ADRDs.
- Advance findings from preclinical and clinical studies of TBI and ADRD to support development, validation, translation and implementation of diagnostic approaches and holistic interventions to prevent or delay the onset of post-TBI ADRD in representative clinical populations.
- Encourage the pre-competitive space regulatory endorsements and partnerships with advanced development and advocacy organizations to collaborate to ensure post-TBI AD/ADRD diagnoses are considered in development of interventions for dementia(s).

- Establish and support use of standard nomenclature for characterizing head trauma exposure(s) and PTNDs to facilitate accessible communication and multi-partner collaborations that promote knowledge sharing and translating findings into clinical practice.
- Build opportunities for knowledge sharing amongst people living with TBI, clinicians, researchers, and other interested communities to optimize engagement with research and maximize clinical translatability in the study of TBI-AD/ADRD.

Session 4: MED Special Topic: LATE (TDP-43 in Common Late-Onset Dementias)

Recommendation 1 – Priority 1. Develop and expand deeply phenotyped cohorts with preferably post-mortem data to evaluate distinct vs. shared features of LATE-NC with FTLD-TDP and mixed etiology dementia (e.g., ADNC + LATE-NC), aiming to identify diagnostic and therapeutic strategies and enhance public and interdisciplinary awareness. (2032)

- Harmonize and expand or develop representative community and other cohorts combining in-vivo neuroimaging, biofluids, and genetic markers with autopsy data, including quantitative digital pathology and ex-vivo MRI to determine the clinical, genetic, pathologic, biomarker, and environmental correlates of LATE-NC.
    - Improve and expand clinically-characterized LATE patient and autopsy-confirmed LATE neuropathologic change (LATE-NC) registries.
        - Incorporate medical, genetic, and exposome information when indicated.
        - Develop prospective cohorts enriched in individuals with LATE-NC.
    - Define the clinical features (cognitive, behavioral, in vivo imaging) and underlying mechanisms of people with pre-clinical/early-stage LATE (cognitively unimpaired persons, SuperAgers, and/or resilient individuals).
    - An ultimate goal is to provide at-risk people with a choice for participating in clinical trials
- Broaden knowledge of the clinical-pathologic spectrum and heterogeneity of LATE and LATE-NC, while integrating genetic and molecular features.
    - Explore LATE-NC heterogeneity (including early initiation of the pathology) – either synergistic with or independent of ADNC.
    - Compare the clinical-pathologic characteristics of pure LATE-NC with LATE-NC comorbid with other neurodegenerative diseases (e.g. LBD).
    - Clarify the clinical features associated with various pathologic stages of LATE-NC (including neuropsychological profiles, neurobehavioral, and neuropsychiatric features, using demographically-adjusted normative samples).
    - Examine the usefulness of digital/quantitative neuropathology rather than only “stage”-based criteria for disease instantiation and severity.
    - Assess the impact of anti-Aβ immunotherapies on LATE-NC (or other mixed pathologies) in ADNC+LATE-NC and the degree to which earlier or later treatment influences outcomes.
- Uncover shared and unique features of LATE-NC vs. FTLD-TDP, ADNC, and mixed neurodegenerative etiologies that may represent diagnostic and therapeutic opportunities.
    - Clarify similarities and differences between severe LATE-NC and early FTLD-TDP, CTE, quadruple misfolded pathology (ADNC+LATE-NC+LBD)
    - Clarify the significance of *GRN*, *TMEM106B*, *SORL1, APOE* and other genetic drivers of LATE-NC.
    - Assess the potential for stratification of LATE-NC risk (vs ADNC, vs ADNC+LATE-NC) for clinical trials and improved clinical care.
- Support research infrastructure on TDP-43 pathophysiology across LATE-NC, and other TDP-43 proteinopathies (e,g., ALS, FTLD) to share and integrate perspectives, and identify opportunities for collaboration.

    - Host a meeting/workshop of TDP-43 pathophysiology that includes interest in LATE-NC with other TDP-43 proteinopathies.
    - Bridge the TDP-43 research-oriented data streams through expansion of knowledge and sharing of datasets and registries.
- Garner and expand awareness and medical education on LATE to clinicians, researchers, and patients.
    - Support medical education and training for neurologists, and PCPs that adds information on all non-Alzheimer's ADRDs, including LATE, as part of the expanded medical education underway for neurodegenerative biomarkers and therapeutics, particularly in the context of available anti-amyloid treatments.
    - Develop easily digestible educational resources on LATE for patients, including psychoeducational tools, which would help garner awareness and further advocacy.
    - Support education and training about LATE and other TDP-43 proteinopathies for clinical researchers and biomarker specialists (including academia and industry representatives).

Recommendation 2 – Priority 2. Develop and validate in-vivo biomarkers, classifiers, risk profiles, and clinical criteria for LATE/LATE-NC in persons without cognitive symptoms and in persons with amnestic or other relevant late-life dementia syndromes, leveraging the existing and new infrastructure from Recommendation 1. (2031)

- Refine our understanding of the cognitive, behavioral, and genetic features associated with LATE-NC alone or in the presence of co-pathology.
- Test (validate) the clinical criteria for LATE using longitudinal observation studies, emerging biofluid and neuroimaging markers, and neuropathology, and update these criteria as necessary based on the latest developments in the field.
- Develop and test (validate) biofluid (e.g., blood or CSF) or neuroimaging (e.g., MRI, PET) biomarkers, or combined fluid and imaging markers that show good discrimination or prediction of the molecular pathophysiology of LATE-NC (i.e., TDP-43) and its stages.

Recommendation 3 – Priority 3. Advance knowledge of the causes of LATE-NC through human (e.g. genetics and tissue studies) and experimental models (e.g. organism, cell culture, biochemical) incorporating aging and behavioral, pathologic, molecular, and structural phenotypes of TDP-43 proteinopathy/co-pathologies to develop targets and test therapeutics. (2034)

- Design, develop, and characterize mechanistic models of LATE-NC that capture TDP-43-dependent clinical, pathological, and molecular phenotypes. This may include:
    - Employing virally transduced, knock-in, gene-edited, transgenic, inducible-promoter, or stress-induced animal models that develop LATE-NC phenotypes including pathology in anatomically relevant areas, age-related pathology, and/or hippocampal sclerosis.
    - Defining glial/neuronal inflammatory contributions to TDP-43 proteinopathy, specifically in aging.
    - Modelling the pathologic intersections between TDP-43 and existing co-pathologies, e.g. amyloid, tau, α-synuclein, arteriolosclerosis.
    - Developing human cell (e.g. iPSC and human brain organoid) models of LATE-NC.
    - Incorporating LATE-specific ultrastructure of TDP-43 and co-deposited proteins (e.g. TMEM106B, ANXA11) in organism, cell culture, and biochemical models of LATE to link structural conversion of TDP-43 in LATE-NC to function/dysfunction transition.

- Study mechanistic basis of disease initiation, neuronal loss, brain region specificity, age-related progression, and prion-like transmission of pathological TDP-43 species to understand the anatomical and time/age progression of LATE-NC and TDP-43 pathology
- Study molecular and cellular features of LATE-NC pathophysiology (e.g., TDP-43 localization, transcriptomic and splicing dysregulation and other loss/gain of function changes, cellular changes associated with LATE-NC) in human tissue and relevant animal/cellular models
- Determine TDP-43 ultrastructure, post-translational modifications, and the composition and importance of binding partners/co-deposited proteins (e.g. TMEM106B, ANXA11) in native/physiological states and their pathological conversion and changes in patient samples and models of disease.
- Discover genetic causative mutations and risk factors for LATE-NC and evaluate if additional risk genes for other TDP-43 pathologies are associated with LATE-NC.
- Take action on testing cellular and animal models in preclinical therapeutic development and testing pipelines for LATE-NC.

Recommendation 4 – Priority 4. Study hippocampal sclerosis of aging (HS-A), and the selective vulnerability of limbic neurons in LATE, FTLD-TDP, and mixed pathologies (e.g. ADNC/LATE-NC), with emphases on advancing clinical and pathologic diagnoses and the mechanistic roles of senescence, vasculopathy, and inflammation. (2032)

- Develop standardized terminology and guidelines for pathologic HS-A; and biomarkers to identify HS of aging (HS-A) clinically.
    - Create consensus guidelines for pathologic classification and standard nomenclarure for HS-A
    - Both neuroimaging and biofluids will be important to investigate as clinical biomarkers, with emphases on quantitative metrics and cutoffs.
    - Antemortem and postmortem imaging studies may link specific MRI changes (shape, signal, texture, particularly in the medial temporal lobe) with HS-A.
    - Risk profiles could be developed, incorporating demographics, biomarkers, genetic polymorphisms, and other risk factors, in association with pathology, to aid in prognostication and clinical trial stratification; again, an emphasis would be on quantitative metrics.
    - Biomarker/risk profiles for HS-A with TDP-43 pathology should be compared to HS-A profiles without TDP-43 pathology.
- Explore pathological variation within the spectrum of HS-A to refine diagnosis of HS-A including characteristic features of protein inclusions, neuronal loss, and glial and vascular changes.
    - Gather and apply new information about pathological variation within the spectrum of HS-A to aid in pathologic diagnosis, biomarker development, and therapeutic strategies.
    - Study pathologic variation in relation to vasculopathy. Determine the structural and biochemical nature of the small vessel disease (SVD) and vessel wall constituent changes seen in LATE+/-HS-A, and ascertain if this differs from SVD without LATE +/- HS-A.
    - Study pathologic variation in relation to aging and senescence. Probe associations between HS-A spectrum disease, chronological aging, and senescence markers.
    - Assess the associations between brain inflammation (microgliosis, astrocytosis), biofluid assays of inflammation (e.g., IL-1B and TNF-alpha), and other inflammatory signaling markers) across the pathologic spectrum of HS-A.
    - Explore the mechanism(s) for the common co-occurrence of LATE-NC, SVD, and HS-A.

Session 5: MED - Basic and Clinical Discovery Research

Recommendation 1 – Priority 1. Conduct new and leverage existing longitudinal studies across broad populations and across sexes integrating cognition and behavior with various combinations of neuroimaging, biofluid, multi-omics, and neurophysiological biomarkers, and post-mortem verification, to identify the relative contribution of regional pathology and validate predictive MED phenotypes, including vascular pathology, risk factors, exposome, and response to therapy. (2032)

- Increase research and training on how multi-modal biomarkers interact with each other and whether there is a need for separate cut points and/or diagnostic decision rules in MED to aid in precision medicine approaches.
- Determine the impact of AD-specific therapies on biomarkers, and other MED pathologies.
- Promote brain and biosample donation and facilitate access to human material to enable correlation of clinical features, genetics and biomarkers with neuropathology.
- Use novel clinical and biomarker AI-aided tools to predict dementia risk, prognosis, response to risk-reducing interventions and therapy across the life course.
- Examine the impact of comorbid conditions and the exposome on established and new biomarkers to define threshold cutoffs (and/or decision rules) and unveil combinations of biomarkers that may indicate mixed pathology.
- Use existing real-world datasets (e.g. claims data, genetic biobanks, digital assessment tools, etc.) to aid in verifying clinical and biomarker findings across diverse ethnic groups and sexes.
- Develop statistical modeling approaches to understand additive, synergistic, mediation and/or moderation effects inherent in multi-etiology disease components.
- Seek input from patient/caregiver communities to help define the highest-priority symptoms for therapeutic targeting.

Recommendation 2 – Priority 2. Advance basic research in experimental models on single, multiple and interacting mechanisms driving mixed pathology, inclusive of comorbidities and across sexes, with emphasis on bidirectional validation in human datasets and identification of therapeutic targets. (2032)

- Develop new animal and non-animal-based (cell, brain on chip, organoids, etc.) models of mixed pathology to better capture the temporal evolution, interactions, critical checkpoints and windows for intervention.
- Encourage the use of protocols that take into account sex, age and comorbidities across all stages of animal development.
- Use state-of-the-art technologies (RNA processing, single cell-spatial -omics, epigenetics, gene editing, repeatomics, medicinal chemistry techniques, etc.) and advanced analytical approaches to identify upstream pathogenic mechanisms driving mixed pathologies and their downstream effectors for therapeutic targeting.
- Establish multidisciplinary and mixed basic-clinical research teams with the expertise to tackle multiple interacting pathogenic factors.
- Establish open-access repositories for experimental designs, methods, negative data and other information that can be shared with the entire scientific community.

- For promising therapeutic targets, promote mechanisms through interdisciplinary public-private partnerships to establish a rapid consensus on models, primary outcomes definitions, sample size, etc. to ensure no delays in translating to clinical trials.

Recommendation 3 – Priority 3. Support research in basic, translational, and clinical data standardization, harmonization and integration using established and new clinical and biomarker data collection approaches. (2032)

- Promote open-source digital imaging tools, AI-driven and machine learning techniques to develop scalable, cost-effective, and quantitative approaches to standardize and harmonize datasets and promote crosstalk across platforms to understand how mixed pathologies develop and interact.
- Develop open-source platforms for storage, analysis, visualization and integration of existing and new data in human, cell-based and animal studies, consistent with national and international policies.
- Focus on approaches providing insight into drug development and repurposing, and promotion of shared analytical practices across MED studies.
- Develop pathways for MED to be coded appropriately in electronic medical records (EMRs) to improve harmonization with EMR-based research and clinical care practices.
- Establish uniform metrics for data integration across biomarker platforms to facilitate cross-study comparisons.
- Convene representatives from all major database groups to enable/create common code/harmonizations with goal of ability to compare datasets interchangeably.
- Data for standardization, harmonization and integration may include but are not limited to multiple biorepositories and cohorts among academic institutions, government, industry, nonprofit organizations, and other agencies (including public-private partnerships).

Recommendation 4 – Priority 4. Enhance ongoing scientific and clinical education and training on MED to increase the size and breadth of the interdisciplinary dementia capable workforce, to improve the understanding, diagnostic accuracy, and appropriate treatment of individuals with multiple pathologies. (2032)

- Develop and/or expand MED clinical trial investigator and early-career/basic and translational research training programs that integrate MED principles into research study design, informatic/data science approaches, use of biosamples, and neuropathological characterization.
- Promote research in implementation science to increase reach to a broader swath of researchers and clinicians, including primary care clinicians, who interact with individuals affected by ADRDs and their families.
- Integrate practical training methods to facilitate earlier adoption of novel diagnostic approaches across MED into research trial design and clinical workflow.
- Ensure new and evolving MED diagnostic and prognostic tools are integrated into clinical trial protocols and tied to ongoing implementation research across a broad spectrum of clinical settings, taking into account diagnostic sensitivity and specificity as well as factors related to ease of access and dissemination.
- Promote education to ensure that clinicians have the skills to use novel diagnostic tools to differentiate AD, ADRD, and MED taking into account the relative contributions of other pathogenic factors and/or alternative diagnoses.

Session 6: Lewy Body Dementias (LBD)

Recommendation 1 – Priority 1. Expand LBD clinical trial infrastructure and perform trials aimed to slow the clinical course, delay, and/or prevent the onset of symptoms, in addition to alleviating clinical symptoms. (2033)

- Promote LBD clinical trials and expand the footprint and scope of LBD clinical trials. Trials should explore novel therapeutics for LBD and repurpose treatments that mechanistically could benefit individuals with LBD. Efforts to develop and test agents must be supported by the knowledge gained from genetic, experimental models, environmental studies, and systematic profiling of well-characterized human samples (see recommendation #2) that identify underlying disease mechanisms and biomarkers (see recommendation #3 and #4). The long-term goal is to identify disease-targeted therapeutic approaches that slow, delay, and/or prevent symptom development, and symptomatic therapeutic approaches that ameliorate the physical, cognitive, and/or psychiatric symptoms of people living with LBD. Symptomatic treatments should focus on inadequately treated symptoms significantly impacting the function of people living with LBD and caregiver burden (for example, cognitive fluctuations, REM sleep behavior disorder (RBD), autonomic dysfunction, apathy, and/or psychosis). Consideration should be given to people living with LBD/caregiver communities to help define the highest-priority symptoms to be targeted (i.e., those responsible for the most significant distress and burden). Disease-targeted therapies aimed at slowing the clinical course and delaying or preventing the onset of symptoms should be informed by recommendations #2, #5, #6, #7, and/or #8. These strategies would include pharmacologic, gene therapy, and regenerative medicine approaches, among others, by enhancing the clearance of protein aggregates, modulating signaling pathways, reducing the accumulation or transmission of toxic protein aggregates, enhancing synaptic function and resistance to disease pathology, and/or immunomodulation.
- Recruit a broad selection of clinical trial participants. Clinical trials should include people living with LBD, either with dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), or Parkinson's disease (PD). Trials should be conducted across the cognitive spectrum, including mild cognitive impairment of Parkinson's disease (MCI-PD), prodromal DLB, and pre-symptomatic stages. Clinical trial participants could include persons with α-synuclein biomarker positive RBD, hyposmia/anosmia, constipation, and/or late-onset psychosis (hallucinations and delusions), or other non-motor symptoms (informed by recommendation #2). Participants could also be recruited based on highly penetrant mutations with mendelian inheritance (e.g., SNCA). The clinical trial participants should represent U.S. individuals living with LBD regarding geographic, racial/ethnic, sex, socioeconomic, and cultural composition.
- Progress promising therapeutic target selection. Promote: 1) a therapeutic trial of at least one novel drug targeting known or emerging genetic (e.g., GBA) or neuropathological targets and mechanisms implicated in LBD; 2) at least one novel approach to address targets to preserve or restore synaptic function in circuits damaged by LBD pathology; 3) an approach focusing on neuroinflammation. By 2029, have at least one additional novel compound strategy focused on symptom modification and at least one current U.S. Food & Drug Administration (FDA)-approved compound enter clinical trials. By 2031, at least two "disease-pathology-targeting" agents and at least three "symptomatic" agents enter clinical trials.
- Enhance the pre-clinical infrastructure required to support LBD drug development. These infrastructure requirements include one or more aspects of the pre-clinical development pipeline (e.g., screening, confirmation, lead compounds optimization, pre-clinical efficacy studies, initial toxicology studies). This infrastructure will also include training for early career individuals and those new to the field to aid in

the clinical trials workforce for LBD.

- Develop and validate LBD-specific scales to refine clinical trial outcome measures. As part of the development of a clinical trial resources, one or more sensitive, LBD-specific clinical outcome measures should be developed by 2028 to encompass the complex phenomenology and heterogeneity inherent to LBD symptomatology. LBD-specific clinical outcome measures should reflect LBD-relevant cognitive, neuropsychiatric/behavioral, motor, sleep, autonomic, sensory, and/or other clinical domains, as well as (instrumental) activities of daily living (ADL). Scalable, easy to use clinical tools to track cognitive changes with consideration to cognitive fluctuations (via neuropsychological measures or batteries) and debilitating symptoms (e.g., autonomic features, etc.) in LBD are urgently needed. Similar or additional tools to track changes in early disease cohorts are also required, including at-risk, pre-symptomatic with biomarker evidence of LBD, and symptomatically prodromal or early manifest disease (see also recommendations #2 and #3). The goal of any composite measure would be to track change over time and be easily used in clinical trials. A key component or supplement to any such measure must include input from persons/families with LBD on the clinical meaningfulness and relevance to the patient and caregiver experience. Proposed metric: develop a consensus proposal for developing and validating one or more clinical outcome measure(s) over the upcoming 3 years. New or existing methods for detecting and tracking LBD features should undergo multicenter validation, and normative data should be generated using these new methods to aid in generalizability. New outcome measures should be developed in consultation and collaboration with global regulatory authorities, including the FDA, the European Medicines Agency (EMA), and others.
- Enhance open-source infrastructure to aid in streamlined sharing of data and samples collected in clinical trials. Clinical trials provide valuable information and lessons that inform future therapeutic endeavors and might explain treatment failures, differential responses, or frequency of adverse reactions to medication.
- Harmonize measures across LBD clinical trials. Cross-study standardization (e.g., clinical, biofluid, imaging, and other outcome measures) must occur to the greatest extent possible (see also recommendations #2, #3, and #4), including harmonization with non-LBD ADRD cohorts. These efforts will help identify and resolve factors needed to standardize measurements for multicenter clinical trials. Since LBD is clinically and pathologically heterogeneous, and several pathologic and genetic factors likely contribute, biomarkers (see also recommendations #3) should be incorporated into trial design and, in many instances, be required as inclusion criteria (e.g., Lewy body pathology biomarkers) during the enrollment. Biomarkers could also stratify to improve the ability to evaluate differential treatment responses in LBD cohorts and account for different progression rates, thus improving statistical power and likelihood of success. Informed consents should contain language that allows for multi-use of data and biospecimens, such as broad data and biospecimen sharing. Proposed metrics: 1) develop a robust infrastructure, including consensus protocol elements, for conducting multi-site LBD clinical trials by 2028 (see recommendation #4), and 2) develop one or more multi-disciplinary working groups of investigators (including statistical, neuropathological, biomarker, and clinical expertise) from relevant pharma companies, medical, and research community, and the general public in 2026 to address barriers to clinical trials in LBD.

Recommendation 2 – Priority 2. Expand and develop clinically, biologically, and/or genetically deeply phenotyped LBD cohorts, representative of the U.S. population with LBD, from pre-symptomatic disease to autopsy. (2033)

- Expanding existing and develop new cohorts with LBD to support diagnostic, epidemiologic, and therapeutic studies. These cohorts should be defined clinically, biologically, and/or genetically. They

should also include at-risk, pre-symptomatic individuals with biomarker evidence of LBD, symptomatically prodromal or early manifest disease, and late disease, through autopsy (see recommendation #6). LBD-specific scales, clinical trial type cohorts, and disease-specific diagnostic and prognostic biomarkers are still being developed. Most LBD recommendations require the support of well-characterized and deeply phenotyped individuals with LBD, along with associated imaging, biosamples, genetic, and neuropathologic characterization, to better prognosticate the disease, identify therapeutic targets, and design adequate clinical trials. These cohorts will enhance clinical trial designs, accelerate recruitment, development, and validation of new biofluid and imaging biomarkers, genetic discoveries, and neuropathologic studies. As there can be discordance between outward signs and symptoms (i.e., clinical diagnoses) and the underlying pathophysiology of disease (neuropathology diagnoses), longitudinal studies with autopsy are highly encouraged. Thus, continued prioritization is needed for efforts to expand longitudinal LBD cohorts with deep phenotyping that share data and samples through a network of repositories with a coordinating center to allow for broad utilization by the LBD research community. Enhancing and streamlining information systems to aid in integrating these specialized data is recommended. These deeply phenotyped cohorts require a considerable time commitment from participants and resources; therefore, additional studies with a lower participant burden might focus on end-of-life aspects, the collection of a large number of samples for genetic research, or remote data collection when appropriate.

- Participants should broadly represent U.S. individuals living with LBD. Broad representation will ensure generalizability of findings across the entire population and allow factors that may influence variability of LBD to be identified Increasing the workforce of specialized researchers and coordinators representing the demographics of the area, who are dedicated to LBD community outreach and education in specific communities is recommended.
- Develop a workforce with the skills necessary to successfully expand the research scope and pipeline in this endeavor. Enhance robust training pipelines for individuals early in their careers with an emphasis on training across repositories to facilitate the exchange of knowledge and expertise in informatics, biosample collection and analysis, genetic, and/or neuropathologic characterization. The inclusion of people with different backgrounds and expertise, who represent persons with LBD across the population in training pipelines is highly encouraged.
- Deep clinical phenotyping is necessary. Deep phenotyping includes the characterization of cognitive, motor, psychiatric, autonomic, and behavioral changes over time, as well as quality of life, function scales, and assessments of caregiver burden. Demographics should also include comorbid health conditions, as well as risk factors. Digital biomarkers could assist with phenotyping across a broad range of participant cohorts with remote, continuous, and/or quantitative data collection (see also Recommendation #3). Studies should consider the sequence and frequency of assessments that are compatible with interventional clinical trials.

- Harmonization of data is necessary across cohorts. Compatible cohorts are needed to enable the development of sufficiently large datasets that can capture the heterogeneity across the spectrum of LBD (including clinical progression, rate of decline, mixed pathologies, etc.), leading to a better design of clinical trials and improved prognosis in clinical practice. This effort would benefit from recommendations for standard phenotyping, imaging, and biofluid collection methods across cohorts, including representative populations and coordination with non-U.S.-based LBD research-based programs. To accomplish this goal, we recommend developing recommendations/guidelines to

harmonize studies to merge datasets across existing and future study cohorts, including LBD-specific measures and with relevant measures to enable comparisons with other ADRD and PD cohorts (both U.S. and non-U.S.-based programs) and develop clinical trial outcome measures (recommendation #1). Datasets should contain cognitive, autonomic, psychiatric, motor, biomarker, and/or neuropathologic characteristics. A multi-disciplinary working group should develop and publish recommended common data elements and collection protocols (see also proposals from other recommendations) to allow the research community to collaborate and utilize data and biological specimens.

Recommendation 3 – Priority 3. Refine and validate existing diagnostic biomarkers and develop new biomarkers related to Lewy body pathology, and identify biomarkers for mixed etiology dementia that includes Lewy body pathology. (2031)

- Current Lewy body-specific diagnostic biomarkers need refinement and validation, and new biomarkers need to be developed. This includes biomarkers that can be translated into clinical use, in addition to clinical trial use. These studies will capitalize on existing or new cross-sectional, case-control, and longitudinal studies of individuals across the LBD spectrum (at risk, pre-symptomatic, as well as symptomatic) in which symptoms of cognitive and/or motor decline, neuropsychiatric, and autonomic changes predominate (see recommendation #2). Building on and extending existing cohort studies and establishing new cohorts will support these aspects of the biomarker discovery and validation portfolio (2026-2031).
- Validate current α-synuclein biomarkers to detect individuals with Lewy body pathology. This includes the α-synuclein seed amplification assay in biofluids or peripheral tissues and immunohistochemistry in peripheral tissue biopsies, in representative cohorts including clinical spectrum (ranging from pre-symptomatic to clinically symptomatic LBD) and neuropathologic heterogeneity (those with concomitant diagnoses such as vascular disease, Alzheimer disease , etc.). Validation should include people that broadly represent U.S. individuals living with LBD for generalizability (see recommendation #2). Validation with post-mortem confirmation of Lewy body pathology should include biomarker collection before symptoms develop, very early in symptom development, with fully manifest symptoms of LBD, and at end-of-life.
- Develop new α-synuclein biomarkers to detect pathology, which are minimally invasive, cost-effective, scalable, and quantify the degree of α-synuclein deposition. Emphasis should be placed on biomarker modalities demonstrating high reproducibility across populations with biomarkers categorized by their scalability to clinical trials (see recommendation #1) and for possible clinical use, including availability and cost. Evaluate the feasibility of novel α-synuclein specific biomarkers developed in the research setting for use in clinical trials where resources may be limited or heterogeneous across sites. Future diagnostic biomarkers should be accessible to individuals that broadly represent U.S. persons living with LBD.
- Develop at least one α-synuclein PET tracer by 2033. The α-synuclein PET tracer should be sensitive and specific to misfolded α-synuclein in the human brain, ideally distinguishing between predominantly neuronal (Lewy bodies) and predominantly glial (glial cytoplasmic inclusions) misfolded α-synuclein. Establish the biochemical and biophysical features of the tracers as well as safety and efficacy in human trials. Validate α-synuclein tracers against post-mortem neuropathology using both in vivo and ex vivo imaging as well as autoradiography studies on human tissues. Compare the performance of α-synuclein tracers with current α-synuclein biomarkers with the seed amplification assay in the CSF and/or immunohistochemistry in peripheral tissue biopsies, as well as with markers of downstream neurodegenerative change such as nigrostriatal dopaminergic imaging or myocardial sympathetic innervation imaging in LBD and other neurodegenerative dementias and parkinsonian disorders.

- Develop approaches to share results of validated biomarkers. This includes educating patients, caregivers, and providers about biomarkers. Study approaches to share results in at-risk and pre-symptomatic populations, and consequences of revealing this information. (2027-2029)
- Develop biomarkers of biological processes that precede and accompany the development of α-synuclein pathology. This includes synaptic, lysosomal, mitochondrial, inflammatory, and other processes related to alpha-synuclein pathology, as informed by recommendation #6 and #7.
- Investigate α-synuclein biomarkers in mixed etiology dementia. Determine current α-synuclein biomarkers, new α-synuclein biomarkers, and imaging α-synuclein biomarkers potential for sensitivity/specificity to identify Lewy body pathology in the setting of individuals with mixed etiology dementia, including individuals with β-amyloid, TDP-43, tau, and other protein deposits as well as vascular pathology. Determine LBD heterogeneity, clinical phenotypes, and pathophysiologic underpinnings of core clinical features of LBD with α-synuclein biomarkers to aid in precision medicine approaches. Develop new and utilize established biological markers and imaging tools to determine the evolution of the multi-proteinopathy, including synergistic interactions of proteins across brain regions and time in LBD. This approach will facilitate the development of synergistic multimodal biomarker strategies to enhance the accuracy of diagnosis and the reliability of progression measurements during all stages of the disease.

Recommendation 4 – Priority 4. Develop and refine biomarkers of neuronal injury, neurotransmitters, pathophysiology, and neurodegeneration that are predictive and prognostic, provide monitoring to track progression, and identify therapeutic target engagement and biological response to therapeutic interventions. (2033)

- Refine, validate, and develop biomarkers across populations and stages of disease. Capitalizing on existing or new cross-sectional, case-control, and longitudinal studies of individuals throughout the course of LBD (from pre-symptomatic biomarker-positive cases through to those with clinical manifestations and associated disability), in which symptoms of cognitive and/or motor decline, neuropsychiatric, and autonomic changes are tracked (see also recommendation #2 and #3).
- Correlate biomarkers with clinically meaningful signs, symptoms and disability in LBD. Biomarkers tracking pre-symptomatic to symptomatic LBD should predict and correlate with meaningful clinical changes.
- Biomarkers should track key biological processes. These can include 1) pathophysiological changes related to LBD (e.g., synaptic, lysosomal, mitochondrial, immunologic, and other processes related to α-synuclein pathology), 2) changes related to multi-neurotransmitter impairment (cholinergic, noradrenergic, dopaminergic, and others), and 3) neurodegenerative changes related to Lewy body pathology as well as changes due to other proteinopathies (such as β-amyloid, tau, and/or TDP-43 deposits) 3) vascular pathologies. The time-course of these biomarker changes should be assessed using new and existing cohorts (see recommendation #2). During biomarker development, the context of use should be defined and validated, such as prediction and prognosis, monitoring, or use in clinical trials, including stratification and enrichment, monitoring response to therapies, and measuring outcomes (see recommendations #1 & #2). Cost-effectiveness and scalability of workflows should also be considered. Proposed metric: at least one panel of biomarkers reflecting the multiple proteinopathies and vascular changes in LBD will undergo validation as having predictive/prognostic value. Prioritize studies of biomarkers and panels with the goal of eventual College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments (CLIA) and FDA approval within 2-7 years.

- Biomarkers should be developed that are sensitive to cellular dysfunction and brain circuit changes. This is critical to determine potentially reversibility of brain changes in LBD, and could be leveraged as a marker in interventional clinical trials.
- Biomarker discovery and evaluation should occur across broad types of human samples and biofluids. Where appropriate, human samples can include skin, colon, salivary gland, peripheral blood mononuclear cells (PBMCs), and others; biofluids can include whole blood, plasma, CSF, urine, saliva, tears, microbiome samples, and others. Novel biomarkers or biomarkers in different tissues should be compared to gold standards (i.e., autopsy diagnoses) wherever possible. Targeted and -omic approaches to biomarker discovery and development should be pursued. To improve scientific rigor, collection and biomarker analysis of CSF, blood, and skin biopsies from participants should occur across two or more cohorts from different sites. Proposed metric: creating a secure catalog of cohorts and samples available at government and non-government organizations (1-2 years, see also recommendations #1 and #2). Biomarker data generated should be deposited into this database to allow sharing of well-curated samples and data following FAIR principles (Findable, Accessible, Interoperable, and Reusable).
- Develop in-vivo imaging biomarkers. Priorities include 1) establish reproducibility and the expected change over time relevant for clinical trials (see recommendation #1); 2) characterize and monitor disease progression in natural history and genetic studies (see recommendations #2) by integrating established and new imaging tools; and 3) validate these tools against post-mortem neuropathology using both in vivo and ex vivo imaging as well as autoradiography studies on human tissues. Utilize a multicenter approach to determine the scalability of techniques and prepare for Phase 2 and Phase 3 trials. Incorporate multimodal analyses, including electroencephalogram, systems-level biomarkers, or biofluid biomarkers to enhance the reliability of prediction of disease progression. Establish open source/access datasets to enable machine learning approaches. For these approaches to be successful, protocol harmonization and data sharing are essential (see recommendation #2); however, post-acquisition harmonization of legacy data should also be considered. Emphasis should be placed on imaging modalities demonstrating high reproducibility across heterogeneous populations, imaging sites, and imaging platforms. Imaging tools should be categorized by their scalability to clinical trials (see recommendation #1) and for possible clinical use, including availability and cost. Evaluate the feasibility of imaging biomarkers developed in the research setting for use in clinical trials where imaging resources may be limited or heterogeneous across sites.
- Bidirectional validation of biomarkers is recommended. Efforts should be made to develop comparable biomarkers in model systems (e.g., animal models; iPSC-derived models, etc.) to those biomarkers identified in human studies that lead to better screening or assessment of therapeutic targets; this process should be bidirectional (see recommendations #7 and #8). (2027-2031).
- Develop and validate digital and neurophysiological approaches to biomarkers. These should include wearables, electroencephalogram, polysomnography, computerized testing, home-based monitoring of lifestyle, behavior, cognition, neuropsychiatric symptoms, autonomic function, activity, and/or sleep across all stages of LBD. Regardless of the approach, attention should be paid to optimizing the assessment to be as unobtrusive or ambient as possible to maximize the ecological validity of the data captured. Attention to feasibility, cost-effectiveness, scalability, acceptability of methods to participants, and compliance is essential. Defining the psychometric properties and validating these approaches to track progression is critical. Quantitative approaches should be adapted for telehealth and clinical trials. Proposed metric: at least one digital biomarker study is initiated in 2-5 years.

Workshops should develop feasibility, acceptability, and compliance metrics to be applied to studies during the next 1-2 years. A workshop should explore how to make data shareable from open-source vs proprietary biomarkers and analytical methods in 1-2 years.

- Biomarkers might have different uses in different disease stages (at-risk, pre-symptomatic, and symptomatic) and phenotypes (motor, sleep, cognitive, and psychiatric) and will need to be evaluated in LBD cohorts across the disease spectrum (recommendation #2).
- Harmonize image acquisition and sample collection and processing protocols. One or more integrative multi-site studies of biomarkers with a multi-disciplinary investigative team of investigators (clinical, biomarker, neuropathology, biology, statistical, and others) will be initiated in 2-5 years.

Recommendation 5 – Priority 2. Integrate functional genomics of LBD by delineating genetic loci and their functions contributing to the onset and progression of LBD using multi-omic characterization analyses, to support drug discovery. (2033)

- Further genetic discovery in LBD. Discover and replicate genetic variants associated with development or progression of LBD. Substantial success has been achieved with the execution of large-scale association studies. Systematic identification and validation of novel genetic, epigenetic, and environmental determinants associated with risk for LBDs; or with core clinical or neuropathological features of LBD remains a major goal. This recommendation also includes the identification of genetic and epigenetic factors influencing the risk of developing dementia in individuals with pre-existing PD, pre-symptomatic LBD or influencing the rate of disease progression. There is a related need to develop polygenic scores for longitudinal prediction of risk of LBD and for clinical trials; (e.g., for enrichment and stratification). Finally, studies that integrate genetic risk with environmental exposures ("gene-exposome studies") are encouraged. (2026-2029)
- Further genetic discovery in LBD with mixed etiology dementia. Studies that include genetically defined cohorts could be leveraged to understand the relationship between β-amyloid, TDP-43, tau, other protein deposits, and cerebrovascular pathology and the development of α-synuclein protein aggregation.
- Integrate genomics with cohorts described in recommendation #2. To advance this research, large cross-sectional and longitudinal cohorts and LBD families are needed. This includes expanding follow-up, recruitment, or phenotyping for existing cohorts and establishing new cohorts.
- Functionalize LBD-associated genetic variants into mechanisms, therapeutic targets, and biomarkers. This recommendation involves both clarifying the target genes underlying genetic association signals and linking these target genes to biological pathways through mechanistic work. Proposed metric: elucidate the functional mechanism of at least one novel genetic locus linked to the risk of LBD (see recommendation #7). (2026-2031)
- Clarify the divergences and convergences in the genetic, molecular, neuropathological, and clinical landscape of LBD and related neurodegenerative diseases. LBD are clinically and neuropathologically heterogeneous (e.g., showing Lewy bodies, amyloid plaques, tangles, etc.), and there is a need to identify aspects of the broad landscape that may be shared with or different from other neurodegenerative diseases and dementias. Successful completion of this goal requires innovative analytical approaches and data sets suitable for these analyses across LBD and related neurodegenerative diseases.
- Prioritize innovative data analytics and data platforms. Although progress has been made on centralizing knowledge, there remains a need to expand on existing platforms and to develop new solutions for streamlined sharing and analysis of data. We recommend development and maintenance of open-source platforms to facilitate data sharing, to generate and harmonize high-dimensional datasets, to visualize

complex data, and to enable comparative analyses between LBD and neurodegenerative diseases that share molecular mechanisms with LBD.

Recommendation 6 – Priority 3. Enhance and harmonize techniques for neuropathologic characterization of LBD, for use in well-characterized and representative LBD pathology cohorts. (2033)

- Enhance practices for neuropathologic evaluation of LBD. Methods to harmonize neuropathologic characterization (e.g., minimal sampling schemes and staining methods) and data collection (e.g., binary, quantitative, and/or semi-quantitative data) should be formalized. Incorporation of emerging digital image analysis and open-source, user-friendly, machine learning techniques to assess histopathological features for clinicopathological correlation and diagnoses (see recommendations #1 through #4) is encouraged. Techniques should be tested for scalability, feasibility, and generalizability across multiple cohorts, anatomical areas, and histologic methods as well as adherence to FAIR principles. (2026-2030)
- Enhance tissue processing and sampling strategies for LBD-associated pathologies. Furthermore, develop molecular neurochemical, and genetic techniques to capitalize on existing human tissue resources. Specifically, strategies to study the pathologic bases of cognitive, non-motor, and motor dysfunction in LBD, especially for the neuroanatomy associated with core LBD clinical features, including cognitive fluctuations, visual hallucinations, and REM sleep behavior disorder (see recommendations #3 and #4 for validation of imaging and biofluid measures). (2026-2029)
- Develop cost-effective scalable methods to assess integrity and quality of existing human tissue samples across multiple cohorts used in molecular, neurochemical, and genetic research (see recommendations #7 and #8). (2026-3031).
- Encourage and enhance infrastructure for collection of peripheral tissue samples (fixed and frozen) from autopsies. Samples can include skin, salivary gland, gastrointestinal, and/or other solid organ tissues outside the central nervous system for detection of non-CNS α-synuclein. Analysis of central and peripheral tissues would include emerging seed amplification assays (see recommendation #3).
- Increase autopsies on individuals at-risk for LBD and pre-symptomatic with biomarker evidence of LBD. Specifically, autopsies from those currently enrolled in prospective longitudinal studies with standardized collection of demographic and clinical data (see recommendation #2). Autopsies should be sought for individuals with mild cognitive impairment and other pre-symptomatic, core, or related features of LBD, such as REM sleep behavior disorder (RBD), pure autonomic failure, anosmia, constipation and Parkinsonism. (2026-2031)
- Lower barriers to autopsy in LBD cohorts. Provide outreach and education to communities representative of the US population and provide logistical support and resources necessary to facilitate brain donations. Increase autopsies on people who broadly represent U.S. individuals living with LBD.
- Streamline the access and querying of LBD samples and data. Create a publicly available portal linking investigators to LBD tissue resources (see recommendation #3 and #4). Design a method in collaboration with data/informatics teams to apply a DOI (free of personal identifiers) to individual research participants who enroll in studies and provide tissue and/or data. This resource would include an online and searchable database that links fixed and frozen autopsy samples, as well as slides and digitized images, to samples with specific clinical, neuroimaging, and ante-mortem biomarkers in the networked repositories (discussed in recommendation #4). (2026-2029)

Recommendation 7 – Priority 1. Develop models to understand the pathogenesis, mechanisms of toxicity, and normal molecular and cellular functions of α-synuclein, to support drug discovery. (2033)

- Enhance studies that inform current clinical therapeutic development targeting α-synuclein. Agents targeting α-synuclein are in clinical development now, and it is important to identify potential safety concerns. Moreover, α-synuclein function and pathophysiology in motor systems may differ in important

ways from its function and pathophysiology in non-motor systems, and it is unknown whether small molecule therapies targeting motor systems will have meaningful effects on non-motor phenotypes such as cognition. We recommend improving knowledge of the normal and disease function of α-synuclein with a particular focus on non-motor systems, whose vulnerability is key to cognitive decline and dementia in LBD (2026-2031).

- Characterize phenotype-specific α-synuclein strains. LBD, PD, and PDD individuals follow different clinical trajectories, but all are characterized by predominantly neuronal α-synucleinopathy. We recommend determinizing whether distinct α-synuclein strains – conformations with fidelity and biological consequences – underlie these differing clinical trajectories by isolating Lewy bodies from a spectrum of α-synucleinopathies and neuroanatomic areas and characterizing them biochemically, biophysically, and in relation to cellular and biological pathways. A related question concerns the number of clinical α-synuclein strains – whether this number is small or large will have ramifications for drug development and development of α-synuclein tracers or other biomarkers (see recommendation #3). Therefore, bidirectional validation is needed in human datasets. (2026-2029)
- Develop in-vitro and in-vivo models of predominantly neuronal α-synucleinopathy. Investigate the cellular, regional, and network consequences of modulating α-synuclein. These studies may encompass in-vitro models utilizing human-derived materials, such as induced pluripotent stem cells and their derivative differentiated cells, or in-vivo models that mimic key clinical and/or pathophysiological components of LBD. These studies may additionally modulate genes or proteins identified in human genetic studies of LBD (see recommendation #5), or other "-omic" scale studies (e.g. CRISPR-based genomic screens, unbiased biomarker studies), to determine their impact on the development of α-synucleinopathy. Promote the discovery of at least one novel target to mitigate effects of synucleinopathy that is validated in human tissues (2026-2033).
- Understand α-synuclein aggregation and development of Lewy body pathology. Study factors that lead to misfolding and aggregation of α-synuclein, as a product of regulation of expression (including post-transcriptional regulation), misfolding, and clearance. Studies are encouraged to examine lysosomal/autophagy function and the role of glucocerebrosidase in α-synuclein accumulation and spread; leads derived from other lysosomal storage disorders resulting in α-synuclein accumulation may also be informative. (2026-2031)
- Understand pathological α-synuclein transmission. A major recent development in how we think about LBD is the hypothesis that pathological α-synuclein can undergo cell-to-cell spread between brain regions in both human brain and wild-type animal models, with possible spread to/from the periphery as well. However, the factors that govern transmission of synucleinopathy are unclear. Moreover, heterogeneity of clinical phenotype in LBD often reflects pathological involvement of different networks in the brain. We recommend understanding the mechanisms underlying release, uptake, and transmission of pathological α-synuclein in neurons and other cell types, as well as mechanisms underlying selective vulnerability to development of αsynucleinopathy. These studies may move forward mechanistically tractable targets for therapy. (2029-2031)

Recommendation 8 – Priority 4. Identify multi-etiology mechanisms of selective vulnerability, disease heterogeneity, disease spread/propagation, and interaction with other age-related pathologies as therapeutic targets. (2033)

- Determine the impact of mixed-pathology in LBD. Most individuals with LBD demonstrate pathologies in addition to α-synuclein pathology. We recommend understanding the impact of additional proteinopathies (e.g. beta-amyloid, TDP-43, tau) and/or vascular pathology on neurodegeneration and clinical course in LBD, especially as several of these additional pathologies are targetable with existing drugs or drugs in clinical trials now. Studies of genetic and molecular interactions of α-synuclein and tau

(e.g. cross-seeding, spread of each proteinopathy) can also inform our understanding of selective vulnerability in the human brain. (2028-2031)

- Understand the factors leading to neurodegeneration. While recommendation #7 focuses on mechanisms underlying the development of α-synuclein pathology, the mechanisms that lead to neurodegeneration may be distinct. We recommend identifying the anatomical, biochemical, molecular, and/or cell biological underpinnings leading to neurodegeneration in specific brain regions. Contributions of immune-mediated mechanisms and inflammation in LBD pathogenesis and cellular vulnerability should be investigated. Where feasible, biospecimens and data from humans, including individuals with PD, PDD, and DLB, should be used for confirmation of findings (see Recommendations #1, #2, and #3), with the goal of target validation for therapeutic development. (2026-2031)
- Develop LBD models that are not exclusively based on α-synuclein. Develop models that identify key processes involved in neuronal damage, vascular change, protein deposition which may synergize with mechanisms underlying α-synucleinopathy (see Recommendation #7). Prioritize the development of LBD models in which more than one pathology is present, as this pre-clinical work will inform therapeutic strategies targeting multiple pathologies in LBD (2026-2029).
- Consider the impact of demographics on LBD pathophysiology and toxic mechanisms underlying disease (along with recommendation #7). The role of aging should be interrogated using LBD-relevant model systems that allow for modeling of this risk factor and also in analyses of available resources such as high-volume “omics” datasets (e.g. transcriptomics, proteomics, metabolomics). Biological mechanisms explaining sex differences in vulnerability/resilience to LBD across heterogeneous cohorts should be identified: to facilitate this, inclusion of samples from both sexes and people who broadly represent U.S. individuals living with LBD at appropriate numbers to support well-powered analyses is required for human studies. The overarching goal of the pre-clinical basic science and translational work (also in recommendations #7) is to prioritize the discovery of at least one novel drug targeting known (e.g. α-synuclein, APOE, GBA) or emerging targets and mechanisms implicated in the development of LBD. To facilitate this goal, there is also a need to enhance or leverage infrastructure to support pre-clinical drug development arising from the mechanistic studies (also in recommendations #7). Infrastructure encompasses development of efficient means for screening, confirmation, lead optimization, and evaluations of efficacy/toxicity, for potential compounds to target mechanisms leading to LBD.

Session 7: Vascular Contributions to Cognitive Impairment and Dementia (VCID)

Recommendation 1 – Priority 1. Understand mechanisms of vascular disease onset and progression in specific cell types and their interactions, in the context of cognitive decline. (2032)

- Include specific cell types of the cerebrovascular system and of the perivascular tissue, such as endothelial cells, pericytes, astrocytes, smooth muscle cells, perivascular macrophages, microglia, oligodendrocytes, and interneurons.
- Improve the understanding of the effects of VCID on the interactions between different cell types, as well as on the movement and/or clearance of molecules and cells in and across the perivascular spaces, CSF, ISF and the blood-brain barrier.
- Vascular pathologies should include cerebral amyloid angiopathy, arteriolosclerosis, atherosclerosis and/or cardiovascular/cerebrovascular risk factors.
- Studies should clarify the mechanisms underlying loss of blood-brain barrier integrity, maladaptive angiogenesis and vascular remodeling, neurovascular coupling, (peri)vascular inflammation and how blood-brain barrier permeability affects the release of brain biomarkers into the blood.
- In addition to cognitive decline itself, consider other cognitive-decline related outcomes including microhemorrhages, white matter hyperintensities, enlarged perivascular space, and hypoperfusion.
- Small vessel pathologies across arterioles, capillaries, and/or venules could be considered.

Recommendation 2 – Priority 2. Discover VCID mechanisms and potential targets by leveraging extant data, and/or by establishing, refining and utilizing human-, animal-, and cell-based experimental models and technologies. (2031)

- Models should include systemic and/or chronic cardiovascular diseases and risk factors such as hypertension, cardiac failure, atrial fibrillation, atherosclerosis, or renal disease to examine their effects on VCID.
- Studies should clarify mechanisms and molecular targets of vessel disease and other key pathogenic processes thought to result in cognitive impairment (examples include microinfarcts, microhemorrhages, superficial siderosis, arteriolosclerosis, atherosclerosis, cerebral amyloid angiopathy, and vascular inflammation), or other early potentially reversible changes that drive VCID.
- Attention should be given to lifestyle, vascular, and metabolic factors associated with normal aging and chronic conditions, in addition to amyloid and tau pathology, to investigate the additive effects on brain pathophysiology. Models should aim to mimic complex human conditions to the extent possible.
- Studies should consider using in vitro and/or iPSC models or 3D/chip models incorporating flow conditions to explore specific molecular mechanisms that complement animal models.
- A priority should be to investigate the influence of sex-linked biology, women's health, menopause, or their intersections on mechanisms of VCID. Sex and age effects need to be incorporated as biological variables to provide translational insights.
- The relative contributions of clearance mechanisms should be clarified, including clearance of metabolic waste across the blood-brain barrier, perivascular clearance, phagocytic degradation, anatomical pathways and driving forces for perivascular clearance under normal conditions and during VCID.
- Models should also consider and study the impact of VCID on Down syndrome ADRD pathology, and the effect of Down syndrome on VCID particularly in relation with CAA.
- Studies should include advanced imaging technologies that can look deep into tissue at high resolution in living animals.

Recommendation 3 – Priority 4. Cross-validate hypothesized mechanisms of VCID among cell-based or animal models, and human studies to ensure face and construct validity, including studies with mixed pathologies, normal vascular aging, and community-based cohorts. (2031)

- Work translationally to characterize the interrelationships of vascular risk factors and AD mechanisms discovered in cell and animal models to biomarkers of cerebrovascular disease, such as endothelial, oligodendrocyte, and pericyte cell viability/function, BBB permeability, interstitial clearance, vascular stiffness, and other measures of vascular physiology in humans.
- Evaluate mechanisms leading to amyloid-related imaging abnormalities (ARIA-E and ARIA-H) associated with amyloid-lowering immunotherapies using both human and experimental models. Studies should also determine the impact that VCID co-morbidity has on ARIA incidence.
- Cross-validation efforts should include sex and age as biological variables and experimental approaches should aim to recapitulate in animal models the extent of diversity (environmental, genetic and other) that is present in human populations.

Recommendation 4 – Priority 3. Develop and advance potential new therapeutics in cell and animal models to prevent or treat VCID, that can be incorporated into the design of early human studies. (2032)

- Cell and animal model-based studies should develop new strategies and drugs to target risk reduction, prevention, and/or treatment of VCID-related cognitive decline, and work towards optimizing translation from cell and animal models to clinical trials.
- If clinical studies are included, outcomes, target engagement studies and biomarkers in humans should reflect those developed in animal models, while conversely ensuring that animal models include readouts informed by clinically relevant patient outcomes.
- Therapeutics, prevention or precision medicine approaches should also address ARIA, as an important component of ARIA involves VCID related abnormalities.

Recommendation 5 – Priority 2. Identify and advance interventions and preventions that reduce vascular disease in clinical populations at increased risk for VCID. (2032)

- Advance and establish randomized (Phase I-IV and pragmatic) clinical trials for VCID testing interventions that show efficacy and effectiveness in reducing cardiovascular and cerebrovascular risk. Interventions known to impact general vascular risk factors, such as management of hypertension, statins, diabetes/metabolic syndrome; facilitating optimal diet, exercise, sleep, environment/neighborhood modification, and behavioral interventions, may also be successful pathways for reducing VCID.
- The interventions could also include reducing risk and/or enhance resilience to vascular diseases.
- Both primary and secondary preventions, including secondary stroke prevention, are important. Other managements such as palliative care are also relevant.
- Social engagement and/or isolation should also be considered in the design of clinical trials.

Recommendation 6 – Priority 4. Understand the impact of specific cerebral small vessel pathologies and vascular risk factors on cognitive decline in humans. (2033)

- Small vessel pathologies can be heterogenous, e.g., atherosclerosis, arteriosclerosis, venous collagenosis, cerebral amyloid angiopathy. Different types of small vessel pathologies likely require different treatments. It is therefore important to understand differentiable cerebral small vessel pathologies and their specific manifestations, mechanisms, and/or biomarkers. The effects of co-occurrence of small vessel pathologies should also be better understood.
- Cerebrovascular pathologies are often accompanied by vascular risks and factors in other organs (heart, kidney, liver, etc.) The significance of these general vascular pathologies should be further elucidated.

- A better understanding of these mechanisms in human populations can be used to guide precise therapeutic development.
- Since mixed pathologies are common in cognitive impairment and dementia, these human disease mechanism studies should be conducted in the clinical context of other dementia risk factors.
- Cerebral small vessel diseases can be studied in the context of optimizing general brain health and brain aging, including the concept of preclinical cerebrovascular health.
- Studies should consider the effect of exposome on VCID including exposure to viral infections, stress, and environmental factors.
- Studies should consider regional specificity and spatial vulnerability of different small vessel pathologies or other co-pathologies on the brain.

Recommendation 7 – Priority 3. Develop and validate candidate biomarkers of VCID in preclinical models and/or high-risk populations that span the types of biomarkers encompassing imaging, biofluid, multi-omic, digital, AI, and other novel biomarkers, with considerations of specific vascular processes, including in the most common scenario where VCID is accompanied by beta amyloid plaques and tau tangles. (2033)

- Conduct discovery of biomarkers that include cognitive, behavioral, imaging, biofluid, and functional measures, which may also incorporate physical function and other measures indicating the presence of VCID. This represents an important step toward selecting the most promising biomarkers for later-stage biomarker development.
- Continue to assess VCID biomarkers detectable with a variety of methods balanced across the full spectrum of technologies.
- Expand the scope of discovery/validation of VCID markers by integrating multi-omic data (e.g., proteomics, metabolomics, transcriptomics, etc.)
- Use AI, machine learning, and advanced mathematical modeling techniques to integrate large datasets and identify potential early markers of VCID.
- Develop and test new biomarkers in preclinical models based on basic science findings that have the potential to be incorporated into the design of future human studies.
- Develop and advance biomarkers that are specific to different small vessel pathologies and cellular/molecular targets hypothesized to be important.
- Biomarkers should consider, when possible and applicable, spatial localization.
- Biomarkers should consider specificity to VCID in the context of MED pathologies.
- Studies should consider biomarkers related to vasodilatory capacity.

Recommendation 8 – Priority 1. Conduct studies of biomarkers in later stage of development through instrumental and clinical validation with defined biomarker category and context of use, including for example integrating activities of daily living, quality of life metrics, with the ultimate goal of regulatory approval. (2036)

- For candidate biomarkers that have undergone early-stage development and testing, further development should include instrumental validation to evaluate the biomarker in terms of metrics such as inter-rater reliability, test-retest repeatability, inter-vendor reproducibility.
- Later-stage biomarker validation should consider “category” and “context of use” following the Biomarkers, EndpointS and other Tools (BEST) glossary. BEST defines seven biomarker categories: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety. Each biomarker should also specify one or more context of use.

- To further advance the biomarker qualification effort, some of the validation studies of biomarkers should be tested in the context of interventions. Many validation studies of biomarkers have so far been conducted in observational studies.
- Advance current and future candidate biomarkers through additional biological and instrumental validation studies to identify those ready to advance to clinical validation.
- Standardize and harmonize biomarker platforms across multiple cohorts, ensuring that biomarkers identified in one population can be replicated and validated in others.
- Develop quantitative performance criteria of current and future candidate biomarkers within specified categories and context of use for each stage of discovery and development, with the end goal of readiness for application to interventional trials, including the possibility of regulatory qualification.
- Leverage current candidate VCID biomarkers by integrating activities of daily living, quality of life metrics into ongoing trials and examining correlations between each and global cognitive performance measures.

Session 8: Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD

Recommendation 1 – Priority 1. Advance community-driven AD/ADRD research to improve representative sampling and retention of populations disproportionately affected by AD/ADRD. (2033)

- Increase the awareness, visibility, and standardization of the science of recruitment and the importance of representative samples for research on prevention of AD/ADRD and care for people with AD/ADRD.
- Enhance support for AD/ADRD recruitment and retention centers with demonstrated excellence in recruitment of disproportionately affected populations.
- Build accountability mechanisms for recruitment goals within existing AD/ADRD research networks.
- Facilitate lifecourse-focused research by augmenting existing resources.
- Reduce the minimum age of inclusion for AD/ADRD research to encompass ages typically conceptualized as "midlife".
- Develop novel approaches to identify and address determinants of participation in AD/ADRD cohorts, registries and clinical trials (e.g., high screen failures). These determinants might include but are not limited to: recruitment and retention practices, economic, geographic including rural communities, or social barriers that reduce access to and quality of healthcare, misinterpretation of early signs of dementia, underdiagnosis by health care providers, and stigma.
- Oversample groups who are disproportionately affected by AD/ADRD into research to ensure adequate statistical power and precision in research findings on prevention and prognosis.

Recommendation 2 – Priority 1. Prioritize infrastructure and policy research to understand individual, community, and societal drivers of cost of care and access to treatments and care to optimize quality of life among individuals living with AD/ADRD, and the impact on AD/ADRD outcomes. (2033)

- Develop and review national definition/standards for dementia 'costs' and 'health outcomes' relevant for the US population as a whole and for populations disproportionately affected by dementia.
- Undertake process to parameterize key-constructs (domains) of a framework that will lead to reliable and valid common data elements for inclusion into a national data repository.
- Identify data sources, data needs and establish a national database for research on social, economic, health related factors as drivers of AD/ADRD treatment and high-quality dementia care and their impact on health and non-health outcomes (e.g., quality of life).
- Expand research on the drivers of access to pharmacological, non-pharmacological and medical and social service care interventions used in routine clinical care for AD/ADRD and impact on cost and health outcomes.
- Increase research on the impact on health outcomes and care quality of managed care and associated access to, use of expanded non-health and health related benefits in populations of persons living with dementia and their caregivers, prioritizing populations with evidence of systematically worse outcomes.
- Promote new research on the role of supply side factors, such as health system ownership of physician practices, labor market conditions, including health support staff availability, and Medicare benefit plan offerings for impacts on access to AD/ADRD treatments and care.
- Increase research on the role of sociocultural, behavioral, physical/built environment, economic and health care system factors on access to and use of different care models and pharmaceutical treatments for the cognitive and behavioral symptoms of dementia.

- Identify preference for adopting telemedicine and/or mobile-healthcare across disproportionately affected populations and strategies to eliminate barriers to access.

Recommendation 3 – Priority 2. Ensure a strong workforce involving biomedical, behavioral, and social scientists conducting research on AD/ADRD in the highest risk populations. (2029)

- Provide training across career stages on best practices for AD/ADRD disparities research –including research on prevention and research on care/treatment for people living with AD/ADRD -- to researchers who are new to health disparities research and/or AD/ADRD disparities research
- Encourage grants to have an experienced health disparities expert as a non-trivial component of the investigative team and embrace a clear plan to assess how the proposed research will impact disproportionately affected populations
- Promote an annual (or regular) meeting to discuss disagreements, areas of consensus, and guidelines, if possible, on best practices for AD/ADRD health disparities research along with forums to encourage dialogue related to explanations for, and best research approaches to, address population differences in AD/ADRD
- Promote ongoing training and professional development for the research staff dedicated to community engaged research
- Convene an external working group with members of the public, individuals from groups most impacted by AD/ADRD (e.g., caregivers or individuals living with AD/ADRD), and constituencies affected by AD/ADRD to support programmatic infrastructure and resources to promote a highly skilled research community.

Recommendation 4 – Priority 2. Assess the social, economic, and structural impediments to access to AD/ADRD assessment, diagnosis, and referrals, care, and impacts on health and economic outcomes. (2031)

- Develop a toolbox of tailored information for patients related to how their diagnosis, treatment, and care may be influenced by their socio demographic background, including education, income, geography including rurality, and racial or ethnic identity. Such information would include validity of typical diagnostic tools and evidence on medication efficacy across groups.
- Determine multi-level determinants of likelihood, quality, and validity of assessment and diagnosis, especially in disproportionately affected populations.
- Expand research into the sociocultural, behavioral, physical/built environment, economic and health care system factors across all levels from community to societal, that impede assessment, detection, diagnosis, and referrals, as barriers to assessment and diagnosis.
- Develop new research on the effects of assessment, detection, diagnosis, and referrals on health, social and economic outcomes.
- Evaluate access to sources of support and care to optimize quality of life after diagnosis.

Recommendation 5 – Priority 3. Improve AD/ADRD assessment tools (cognitive, biomarkers, -omics) and analytic methods to enhance generalizability of scientific research. (2029)

- Cognitive assessments: (a) Develop novel and valid normative methods for cognitive assessments as well as recommendations for when to use group-specific norms; (b) Continue to develop harmonized cognitive assessments that are valid across many different cross-cultural settings; (c) Foster adoption of a minimum set of harmonized cognitive assessments across existing and future studies.
- Biomarkers: Increase biomarker collection and analysis of disproportionately affected groups to address the fundamental questions of validity of biomarkers for different clinical phenotypes of and disease processes contributing to AD/ADRD. Existing frameworks may not apply as well in disproportionately

affected groups given differential contributions of vascular disease and socioeconomic factors. Prioritize biomarkers that are viable in large population samples (e.g., blood biomarkers) to increase inclusion.

- Omics: Expand the scope of data collection, including multi-omics in disproportionately affected populations.
- Increase investigation of other potential markers of disease, e.g., microbiome, prioritizing early markers of disease prior to cognitive manifestations or markers specific to disease pathology.
- Enhance inclusion of digital "biomarkers" (e.g., blood pressure, heart rate, sleep data) in existing and large prospective cohort studies of disproportionately affected groups.
- Develop and validate statistical methods to quantify selection bias, especially in clinical data sources or convenience samples, and support generalizability of results from non-representative samples. For example, require retention of information about individuals screened but who did not participate when developing new samples.
- Utilize secondary data for the development of methods for analyzing large scale multidimensional data generated from samples representative of the heterogeneity of the United States population.

Recommendation 6 – Priority 3. Identify life course and multi-level mechanisms of and pathways to AD/ADRD and use the discoveries to prevent AD/ADRD and reduce disparities. (2033)

- Make it standard practice to propose a conceptual model that describes the underlying reasons some populations are disproportionately affected by AD/ADRD.
- Support research to interrogate how etiologies contributing to AD/ADRD may differ across populations and implications of these differences for prevention and care for individuals with AD/ADRD.
- Measure determinants (both established and novel), over the lifecourse and across generations, of AD/ADRD and its consequences (i.e., cognitive, behavioral, and functional outcomes) among disproportionately affected populations. Examples of potential determinants should be drawn from across the levels of influence in the NIH Health Disparities Framework (biological, behavioral, sociocultural, and environmental):
    - Structural and policy-level factors (e.g., access to social resources such as banking and lending, housing, education, occupation, economic policies)
    - Exposures to toxicants in the environment (e.g., air/water pollutants)
    - Characteristics of the residential community (e.g., housing characteristics, schooling context, built environment, neighborhood disorder, safety, green space)
    - Occupational features (e.g., hazards, job security and precarity, income, occupational complexity)
    - Psychosocial trauma
    - Psychosocial exposures and conditions (e.g., stress, depression)
    - Modifiable clinical conditions, including vascular, infectious, and metabolic conditions
    - Early-life exposures (e.g., perinatal health, adverse childhood circumstances and events)
    - Behavioral patterns relevant to health (e.g., smoking, exercise)
- Evaluate how multiple layers of experience and overlapping risk factors contribute to AD/ADRD
- Improve data resources to evaluate the influence of and interaction between social, environmental, and biological mechanisms in producing AD/ADRD inequities by: leveraging existing cohorts and trial data, including those evaluating other disease outcomes; augmenting or expanding existing cohorts to better represent the US population, especially disproportionately affected populations; harmonizing existing data source to increase sample size especially for disproportionately affected populations; and

developing tools to quantify and remediate biases introduced via sampling or recruitment. Important constructs to measure include but are not limited to:
    - Potential determinants of AD/ADRD described above
    - Deep phenotyping of vascular, metabolic and other systems
    - Genetic, epigenetic, transcriptomic, proteomic, and metabolomic factors thought to influence AD/ADRD
    - AD/ADRD biomarkers, including but not limited to beta-amyloid, tau, neurodegeneration, and VCID
    - Collect surrogate and diagnostic endpoints including but not limited to MRI, PET, CSF, blood biomarkers, and autopsy and other tissue when possible, and longitudinal cognitive and functional status
- Develop and standardize statistical approaches to evaluating and interpreting gene-by-environment interactions. Incorporate investigation of environmental modifiers into genetic research. Genetic discoveries need to be examined in the context of environmental, behavioral, and socioeconomic and cultural factors.
- Enhance access to statistical methodologies to improve causal inference from non-randomized data sources and improve the relevance of research to disproportionately affected populations.
- Apply methods to translate scientific discoveries based in highly selected clinical or convenience samples to the disproportionately affected groups and region(s), e.g., transport methods.
- Support evidence dissemination to people who may act on that evidence to prevent AD/ADRD in themselves, their family members, their patients, and their communities.

Recommendation 7 – Priority 4. Enhance access to research training, especially for individuals who encounter educational barriers, to ensure an outstanding AD/ADRD scientific workforce. (2029)

- Develop, evaluate, and disseminate best practices for mentoring AD/ADRD workforce and career transitions (e.g., legacy planning, PI transitions on major grants) to grow and nurture the next generation of researchers to foster the most effective, innovative, and talented workforce achievable.
- Evaluate training programs and mentoring approaches to identify those that deliver the best outcomes for excellence in AD/ADRD research careers
- For individuals without a strong mentoring track record, mandate training on evidence-based practices for successful mentoring
- Emphasize mentoring with a demonstrated track record of helping trainees who faced barriers, for example with resources embedded in the career development award or direct to the mentor (e.g., following the Alzheimer's Association award model)
- Emphasize the quality of research training for promising scholars.
- Promote a highly skilled workforce, with particular attention to current workforce gaps, based on anticipated need for scientific skills, including for
    - mid-career researchers,
    - career transitions, and
    - with consideration for overcoming barriers that commonly deter promising scholars from succeeding in research careers.
- Create a network to grow and sustain an excellent workforce to disseminate needed training skills tailored to various career stages through publicly available venues
    - webinars to enhance skills related to leadership, management, and grants administration, among other topics, targeted to all researchers, including early, mid- and senior career stages.

- workshops for mentoring training for mid- and late-life career researchers

Recommendation 8 – Priority 4. Monitor progress in AD/ADRD overall and in AD/ADRD disparities with respect to prevention (i.e., incidence of AD/ARRD), diagnosis, treatment and care by applying existing and novel surveillance methods. (2031)

- Periodically field nationally representative samples (potentially embedded within ongoing representative cohorts) with detailed cognitive characterization and over-representation of disproportionately affected populations to monitor trends in disparities over time. Design the sampling of these studies to facilitate precise estimates for disproportionately affected groups and incorporate methods to evaluate AD/ADRD phenotypes.
- Evaluate methods for determining population and subpopulation prevalence and incidence of rare dementias adapted from other fields, e.g., multi-system estimation.
- Create accountability to disseminate information about progress made or lost ground with respect to incidence of AD/ADRD and adequacy of care for people living with AD/ADRD across representative populations.

Session 9: MED: Impact of the Exposome on AD/ADRD Risk and Outcomes

Recommendation 1 – Priority 1. Investigate how the exposome and the human body interact to influence AD/ADRD, with a focus on microbes and infectious diseases that may alter risk or the progression of AD/ADRD and MED. (2032)

- Develop and utilize advanced animal models and technologies that enable repeated, lifespan measurements to investigate how infectious diseases influence the onset and progression of AD/ADRD.
- Determine both in animal models of AD/ADRD and humans whether there are differences in the microbiome (e.g., gut, skin, respiratory tract) between different clinical stages. Also assess how other factors (e.g., chronic health related conditions), genetic susceptibility (eg. ApoE), medications may affect the microbiome. Determine how manipulation of the microbiome by different methods influences pathology and clinical manifestations at different stages of AD/ADRD.
- Determine both in animal models of AD/ADRD and humans whether there are differences in microbial infections. Determine how manipulation of the infectious agents by different methods (e.g., vaccines, antibiotics, antivirals) alters different stages of AD/ADRD.
- Determine both in animal models of AD/ADRD and humans whether there are differences in immune responses (adaptive and innate) between different stages of AD/ADRD clinically and pathologically. Determine how manipulation of the immune system by different methods at different stages of AD/ADRD in animal models and in humans influences AD/ADRD pathology and clinical manifestations.
- Determine both in animal models with different aspects of AD/ADRD and humans with AD/ADRD differences in sleep and circadian rhythm at different stages of disease utilizing different methodologies. Also determine whether manipulation of sleep and the circadian rhythm in different ways (genetic, pharmacological, behavioral, etc.) influence the course of disease in animal models of AD/ADRD and in humans and how they correlate with changes in microbiome and immune system.
- Investigate the infectious etiology of AD/ADRD to explore the neuropathologic interactions between enduring neurological and cognitive sequelae of infectious diseases and AD/ADRD.

Recommendation 2 – Priority 2. Advance mechanistic studies on the interaction between the exposome and AD/ADRD neuropathology by exploring pathogenic mechanisms relative to known environmental exposures. (2032)

- Investigate the role of environmental exposures across critical developmental and aging windows: Examine how early-life (including in utero) and later-life environmental exposures impact AD/ADRD neuropathology, cognitive decline, and aging processes in humans and animal models. Identify sensitive periods when interventions might be most effective to mitigate neurodegeneration.
- Elucidate the synergistic effects of multiple environmental factors on neurodegeneration: Explore how combinations of exposures, such as air pollution and toxic metals, interact to accelerate aging and AD/ADRD progression via mechanisms like neuroinflammation and oxidative stress. Use multi-exposure models to capture complex, real-world risk factors and assess their impact across life stages.
- Advance dynamic technologies to study environmental impacts on AD/ADRD: Develop and apply novel real-time monitoring tools, such as in vivo biosensors, and high-throughput screening, to track the influence of environmental factors on molecular, cellular, and epigenetic processes. Leverage these tools to identify biomarkers of early pathology and track disease progression.
- Target epigenetic and molecular mechanisms influenced by environmental exposures for therapeutic intervention: Investigate how the exposome affects the epigenetic clock and key pathogenic pathways, such as amyloid-beta deposition, tau aggregation, and neuroinflammation. Assess whether manipulating

specific epigenetic factors enhances AD/ADRD resilience or alters disease trajectories, with a focus on high-risk populations most vulnerable to environmental exposures.

Recommendation 3 – Priority 3. Establish research infrastructure to facilitate clinical and epidemiological studies on how the exposome impacts AD/ADRD risk and outcomes, while characterizing clinical phenotypes and developing diagnostic criteria for neurocognitive impairments linked to environmental exposures. (2032)

- Identify environmental risk and resilience factors and determine pathogenic causality of environmental risk factors of AD/ADRD, including infectious disease, environmental toxicants/toxins, air pollution and climate change, and occupational exposures, diet and nutrition, and environmental differences.
- Improve the characterization of environmental exposures and create the necessary tools and technologies to measure the impact of the exposome on AD/ADRD risk and progression. Conduct impact assessment research to study individual or cumulative risk of the environmental factors and gene-environment interactions across the life course to gain insights into biological mechanisms.
    - Initiate a consortium of existing aging cohorts to leverage ongoing research and conduct cohesive, rigorous studies of the exposome with a larger collective sample size conducive to evaluating causal inference.
    - Provide new infrastructure and equipment for improving evaluation of exposome, such as more sterile pathological suites for sample collections at autopsy.
    - Establish an AD/ADRD biobank and laboratory core to provide consistent analysis of biological samples (e.g. peripheral blood, saliva, urine, extracted teeth, nail clippings) for biological indicators of environmental toxicants, epigenetics, metabolomics, nutrients, inflammatory biomarkers, and physiological biometrics in aging cohorts.
- Characterize clinical and neuropathologic phenotypes and develop diagnostic criteria and biomarkers for neurocognitive impairments associated with environmental exposures related to AD/ADRD.
    - Development of a consensus of protocols for exposome metrics (e.g., measurements of clinical and pathological phenotypes).
    - Establish an advisory committee to determine priority exposures (e.g. xenobiotics, heavy metals, endocrine disrupting chemicals, mutagens) and best practices for exposure assessment.
    - Establish a core of experts in appropriate AD/ADRD diagnostic criteria and cognitive performance measures as guidelines for future studies.
- Prioritize clinical and epidemiological research and clinical trials on populations disproportionately exposed to environmental and social and lifestyle risk factors of AD/ADRD. Specifically, focus on solutions-oriented studies to identify immediate and long-term strategies for reducing risk, increasing resilience and slowing the progression of AD/ADRD.
    - Establish new Aging and Disability Resource Centers in high exposome risk areas and neighborhoods with significant economic disinvestment.
    - Encourage studies using the stress-exposure disease framework to investigate augmented AD/ADRD risk from intersecting exposome and social stressors - at the individual and community-level - across the life course.
    - Build on information gained from risk assessment studies and identify reasons for exposure-disease disparities and barriers to solutions to better inform multilevel interventions for various interested parties, including individuals, communities, clinicians, and policy makers.

Recommendation 4 – Priority 4. Develop countermeasures and therapeutics informed by a mechanistic understanding of the interactions between the exposome and AD/ADRD, focusing on early interventional trials for beneficial effects at both individual and community levels. (2032)

- Investigate precise mechanisms of recognized positive beneficial exposures on AD/ADRD.
- There are known benefits to positive exposures on the interpersonal, community and societal levels (e.g., intergenerational connections, group activities) but precise mechanisms of the benefits on AD/ADRD remain to be revealed and these studies can also elucidate more direct targeted interventions by understanding how these factors work.
- Cultivating social networks, including participation in civic activities, feelings around neighborhood safety, and connections with family and friends could improve mental health, physical activity, and overall quality of life to reduce neuroinflammation and AD/ADRD risk.
    - Use longitudinal studies to analyze biomarkers for stress in relation to measures of social interaction to monitor cognitive performance and trajectories in older adults.
    - Evaluate barriers to social interaction and assess the effectiveness of implementing programs to improve social interaction for reducing AD/ADRD risk and disease progression.
- Social, economic, and environmental factors are hypothesized to alter the risk, onset, and progression of AD/ADRD. Studies should focus on identifying which factors drive risk and mechanisms by which they do so.
- Aside from age and genetics, early-life education level is one of the biggest predictors of risk for AD/ADRD. Studies to determine the potential mechanisms that contribute to the protective effects of education could bolster interventions for AD/ADRD prevention or establish measures for slowing progression.
    - Investigate associations between education and AD/ADRD risk to disentangle lifestyle factors contributing to the direct and/or indirect effect of education on AD/ADRD, including income, poverty level, healthcare access, better diet, and less smoking.
    - Using longitudinal studies across the life course to measure brain connectivity and function during early and middle life to evaluate the importance of education in building cognitive resilience or reserve.
    - Evaluate the effectiveness of mental stimulation and/or continuing educational activities across the life-span to potentially alter cognitive trajectories, reduce AD/ADRD risk, and slow disease progression.

ADRD Summit 2025 Committee Rosters

TABLE 1: ADRD Summit 2025 Steering Committee

NAME, DEGREE(s)	TITLE & AFFILIATION	COMMITTEE ROLE(s)	
Katherine Possin, PhD (Chair)	John Douglas French Alzheimer's Foundation Endowed Professorship Professor; Department of Neurology Memory and Aging Center, University of California, San Francisco, CA	Working Group of Council, Chair	Summit Scientific Chair; Session Chair
Cynthia Carlsson, MD	Professor, University of Wisconsin-Madison School of Medicine, WI	Working Group of Council	Session Chair
Kristen Dams-O'Connor, PhD	Professor, Depts. of Rehabilitation & Human Performance and Neurology, Mount Sinai, New York, NY	Working Group of Council	Session Chair
Kacie Deters, PhD	Assistant Professor of Integrative Biology and Physiology, University of California, CA	Working Group of Council	Session Chair
Silvia Fossati, PhD	Director of the Alzheimer's Center at Temple, Professor of Neural Sciences, Temple University LKSOM, Philadelphia, PA	Working Group of Council	Session Chair
James Galvin, MD, MPH	Professor of Neurology, Psychiatry & Behavioral Sciences, University of Miami, FL	Working Group of Council	Session Chair
Maria Glymour, ScD	Chair and Professor, Epidemiology, Boston University, MA	Working Group of Council	Session Chair
Costantino Iadecola, MD	Director and Chair of the Feil Family Brain and Mind Research Institute, Professor of Neurology, Weill Cornell Medical College, New York, NY	Working Group of Council	Session Chair

David Irwin, MD	Associate Professor, Department of Neurology, University of Pennsylvania, PA	Working Group of Council	Session Chair
Celeste Karch, PhD	Associate Professor, Dept. of Psychiatry, Washington University School of Medicine, St. Louis, MO	Working Group of Council	Session Chair
Jonathan Kipnis, PhD	Professor of Pathology and Immunology, Washington University in St. Louis, MO	Working Group of Council	Session Chair
Jin-Moo Lee, MD, PhD	Professor of Neurology, Washington University in St. Louis, School of Medicine, MO	Working Group of Council	NANDS Council Representative
Hanzhang Lu, PhD	Professor, Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, MD	Working Group of Council	Session Chair
Farah Lubin, PhD, FAES	Professor, Department of Neurobiology, University of Alabama at Birmingham, AL	Working Group of Council	Session Chair
Adrienne Mims, MD	Chief Medical Officer, Rainmakers Strategic Solutions LLC, AZ	Working Group of Council	NAPA Council Chair
Thomas Montine, MD, PhD	Professor and Chair, Dept. of Pathology, Stanford University, Stanford, CA	Working Group of Council	Past ADRD Summit Chair
Kathleen Poston, MD	Edward F. and Irene Thiele Pimley Professor in Neurology and Neurological Sciences, Stanford University, CA	Working Group of Council	Session Chair
Henry Paulson, PhD	Professor, Department of Neurology, University of Michigan, MI	Working Group of Council	NANDS Council Representative
Natalia Rost, MD, MPH	Chief, Stroke Division, Dept. of Neurology; Massachusetts General Hospital (MGH); Professor, Harvard Medical School, Boston, MA	Working Group of Council	Past ADRD Summit Chair
Julie Schneider, MD	Professor of Pathology and Neurological Sciences, Rush University Medical Center, Chicago, IL	Working Group of Council	Past ADRD Summit Chair

David Wolk, MD	Professor, Department of Neurology, Chief of the Division of Cognitive Neurology, Director, Penn Alzheimer's Disease Research Center, University of Pennsylvania, Philadelphia, PA	Working Group of Council	Session Chair
Roderick Corriveau, PhD	Program Director and AD/ADRD Program Lead, Division of Neuroscience, NINDS	ex-officio†	Past ADRD Summit Lead
Stephanie Courchesne-Schlink, Ph.D.	Acting Deputy Director, Chief of Staff, Division of Neuroscience, NIA	ex-officio	NIA
Sara Dodson, PhD	Senior Health Science Policy Analyst, Office of Science Policy & Planning, NINDS†	ex-officio†	NINDS
Walter Koroshetz, MD	Director, NINDS	ex-officio	NINDS Director
Helen Lamont, PhD	Director, Director of the Division of Disability and Aging Policy, Office of the Assistant Secretary for Planning and Evaluation (ASPE)	ex-officio	Federal Official for the NAPA Council
Amber McCartney, PhD	Scientific Project Manager, Division of Neuroscience, NINDS	ex-officio	NIH ADRD Summit 2025 Lead
Annapurna Poduri, M.D., M.P.H.	Deputy Director, NINDS	ex-officio†	NINDS Deputy Director

Table 1 †NINDS ex-officio members that were separated from the government prior to submission of this report.

TABLE 2: ADRD Summit 2025 Non-Federal Committee Members

SESSION	NAME, DEGREE(S)	TITLE, AFFILIATION
1. **Multiple Etiology Dementias (MED) – Research for Implementation of Discoveries into Practice**	Katherine Possin, PhD (Session Chair)	Professor, Department of Neurology Memory and Aging Center, University of California, San Francisco, CA
	Jeffrey M Burns, MD	Professor of Medicine, University of Kansas Medical Center, Kansas City, KS
	Cynthia Carlsson, MD	Professor, Department of Medicine, University of Wisconsin-Madison, Wisconsin, WI
	Joshua Chodosh, MD, MSHS	Professor, Department of Medicine, NYU Grossman School of Medicine, New York, NY
	Nicole Fowler, PhD, MHSA	Associate Professor of Medicine, Indiana University School of Medicine, Indianapolis, IN
	Lee Jennings, MD, MSHS, AGSF	Associate Professor, Department of Medicine, Oklahoma University College of Medicine, Oklahoma City, OK
	Jason Karlawish, MD	Professor of Medicine (Geriatrics), Department of Neurology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
	Ian Kremer, JD	Executive Director of Leaders Engaged on Alzheimer's Disease (LEAD) Coalition, Washington, DC
	Jennifer Hagerty Lingler, PhD	Professor and Vice Chair for Research in Health & Community Systems, University of Pittsburgh, School of Nursing, Pittsburgh, PA
	Joelle Millikin, MD	Board-certified Internal and Geriatric Medicine Doctor, Aspirus Rhinelander Hospital, Lewiston, ID

	Huong Nguyen, PhD, RN	Professor, Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Southern California, CA
	Ozioma Okonkwo, PhD	Professor, Department of Medicine, University of Wisconsin-Madison School of Medicine and Public Health, Madison WI
	Christine Ritchie, MD, MPH	Director of Research, Division of Palliative Care and Geriatric Medicine, Center for Palliative Care, Massachusetts General Hospital at Harvard Medical School, Boston, MA
	Heather Snyder, PhD	Vice President, Medical and Scientific Relations, Alzheimer's Association, Chicago, IL
	Michael Wolf, PhD, MPH	Associate Vice Chair for Research, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL
	Julie Wood, MD, MPH, FAAFP	Senior Vice President of research, science, and health of the public, American Academy of Family Physicians (AAFP) Foundation, Leawood, KS
2. Frontotemporal Degeneration (FTD)	David Irwin, MD (Session Chair)	Associate Professor, Department of Neurology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
	Celeste Karch, PhD (Session Chair)	Associate Professor, Department of Psychiatry, Washington University in St. Louis, St. Louis, MO
	Sami Barmada, MD, PhD	Associate Professor of Neurology, University of Michigan Neuroscience Institute, Ann Arbor, MI
	Nicole Bjorklund, PhD	Director of Research & Grants, The Association for Frontotemporal Degeneration, King of Prussia, PA

	Adam Boxer, MD, PhD	Professor, Department of Neurology, University of California, San Francisco, CA
	Kristophe Diaz, PhD	Executive Director, Chief Science Officer, CurePSP, New York, NY
	Bess Frost, PhD	Professor of Molecular Biology, Cell Biology and Biochemistry, Director of the Center for Alzheimer's Disease Research, Brown University, Providence, RI
	Danielle Graham, PhD	Head of biomarkers and system biology, Biogen, Concord, MA
	Aaron Gitler, PhD	Professor, Department of Genetics, Stanford University, Stanford, CA
	Linde Lee Jacobs, RN	Cure MAPT FTD, AD/ADRD lived experience expert, WI
	Aimee Kao, MD, PhD	Professor of Neurology, University of California, San Francisco, CA
	Cristian Lasagna-Reeves, PhD	Associate professor, Department of Neurology, Baylor College of Medicine, Houston, TX
	M Carmela Tartaglia, MD, FRCPC	Professor, University of Toronto, Ontario, Canada
3. MED – Post Traumatic Brain Injury (TBI) AD/ADRD	Kristen Dams-O'Connor, PhD (Session Chair)	Professor, Department of Rehabilitation and Human Performance, Icahn School of Medicine at Mount Sinai, New York, NY
	Regina Armstrong, PhD	Professor and Chair, Department of Anatomy, Physiology and Genetics, the F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD
	Bernadette D'Alonzo	Postdoctoral Fellow, Department of Neurology, University of Pennsylvania, Philadelphia, PA

	Brian Edlow, MD	Associate Professor, Department of Neurology, Massachusetts General Hospital at Harvard Medical School, Boston, MA
	Neil Graham, MRCP,PhD	NIHR Clinical Lecturer in Dementia, Department of Brain Sciences, Imperial College London, London, United Kingdom
	David Gutman, MD, PhD	Associate professor, Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA
	Scott Hamilton	AD/ADRD lived experience expert and advocate, Massachusetts and London, England
	Victoria Johnson, MBChB, PhD	Associate Professor, Department of Neurosurgery, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
	C Dirk Keene, MD, PhD	Professor, Department of Laboratory Medicine and Pathology, University of Washington School of Medicine, Seattle, WA
	Edward Lee, MD, PhD	Associate Professor, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
	Ann McKee, MD	Professor, Department of Neurology and Pathology, Boston University, Boston, MA
	Andre Obenaus, PhD	Professor, Department of Biomedical Sciences, University of California, Riverside, CA
	Monique Pappadis, MEd, PhD	Associate Professor, Department of Population Health & Health Disparities, University of Texas Medical Branch, Galveston, TX
	Mary Jo Pugh, PhD, RN	Professor, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT

	Heather Snyder, PhD	Vice President, Medical and Scientific Relations, Alzheimer's Association, Chicago, IL
	Robert Turner II, PhD	Associate Professor, Department of Clinical Research & Leadership, The George Washington University School of Medicine & Health Science, Washington, DC
4. MED – LATE (TDP-43 in Common Late-Onset Dementias)	David Wolk, MD (Session Chair)	Professor, Department of Neurology, Chief of the Division of Cognitive Neurology, Director, Penn Alzheimer's Disease Research Center, University of Pennsylvania, Philadelphia, PA
	Konstantinos Arfanakis, PhD	Professor, Department of Biomedical Engineering, Rush University Medical Center, Chicago, IL
	Penny Dacks, PhD	Senior Director of Scientific Initiatives, Association for Frontotemporal Degeneration, King of Prussia, PA
	Tamar Gefen, PhD	Associate Professor, Department of Psychiatry & Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL
	Claudia Kawas, MD	Professor, Department of Neurobiology and Behavior, University of California, Irvine, CA
	Nicolas Lux Fawzi, PhD	Professor of Medical Science, Brown University, Providence, RI
	Peter Nelson, MD, PhD	Professor, Department of Pathology and Laboratory Medicine, University of Kentucky College of Medicine, Lexington, KY
	Leonard Petrucelli, PhD	Professor and Chair, Department of Neuroscience, Mayo Clinic, Jacksonville, FL
	Rosa Rademakers, PhD	Group Leader, Center for Molecular Biology, VIB-University of Antwerp, Belgium

	Deidre Robokos	Family Advocate, Partner in Kiernan Trebach LLC's, AD/ADRD Lived Experience Experts Washington, DC
	Anja Schneider, MD	Professor and Chair, Department of Neurodegenerative Diseases and Geriatric Psychiatry, Bonn University Hospital, and Senior group Leader at German Research Center of Neurodegenerative Diseases, Bonn, Germany
	Julie Schneider, MD, MS	Professor of Pathology and Neurological Sciences, Rush University Medical Center, Chicago, IL
	Philip Wong, PhD	Professor of Pathology and Neuroscience, Johns Hopkins University, School of Medicine, Baltimore, MD
	Hyun-Sik Yang, MD	Assistant Professor, Department of Neurology, Brigham and Women's Hospital & Harvard Medical School, Boston, MA
	Paul Yushkevich, PhD	Professor, Department of Radiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
5. MED – Basic and Clinical Discovery Research	Cynthia Carlsson, MD, MS (Session Chair)	Professor of Medicine, University of Wisconsin-Madison, Madison, WI
	Costantino Iadecola, MD (Session Chair)	Director and Chair of the Feil Family Brain and Mind Research Institute, Professor of Neurology, Weill Cornell Medical College, New York, NY
	Diane Bovenkamp, PhD	Vice President of Scientific Affairs, BrightFocus Foundation, Clarksburg, MD
	Ana Maria Cuervo, MD, PhD	Professor, Department of Developmental & Molecular Biology, Albert Einstein College of Medicine, Bronx, NY
	David Fardo, PhD	Professor, Department of Biostatistics, University of Kentucky College of Public Health, Lexington, KY

	Yadong Huang, MD, PhD	Professor of Neurology and Pathology, J. David Gladstone Institutes at University of California, San Francisco, San Francisco, CA
	Bistra Iordanova, PhD	Assistant Professor, University of Pittsburgh, Swanson School of Engineering, Pittsburgh, PA
	Gregory Jicha, MD, PhD	Professor, Department of Neurology, University of Kentucky College of Medicine, Lexington, KY
	Caitlin Latimer, MD, PhD	Assistant Professor, Department of Laboratory Medicine & Pathology, University of Washington, School of Medicine, Seattle, WA
	Jason Meyer, PhD	Professor, Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN
	Gil Rabinovici, MD	Professor, Department of Neurology, University of California, San Francisco, CA
	Laura Ranum, PhD	Professor, Department of Molecular Genetics and Microbiology, University of Florida, Gainesville, FL
	Meg Smith, JD	Chief Executive Officer, Cure Alzheimer's Fund, Wellesley Hills, MA
	Larry & Karen Squiers	AD/ADRD Lived Experience Experts, Wisconsin
	Keith Vossel, MD	Chair and Professor of Neurology, the David Geffen School of Medicine, University of California, Los Angeles, California, CA
6. Lewy Body Dementias (LBD)	James Galvin, MD, MPH (Session Chair)	Professor, Department of Neurology, University of Miami, Miller School of Medicine, Miami, FL
	Kathleen Poston, MD, MS (Session Chair)	Professor, Department of Adult Neurology, Stanford University, Palo Alto, CA

	John Alam, MD	Chief Executive Officer, CervoMed, Boston, MA
	Bradley Boeve, MD	Chair, Behavioral Neurology, Department of Neurology, Mayo Clinic, Rochester, MN
	Alice Chen-Plotkin, MD	Professor, Department of Neurology, University of Pennsylvania, Philadelphia, PA
	Brittany Dugger, PhD	Associate Professor, Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA
	Douglas Galasko, MD	Professor, Department of Neurosciences, University of California, San Diego, CA
	Laurence Guttmacher, MD	Professor Emeritus, Department of Psychiatry, University of Rochester, School of Medicine and Dentistry, Rochester, NY
	Elizabeth Mormino, PhD	Associate Professor (Research), Department of Neurology Research, Stanford University, Stanford, CA
	Angela Taylor	Vice President of Strategic Partnerships, Lewy Body Dementia Association, Lilburn, GA
	John-Paul Taylor, MBBS (Hons), PhD, MRCPsych	Professor, Translational and Clinical Research Institute, Newcastle University, UK
	Juan (Jon) Toledo Atucha, MD, PhD	Assistant Professor, Department of Neurology, Houston Methodist Hospital, Houston, TX
7. Vascular Contributions to Cognitive Impairment and Dementia (VCID)	Silvia Fossati, PhD (Session Chair)	Director, Alzheimer's Center at Temple, Professor of Neural Sciences, Temple University LKSOM, Philadelphia, PA
	Hanzhang Lu, PhD (Session Chair)	Professor, Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, MD
	Candice Brown, PhD	Assistant Professor, West Virginia University School of Medicine, Morgantown, WV

	Susan Catalano, PhD	Chief Scientific Officer at Capsida Biotherapeutics Inc., Thousand Oaks, CA
	Crystal Glover, PhD	Associate Professor of Neurology, UC Irvine, Irvine, CA
	Gareth Howell, PhD	Professor and the Diana Davis Spencer Foundation Chair for Glaucoma Research, The Jackson Laboratory (JAX), Bar Harbor, ME
	Costantino Iadecola, MD	Director and Chair of the Feil Family Brain and Mind Research Institute, Professor of Neurology, Weill Cornell Medical College, New York, NY
	David Kleinfeld, PhD	Professor, Departments of Physics, Neurobiology, and Neurosciences, University of California San Diego, La Jolla, CA
	David Knopman, MD	Professor, Department of Neurology, Mayo Clinic, Rochester, MN
	Jin-Moo Lee, MD, PhD	Professor, Department of Neurology, Washington University in St. Louis, St. Louis, MO
	Anne Leonard, MPH, RN	Senior Science and Medicine Advisor, American Stroke Association (ASA)/American Heart Association (AHA), Dallas, TX
	Yakeel Quiroz, PhD	Associate Professor, Department of Psychiatry, Massachusetts General Hospital/Harvard Medical School, Boston, MA
	Natalia Rost, MD, MPH	Chief, Stroke Division, Department of Neurology, Massachusetts General Hospital (MGH), Professor, Harvard Medical School, Boston, MA
	Julie Schneider, MD, MS	Professor of Pathology and Neurological Sciences, Rush University Medical Center, Chicago, IL

	Azizi Seixas, PhD	Associate Professor, Department of Informatics and Health Data Science, Miami University, Miller School of Medicine, Miami, FL
	Sudha Seshadri, MD, DM	Professor, Department of Neurology, Director, Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health, San Antonio, TX
	Heather Snyder, PhD	Vice President, Medical and Scientific Relations, Alzheimer's Association, Chicago, IL
	Farzaneh Sorond, MD, PhD	Professor, Neurology (Stroke and Vascular Neurology), Northwestern University Feinberg School of Medicine, Chicago, IL
	Andrew Yang, PhD	Assistant Professor, Department of Neurology and Anatomy, University of California, San Francisco, CA
	Kristen Zuloaga, PhD	Professor, Department of Neuroscience and Experimental Therapeutics, Albany Medical College, Albany, NY
8. Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD	Kacie Deters, PhD (Session Chair)	Assistant Professor of Integrative Biology and Physiology, University of California, Los Angeles, CA
	Maria Glymour, ScD (Session Chair)	Professor, Department of Epidemiology, Boston University, Boston, MA
	Miguel Arce-Renteria, PhD	Assistant Professor, Department of Neurology, Columbia University, New York, NY
	Paola Gilsanz, ScD	Research Scientist II, Division of Research, Kaiser Permanente Northern California, Pleasanton, CA
	Carl Hill, PhD, MPH	Chief Diversity, Equity and Inclusion Officer, Alzheimer's Association, Chicago, IL
	Timothy Hohman, PhD	Professor of Neurology, Vanderbilt University Medical Center, Nashville, TN

	Virginia Howard, PhD	Distinguished Professor of Epidemiology, University of Alabama at Birmingham, Birmingham, AL
	Elizabeth Rose Mayeda, PhD, MPH	Associate Professor, Department of Epidemiology, University of California, Los Angeles, CA
	Ralph Richards	Community Advisory Board Member, Indiana Alzheimer's Disease Research Center; AD/ADRD Lived Experience Expert, Indianapolis, IN, USA
	Mollie Richards	Community Advisory Board Member, Indiana Alzheimer's Disease Research Center; AD/ADRD Lived Experience Expert, Indianapolis, IN, USA
	Jacqueline Torres, PhD, MA, MPH	Associate Professor, Department of Epidemiology & Biostatistics, University of California, San Francisco, CA
	Charles Windon, MD	Assistant Professor of Clinical Neurology, University of California, San Francisco, CA
	Charisse Winston, PhD	Assistant Professor, Department of Physiology and Neuroscience, University of Southern California, Keck School of Medicine, Los Angeles, CA
	Michael Wolf, PhD, MPH	Associate Vice Chair for Research, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL
9. MED – Impact of Exposome on AD/ADRD Risk & Outcomes	Jonathan Kipnis, PhD (Session Chair)	Distinguished Professor of Pathology and Immunology; Professor of Neurology, Neuroscience and Neurology, Washington University in St. Louis, MO
	Farah Lubin, PhD, FAES (Session Chair)	Distinguished Professor, Department of Neurobiology, University of Alabama at Birmingham, Birmingham, AL
	Staci Bilbo, PhD	Professor, Department of Psychology & Neuroscience, Duke University, Durham, NC

	Aisha Dickerson, PhD, MSPH	Associate Professor, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
	Joseph Thomas Flies-Away, MPA, JD	Community Nation Building Consultant, Native Nations Institute, University of Arizona, Tucson, AZ
	David Gate, PhD	Assistant Professor, Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL
	David Holtzman, MD	Professor of Neurology, Professor of Developmental Biology, Washington University in St. Louis, St. Louis, MO
	Melissa Lamar, PhD	Professor, Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, IL
	Vijay Limaye, PhD	Senior Scientist, Science Office & International, Natural Resources Defense Council (NRDC), New York, NY
	Xiao-Hong Lu, PhD	Associate Professor, Department of Pharmacology, Toxicology and Neuroscience, Louisiana State University, Shreveport, LA
	Amy Nelson, PhD	Assistant Professor, Department of Physiology and Cell Biology, University of South Alabama, Mobile, AL
	Meg Smith, JD	Chief Executive Officer, Cure Alzheimer's Fund, Wellesley Hills, MA

TABLE 3: ADRD Summit 2025 Federal Committee Members

NAME, DEGREE(S)	TITLE, AFFILIATION	ROLE
Walter Koroshetz, MD	Director, NINDS	Steering Committee, ex-officio
Amber McCartney, PhD	Scientific Project Manager, Division of Neuroscience, NINDS	NIH Summit Lead; Steering Committee, ex-officio, NIH Session lead, VCID
Herson Astacio, PhD	Health Program Specialist, Division of Neuroscience, NINDS	Organizing Committee
Hibah Awwad, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead, MED – Post Traumatic Brain Injury (TBI) AD/ADRD
Debra Babcock, MD, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead, Lewy Body Dementias
Kiara Bates	Program Specialist, Division of Neuroscience, NINDS	Organizing Committee
Richard Benson, MD, PhD	Program Director, Division of Clinical Research, NINDS	NIH Session Lead, Health Equity in AD/ADRD
Joe Bonner, PhD	Program Officer, National Center for Medical Rehabilitation Research, NICHD	Committee: MED – Post Traumatic Brain Injury (TBI) AD/ADRD
Marishka Brown, PhD	Director, National Center on Sleep Disorder Research, NHLBI	Committee: Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD
Selen Catania, PhD	Program Officer, Vascular Biology & Hypertension Branch, NHLBI	Committee: MED – LATE (TDP-43 in Common Late-Onset Dementias)
Jue Chen, MB, MS, PhD	Branch Chief, Aging biology, Pharmacology and toxicology, NHLBI	Committees: VCID
Sophie (Hyun Joo) Cho, MD	Program Director, Division of Clinical Research, NINDS†	NIH Session Lead: MED-Research for Implementation of Discoveries into Practice
Roderick Corriveau, PhD	Program Director, Division of Neuroscience, NINDS†	NIH Session Lead: VCID
Lenise Cummings-Vaughn, MD	Medical Officer, Centers for Medicare & Medicaid Services (CMS/CCSQ), Baltimore, MD	Committee: MED- Research for Implementation of Discoveries into Practice

William Daley, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead, MED-Impact of the Exposome on AD/ADRD Risk & Outcomes
Neel Dhruv, PhD	Program Director, Division of Translational Research, NINDS	NIH Session Lead, MED-Impact of the Exposome on AD/ADRD Risk & Outcomes
Sara Dodson, PhD	Senior Science Policy Analyst, Office of Science Policy & Planning, NINDS†	Organizing Committee; NIH Session Lead, Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD
Sarah Fontaine, PhD	Health Science Program Manager, Congressionally Directed Medical Research Programs (CDMPR), United States Department of Defense	Committee: MED – Post Traumatic Brain Injury (TBI) AD/ADRD
Rebecca Gottesman, MD, PhD	Senior Investigator and Stroke Branch Chief, Intramural Research, NINDS	Committees: MED – Basic and Clinical Discovery Research, and VCID
Senthil Gounder, PhD	Heath Program Specialist, Division of Translational Research, NINDS	Organizing Committee
Jalina Graham, PhD	Heath Program Specialist, Division of Neuroscience, NINDS†	Organizing Committee
Stuart Hoffman, PhD	Program Manager, Brain Health & Injury Portfolio, Rehabilitation Research and Development Service, Department of Veterans Affairs, Washington DC	Committee: MED – Post Traumatic Brain Injury (TBI) AD/ADRD
Rebecca Hommer, MD	Program Director Division of Clinical Research, NINDS	NIH Session Lead, MED-Research for Implementation of Discoveries into Practice; Committees: Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD and MED – Basic and Clinical Discovery Research
David Jett, PhD	Program Director, Division of Translational Research, NINDS	NIH Session Lead, MED-Impact of the Exposome on AD/ADRD Risk & Outcomes
Helen Lamont, PhD	Director, Director of the Division of Disability and Aging Policy, Office of the Assistant Secretary for Planning and Evaluation, US Department of Health and Human Services	Steering Committee, ex-officio

Tong Li, PhD	Program Director, Division of Neuroscience, NIA	Committee: MED – LATE (TDP-43 in Common Late-Onset Dementias)
Shari Ling, MD	Deputy Chief Medical Officer, Centers for Medicare and Medicaid Services (CMS), Baltimore, MD	Committee: MED- Research for Implementation of Discoveries into Practice
Demali Martin, PhD	Chief of the Population Studies and Genetics Branch, Division of Neuroscience, NIA	Committee: Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD
Elizabeth Newman, PhD	Program Director, Division of Neuroscience, NIA	Committees: VCID
Lisa Opanashuk, PhD	Program Director, Division of Neuroscience, NIA	Committee: FTD; MED – Post Traumatic Brain Injury (TBI) AD/ADRD
Marcy Pape, PT, DPT	Health Program Specialist, Division of Clinical Research, NINDS	Committee: Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD
Linda McGavern, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead, MED – LATE (TDP-43 in Common Late-Onset Dementias) and MED – Basic and Clinical Discovery Research
Annapurna Poduri, M.D., M.P.H.	Deputy Director, NINDS†	Steering Committee, ex-officio
Alessandra Rovescalli, PhD	Program Director, Division of Neuroscience, NIA	Committee: FTD
Sonja Scholz, MD, PhD	Lasker Clinical Research Scholar, Investigator, Neurogenetics Branch, Division of Intramural Research, NINDS	Committee: Lewy Body Dementias
Frank Shewmaker, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead, FTD
Arvind Shukla, PhD	Scientific Program Manager, Division of Neuroscience, NINDS	Organizing Committee
Nina Silverberg, PhD	Director, Alzheimer's Disease Research Centers Program, Division of Neuroscience, NIA	Committees: MED – LATE (TDP-43 in Common Late-Onset Dementias), and MED – Basic and Clinical Discovery Research
George Sopko, MD, MPH	Program Director and Medical Officer, Division of Cardiovascular Sciences, NHLBI	Committee: MED – Post Traumatic Brain Injury (TBI) AD/ADRD

Indira Turney, PhD	Stadtman Investigator, Intramural Research Program, NIA	Committee: Research to Improve Outcomes for Representative Populations at Risk and Living with AD/ADRD
Nsini Umoh, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead: MED – Post Traumatic Brain Injury (TBI) AD/ADRD
Keenan Walker, PhD	Investigator, Intramural research Program, NIA	Committee: MED – Post Traumatic Brain Injury (TBI) AD/ADRD
Michael Ward, MD, PhD	Senior Investigator, NINDS, Intramural Research Program, Bethesda, MD	Committee: FTD
Xiling Yin, MD, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead: VCID

Table 2 - †NINDS staff separated from the government prior to submission of this report.

Appendix 1: List of Past and Current NINDS ADRD Funding Initiatives

The following list presents all NINDS led AD/ADRD funding initiatives aligned with ADRD research milestones since FY2015. It includes both active initiatives currently accepting applications and past initiatives that have awarded grants but are no longer open.

Cross-cutting AD/ADRD Topics

RFA-NS-25-014: Mechanisms of Cognitive Fluctuations in ADRD Populations (R01)

RFA-NS-25-011: Functional Target Validation for Alzheimer's Disease-Related Dementias (R61/R33)

PAR-24-270: ADRD Risk and Disease Following Nervous System Exposures at Biological Interfaces with the Environment (R01)

PAR-24-234: Mechanistic Investigations into ADRD Associated Protein Structures in Biological Settings (R01)

PAR-24-213: NINDS Alzheimer's Disease-Related Dementias (ADRD) Advanced Postdoctoral Career Transition Award (K99/R00)

NOT-NS-24-135: Notice of Special Interest (NOSI): Administrative Supplement Program to Add Fluid-based Biomarkers and APOE Genotyping to NINDS ADRD Human Subjects Research Grants

RFA-NS-24-037: Optimization of Genome Editing Therapeutics for Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD) (U01)

RFA-NS-24-032: Development and Validation of Human Cellular Models for Alzheimer's Disease-Related Dementias (ADRD) (R01)

RFA-NS-24-026: Validating digital health technologies for monitoring biomarkers in ADRD clinical trials (R61/R33)

RFA-NS-24-011: Center without Walls for PET Ligand Development for Alzheimer's disease-related dementias (ADRDs) (U19)

RFA-NS-24-010: Early-Stage Therapy Development for Alzheimer's Disease-Related Dementias (ADRD) (R61/R33)

RFA-NS-24-009: Optimization of Genome Editing Therapeutics for Alzheimer's Disease-Related Dementias (ADRD) (U01)

RFA-NS-24-001: Using Multimodal Biomarkers to Differentially Diagnose ADRDs for Clinical Trials (U19)

PAR-23-195: Simultaneous and Synergistic Multi-Target Validation for Alzheimer's Disease-Related Dementias (R61/R33)

PAR-23-154: Development and Validation of Models for Alzheimer's Disease-Related Dementias (ADRD) (R61/R33)

PAR-23-113: NINDS Institutional AD/ADRD Research Training Program (T32)

RFA-NS-23-017: Optimization of Genome Editing Therapeutics for Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD) (U01)

PAR-23-023: Cellular and Molecular Mechanisms of Prion-Like Aggregate Seeding, Propagation, and Neurotoxicity in AD/ADRD (R01)

PAR-22-211: Impact of the Microbiome-Gut-Brain Axis on AD/ADRD (R01)

PAR-22-208: Structural Biology of Alzheimer's Disease Related Dementias (ADRDs) Proteinopathies (R01)

PAS-22-197: Advancing Research on Alzheimer's Disease (AD) and AD-Related Dementias (ADRD) (R41/R42)

PAS-22-196: Advancing Research on Alzheimer's Disease (AD) and AD-Related Dementias (ADRD) (R43/R44)

PAR-22-093: Research on Current Topics in Alzheimer's Disease and Its Related Dementias (R01)

RFA-NS-22-062: Connecting Machine Readable Digital Human AD/ADRD Neuropathological Library Platforms for Advanced Analytics (U24)

PAR-22-059: Prodromal Synaptic and Circuit Changes that Contribute to AD/ADRD Onset and Progression (R01)

RFA-NS-22-055: Functional Target Validation for Alzheimer's Disease-Related Dementias (ADRDs) (R61/R33)

PAR-22-048: Clinical Relevance of the Linkage between Environmental Toxicant Exposures and Alzheimer's Disease and Related Dementias (R01)

PAR-22-029: Longitudinal Single Cell Characterization of ADRD Postmortem Tissue (R01)

PAR-22-023: Multi-Disciplinary Collaborations to Understand Mechanisms of Systemic Immune Signaling and Inflammation in ADRD and its Progression (R01)

PAR-22-021: NINDS Institutional AD/ADRD Research Training Program (T32)

RFA-NS-22-006: Leveraging Existing Data Resources for Computational Model and Tool Development to Discover Novel Candidate Mechanisms and Biomarkers for ADRD (R01)

NOT-AG-21-051: Sleep Disorders and Circadian Clock Disruption in Alzheimer's Disease and other Dementias of Aging

NOT-NS-21-041: Notice of Special Interest (NOSI): Characterization of Genomics of Induced Pluripotent Stem Cell Lines for AD/ADRD Research

NOT-NS-21-040: Notice of Special Interest (NOSI): Administrative Supplements for Collaborative Activities to Promote Sleep/Circadian Research in ADRD

NOT-AG-22-025: Alzheimer's-Focused Administrative Supplements for NIH Grants that are Not Focused on Alzheimer's Disease

NOT-NS-21-041: Notice of Special Interest (NOSI): Characterization of Genomics of Induced Pluripotent Stem Cell Lines for AD/ADRD Research

NOT-NS-21-040: Notice of Special Interest (NOSI): Administrative Supplements for Collaborative Activities to Promote Sleep/Circadian Research in ADRD

NOT-AG-21-018: Alzheimer's-Focused Administrative Supplements for NIH Grants that are Not Focused on Alzheimer's Disease

NOT-AG-20-034: Alzheimer's-Focused Administrative Supplements for NIH Grants that are Not Focused on Alzheimer's Disease

NOT-AG-20-008: Alzheimer's-Focused Administrative Supplements for NIH Grants that are Not Focused on Alzheimer's Disease

PAR-19-167: Development and Validation of Advanced Mammalian Models for Alzheimer's Disease-Related Dementias (ADRD) (R61/R33)

RFA-NS-19-027: Human Three-Dimensional Cell Model Systems for Alzheimer's Disease-Related Dementias (ADRDs) (UG3/UH3)

RFA-NS-19-015: Functional Target Validation for Alzheimer's Disease-Related Dementias (ADRDs) (UG3/UH3)

RFA-NS-19-014: Center without Walls for PET Ligand Development for Alzheimer's disease related dementias (ADRDs) (U19)

PAR-18-661: Pathway and Target Identification for Alzheimer's Disease Related Dementias (ADRDs) (U01)

PAR-18-596: Research on Current Topics in Alzheimer's Disease and Its Related Dementias (R01)

RFA-NS-18-025: Center without Walls for PET Ligand Development for Alzheimer's disease related dementias (ADRDs) (U19)

NOT-AG-18-039: Alzheimer's-focused administrative supplements for NIH grants that are not focused on Alzheimer's disease

RFA-NS-18-015: Structural Biology of Alzheimer's Disease Related Dementias (ADRDs) Proteinopathies (U01)

NOT-AG-18-008: Alzheimer's Disease and its related Dementias (AD/ADRD)-focused Administrative supplements for NIH grants that are not focused on Alzheimer's disease

Health Disparities

RFA-NS-25-013: Clinical Trial Readiness to Understand and Develop Solutions to Social, Ethical, Behavioral Implications and Barriers to Health Equity in ADRD (R01)

PAR-24-212: NINDS Alzheimer's Disease-Related Dementias (ADRD) Advanced Postdoctoral Career Transition Award to Promote Diversity (K99/R00)

NOT-NS-24-071: Notice of Special Interest (NOSI): Administrative Supplements to Promote Diversity for NINDS ADRD Awardees

RFA-NS-24-024: Role of Environmental Stress in the Health Inequities of Alzheimer's Disease-Related Dementias (ADRD) (R01)

RFA-NS-23-001: Pragmatic Clinical Trials in Community Settings to Decrease or Prevent VCID Outcomes, Including in Populations that Experience Health Disparities (U01)

PAR-22-221: AD/ADRD, Adverse Childhood Experiences, and Social Determinants of Health Ancillary Studies of Existing Longitudinal Cohorts (R01)

PAR-22-022: NINDS Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD) Advanced Postdoctoral Career Transition Award to Promote Diversity (K99/R00)

RFA-NS-22-009: Detecting Cognitive Impairment, Including Dementia, in Primary Care and Other Everyday Clinical Settings for the General Public and Health Equity, Pragmatic Clinical Trials (U01)

NOT-NS-21-047: Administrative Supplements to Promote Diversity for NINDS Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD) Awardees

NOT-NS-20-089: Notice to Encourage Eligible NINDS Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD) Awardees to Apply for PA-20-222 "Research Supplements to Promote Diversity in Health-Related Research"

RFA-NS-20-013: White Matter Lesion Etiology of Dementia in the U.S. Including in Health Disparity Populations (U19)

RFA-NS-19-012: Post-Stroke Vascular Contributions to Cognitive Impairment and Dementia (VCID) in the United States Including in Health Disparities Populations (U19)

NOT-NS-19-003: Notice to Encourage Eligible NINDS Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD) Initiative Awardees to Apply for PA-18-906 "Research Supplements to Promote Diversity in Health-Related Research"

RFA-NS-17-012: Detecting Cognitive Impairment, Including Dementia, in Primary Care and Other Everyday Clinical Settings for the General Public and in Health Disparities Populations (UG3/UH3)

PAR-15-349: Health Disparities and Alzheimer's Disease (R01)

Frontotemporal Degeneration (FTD)

RFA-NS-22-056: Treatments for Lewy Body Dementias and Frontotemporal Degeneration - Exploratory Clinical Trial (U01)

RFA-NS-21-007: Mechanisms of Selective Vulnerability in LBD and FTD (R01)

RFA-NS-21-006: Mechanisms of Pathological Spread of Abnormal Proteins in LBD and FTD (R01)

RFA-NS-21-003: Center without Walls for Mechanisms of Neurodegeneration in Frontotemporal Dementia (U54)

NOT-NS-18-082: Notice of the NINDS' Participation in PAR-18-296 and interest in Clinical Trial readiness applications for Frontotemporal Degeneration (FTD) by the NIA and the NINDS

RFA-NS-17-017: Frontotemporal Degeneration (FTD) Sequencing Consortium: Discovery, Replication and Validation (UG3/UH3)

RFA-NS-16-023: Center without Walls for the Identification and Validation of Molecular Mechanisms Contributing to Tau Pathogenesis and Associated Neurodegeneration in Frontotemporal Degeneration (U54)

Vascular Contributions to Cognitive Impairment and Dementia (VCID)

RFA-NS-24-027: VCID Center Without Walls for Understanding and Leveraging Small Vessel Cerebrovascular Disease Mechanisms in ADRD (R01)

RFA-NS-24-013: Efficacy and Safety of Amyloid-Beta Directed Antibody Therapy in Mild Cognitive Impairment and Dementia with Evidence of Both Amyloid-Beta and Vascular Pathology (U01)

PAR-24-198: Protective Strategies to Reduce Amyloid Related Imaging Abnormalities (ARIA) After Anti-Amyloid Beta Immunotherapy (R01)

PAR-24-196: Mechanistic and Hemodynamic Basis of Diffuse White Matter Disease in Vascular Contributions to Cognitive Impairment and Dementia (VCID)(R01)

PAR-23-140: Blood Brain Barrier Response to Antibodies Targeting Beta-Amyloid (R01)

RFA-NS-23-001: Pragmatic Clinical Trials in Community Settings to Decrease or Prevent VCID Outcomes, Including in Populations that Experience Health Disparities (U01)

PAR-22-235: Blood Brain Barrier Response to Antibodies Targeting Beta-Amyloid (R01)

PAR-22-037: Role of Astrocytes in Degeneration of the Neurovascular Unit in AD/ADRDs (R01)

PAR-22-026: Selectively Target Technology Development to Understand How Changes or Dysfunction at the Capillary, Arterioles, and Small Lymphatic Vessels Level Can Have Long-term Impact on AD/ADRD (R01)

RFA-NS-22-017: Small Vessel VCID Biomarkers Validation Consortium Coordinating Center (U24)

NOT-NS-21-039: Notice of Special Interest: Innovative Approaches or Technologies to Investigate Regional, Structural and Functional Heterogeneity of CNS Small Blood and Lymphatic Vessels in AD/ADRD

NOT-NS-21-038: Notice of Special Interest (NOSI): Hyperacute MRI Imaging Studies to Understand How Brain Changes Affect AD/ADRD-Relevant Trajectories and Outcomes Post-Stroke

RFA-NS-21-005: Small Vessel VCID Biomarker Validation Consortium Sites (U01)

RFA-NS-21-004: Small Vessel VCID Biomarkers Validation Consortium Coordinating Center (U24)

RFA-NS-20-012: Clinical Trials Planning for Symptomatic Vascular Contributions to Cognitive Impairment and Dementia (VCID) (R34)

RFA-NS-20-004: Molecular Mechanisms of Blood-Brain Barrier Function and Dysfunction in Alzheimer's disease and Alzheimer's related dementias (AD/ADRD) (R01)

RFA-NS-19-039: Mechanistic Basis of Diffuse White Matter Disease in Vascular Contributions to Cognitive Impairment and Dementia (VCID) (R01)

PAR-18-413: Mechanistic Basis of Diffuse White Matter Disease and Small Vessel Pathology in Vascular Contributions to Cognitive Impairment and Dementia (VCID)(R01)

RFA-NS-16-021: Mechanistic Basis of Diffuse White Matter Disease in Vascular Contributions to Cognitive Impairment and Dementia (VCID)(R01)

RFA-NS-16-019; RFA-NS-16-020: Small Vessel Vascular Contributions to Cognitive Impairment and Dementia (VCID) Biomarkers Consortium: Coordinating Center (U24); Biomarkers Development Projects (UH2/UH3)

RFA-AG-15-010: Interdisciplinary Research to Understand Vascular Contributions to Alzheimer's Disease (R01)

Lewy Body Dementias (LBD)

RFA-NS-25-010: Safety and Efficacy of Amyloid-Beta Directed Antibody Therapy in Mild Cognitive Impairment and Dementia with Evidence of Lewy Body Dementia and Amyloid-Beta Pathology (U01)

PAR-24-249: Interaction Between Environmental Factors and Lewy Body Dementia (R01)

RFA-NS-22-056: Treatments for Lewy Body Dementias and Frontotemporal Degeneration - Exploratory Clinical Trial (U01)

RFA-NS-22-001: Biomarkers for the Lewy Body Dementias (U01)

RFA-NS-21-008: Treatments for Lewy Body Dementias--Exploratory Clinical Trial (U01)

RFA-NS-21-007: Mechanisms of Selective Vulnerability in LBD and FTD (R01)

RFA-NS-21-006: Mechanisms of Pathological Spread of Abnormal Proteins in LBD and FTD (R01)

NOT-NS-21-001: Notice of Special Interest: Administrative Supplements for Connecting Pre-mortem Clinical Information with Post-Mortem Brain Analysis

RFA-NS-20-014: Peripheral Pathology in the Lewy Body Dementias (R01)

PAS-19-210: Progression Markers for Cognitive Impairment in Parkinson's Disease Dementia (R01)

PAR-19-170: Progression Markers for Cognitive Impairment in Parkinson's Disease Dementia (R01)

RFA-NS-19-013: Lewy Body Dementia Center Without Walls (CWOW) (U54)

RFA-NS-18-024: Lewy Body Dementia Center Without Walls (CWOW) (U54)

RFA-NS-18-017: Planning Grant to Develop Phase III Clinical Trials for Lewy Body Dementia (R34)

RFA-NS-17-016: Leveraging Existing Resources for Research on Lewy Body Dementia (R03)

RFA-NS-16-022: Biomarkers for the Lewy Body Dementias (U01)

Multiple Etiology Dementias (MED)

PAR-24-147: Mechanistic Investigations into ADRD Multiple Etiology Dementias (R01)

PAR-23-211: Mechanistic Investigations into ADRD Multiple Etiology Dementias (R01)

PAS-17-028: Common Mechanisms and Interactions Among Neurodegenerative Diseases (R01)

PAR-15-358: Capturing Complexity in the Molecular and Cellular Mechanisms Involved in the Etiology of Alzheimer's Disease (R01)

Traumatic Brain Injury (TBI)

RFA-NS-24-003: Assessment of TBI-related ADRD Pathology Related to Cognitive Impairment and Dementia Outcomes (U01)

PAR-23-218: Development & Characterization of Experimental models of post-TBI ADRD (R01)

RFA-NS-23-002: Tools and resources to understand the vascular pathophysiology of in vivo neuroimaging findings in TBI-related dementia and/or VCID (U24)

RFA-NS-22-061: Training Award to Promote Cross-Training in the Fields of Traumatic Brain Injury (TBI) as a Risk Factor for Alzheimer’s Disease/Alzheimer’s Disease Related Dementias (AD/ADRD) (K18)

PAR-22-024: Clinical and Biological Measures of TBI-related Dementia Including Chronic Traumatic Encephalopathy (R01)

NOT-NS-22-002: Notice of Special Interest: Adding TBI Assessments to AD/ADRD Cohorts

RFA-NS-19-030: Neuropathological Assessment of TBI-related Neurodegeneration and Neurocognitive Decline - Center Without Walls (NATBI CWOW) (U54)

RFA-NS-19-026: Clinical and Biological Measures of TBI-related dementia including Chronic Traumatic Encephalopathy (CTE) (R01)

TDP-43 Pathology in Common, Late-Onset Dementias (LATE)

PAR-24-148: Investigating Distinct and Overlapping Mechanisms in TDP-43 Proteinopathies, including in LATE, FTD & other ADRDs (R01)

PAR-23-212: Investigating Distinct and Overlapping Mechanisms in TDP-43 Proteinopathies, including in LATE, FTD & other ADRDs (R01)

RFA-NS-20-005: Mechanistic Basis of TDP-43-dependent Pathobiology in Common Dementias (R01)

COVID-19 on AD/ADRD Risk and Outcomes

PAR-24-203: Neuropathological Interactions Between COVID-19 and ADRD (R01)

PAR-23-214: Neuropathological Interactions Between COVID-19 and ADRD (R01)

NOT-NS-23-001: COVID-19 Related Revisions to NINDS ADRD Human Subjects Cooperative Agreement Programs

NOT-NS-21-037: Notice of Special Interest: Impact of COVID-19 on Dementia Risk, Progression and Outcomes in ADRD Populations

Appendix 2: ADRD Summit 2022 Milestones and NINDS Response[20]

ADRD Summit 2022 Session 1: Health Equity in AD/ADRD		
Milestone # (Priority Level) Milestone Text	**11/2024 Status**	**Response**
1(1) Advance equity in AD/ADRD research via inclusion science to improve representative sampling and retention of diverse communities. AD+ADRD Research Implementation Milestone Database (12.L) https://www.nia.nih.gov/research/milestones/translational-research-and-clinical-interventions/health-equity-inclusion	In-progress	RFA-NS-17-012 created DetectCID PAR-22-221 RFA-NS-22-009 RFA-NS-23-001 RFA-NS-25-013
2(1) Increase training support and capacity of an AD/ADRD scientific workforce of persons historically under-represented in biomedical, behavioral, and social sciences. AD+ADRD Research Implementation Milestone Database (4.S) https://www.nia.nih.gov/research/milestones/enabling-infrastructure/milestone-4-s	In-progress	NOT-NS-19-003 NOT-NS-21-047 PAR-22-022 PAR-24-212 NOT-NS-24-071

[20] "Response" in this Appendix includes NINDS led Notices of Funding Opportunities (NOFOs) and hyperlinks to published NOFOs. Additionally, links are provided to online resources with information about large programs funded under these NOFOs. A comprehensive list of awards is available on NIH Reporter (https://reporter.nih.gov/) using the search function. Cross-cutting ADRD NOFOs invite applications to any ADRD and may be relevant to multiple milestones. Links are provided to each milestone specific website on the NIA AD and ADRD Research Implementation Milestones Database (https://www.nia.nih.gov/research/milestones) which includes annually updated implementation plans and progress toward the goal of effectively treating and preventing AD/ADRD, and is used to inform the development of the annual NIH Alzheimer's Disease Bypass Budget (https://www.nia.nih.gov/about/professional-judgment-budget-proposal).

3(2) Promote career development of biomedical, behavioral, and social scientists conducting AD/ADRD health equity research. AD+ADRD Research Implementation Milestone Database (4.Z) https://www.nia.nih.gov/research/milestones/research-resources/health-equity-career-development	In-progress	NOT-NS-21-047 PAR-22-021 PAR-22-022 PAR-23-113 PAR-24-212 NOT-NS-24-071
4(2) Assess the social, economic, and structural impediments to equity in AD/ADRD assessment, diagnosis, and referrals, as well as impacts on health and economic outcomes. AD+ADRD Research Implementation Milestone Database (1.S) https://www.nia.nih.gov/research/milestones/epidemiology-population-studies/health-equity-understand-and-reduce-barriers	In-progress	RFA-NS-19-012 created DISCOVERY PAR-22-221 RFA-NS-23-001 RFA-NS-24-024 RFA-NS-25-013
5(3) Improve AD/ADRD assessment tools (cognitive, biomarkers, -omics) and analytic methods to enhance generalizability and equity of scientific research. AD+ADRD Research Implementation Milestone Database (11.H) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-11-h	In-progress	RFA-NS-17-012 created DetectCID RFA-NS-19-012 created DISCOVERY RFA-NS-20-013 created DiverseVCID RFA-NS-22-009 PAR-22-048 PAR-24-249 RFA-NS-24-024 PAR-24-270 RFA-NS-25-013
6(3) Apply existing and novel surveillance methods to assess inequities, including trends in inequities, in AD/ADRD prevalence, incidence, diagnosis, treatment, and care. AD+ADRD Research Implementation Milestone Database (1.J) https://www.nia.nih.gov/research/milestones/population-studies-precision-medicine-health-disparities/milestone-1-j	In-progress	PAR-15-349 PAR-15-350 RFA-NS-17-012 created DetectCID RFA-NS-19-012 created DISCOVERY NOT-NS-20-089 NOT-NS-21-047 RFA-NS-22-009 RFA-NS-22-017 RFA-NS-23-001 RFA-NS-25-013

7 (4) Identify life course and multi-level mechanisms of and pathways to AD/ADRD inequities and use the discoveries to reduce these inequities. AD+ADRD Research Implementation Milestone Database (1.i) https://www.nia.nih.gov/research/milestones/epidemiology-population-studies/milestone-1-i	In-progress	PAR-15-349 RFA-NS-17-012 created DetectCID RFA-NS-19-012 created DISCOVERY RFA-NS-20-013 created DiverseVCID RFA-NS-22-009 PAR-22-221 RFA-NS-23-001
8 (4) Prioritize infrastructure and policy research to understand individual, community, and societal drivers of inequities in cost of and access to treatments and care, and the impact on AD/ADRD outcomes AD+ADRD Research Implementation Milestone Database (13.M) https://www.nia.nih.gov/research/milestones/care-caregiver-support/milestone-13-m	In-progress	NOT-NS-21-047 RFA-NS-22-009 RFA-NS-22-017 PAR-22-022 PAR-22-221 RFA-NS-23-001 PAR-24-212 NOT-NS-24-071 RFA-NS-25-013

ADRD Summit 2022 Session 2: Frontotemporal Degeneration (FTD)		
Milestone # (Priority Level) Milestone Text	**11/2024 Status**	**Response**
1(1) Understand FTD epidemiology and genetics in diverse populations, including how socioeconomic and ethnocultural status affects disease risk and manifestations. AD+ADRD Research Implementation Milestone Database (1.T) https://www.nia.nih.gov/research/milestones/epidemiology-population-studies/ftd-studying-ftd-causes-and-risk-factors-people	In-progress	RFA-NS-17-017 RFA-NS-21-003 PAR-18-296 (NIA led ALLFTD (Reporter link)
2(2) Develop an array of FTD biomarkers for diagnosis, prediction, disease monitoring, target engagement, and patient stratification for clinical trials. AD+ADRD Research Implementation Milestone Database (9.Q) https://www.nia.nih.gov/research/milestones/diagnosis-assessment-and-disease-monitoring/milestone-9-q	In-progress	PAR-18-661 RFA-NS-19-014 created CW2IP2 RFA-NS-21-003 RFA-NS-22-006 PAR-22-029 PAR-18-296 (NIA led ALLFTD (Reporter link)
3(3) Accelerate the evaluation of novel FTD treatments by developing new clinical trial resources and FTD-specific designs, and by conducting new prevention and treatment trials. AD+ADRD Research Implementation Milestone Database (9.S) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-s	In-progress	RFA-NS-22-056
4(4) Identify overlapping pathogenic mechanisms between FTD and other neurodegenerative disorders and syndromes. AD+ADRD Research Implementation Milestone Database (2.Z) https://www.nia.nih.gov/research/milestones/disease-mechanisms/ftd-understanding-different-potential-causes-ftd	In-progress	RFA-NS-16-023 RFA-NS-21-006 RFA-NS-21-007 PAR-23-212 PAR-24-148

5(1) Advance understanding of FTD and identify therapeutic targets through the creation, validation, and use of pre-clinical and translational tools and resources. AD+ADRD Research Implementation Milestone Database (4.Q) https://www.nia.nih.gov/research/milestones/enabling-infrastructure/milestone-4-q	In-progress	RFA-NS-19-027 PAR-19-167 NOT-NS-21-041 RFA-NS-21-007 RFA-NS-21-003 PAR-22-059 RFA-NS-22-056 PAR-23-154 RFA-NS-24-032
6(2) Accelerate pre-clinical disease-modifying and symptomatic therapeutic development in FTD. AD+ADRD Research Implementation Milestone Database (7.F) https://www.nia.nih.gov/research/milestones/translational-and-clinical-research-interventions-pharmacological/ftd	In-progress	PAR-18-661 RFA-NS-19-015 RFA-NS-22-055 RFA-NS-22-056 RFA-NS-23-017 PAR-23-195 RFA-NS-24-037 RFA-NS-25-011
7(3) Elucidate the mechanisms of cell type vulnerability and cell-intrinsic and –extrinsic effects on FTD pathogenesis, with the goal of accelerating development of therapeutic targets. AD+ADRD Research Implementation Milestone Database (2.AA) https://www.nia.nih.gov/research/milestones/disease-mechanisms/ftd-find-potential-drug-targets-ftd	In-progress	RFA-NS-19-027 RFA-NS-21-007 RFA-NS-22-006 PAR-23-212 PAR-24-148 RFA-NS-24-032
8(4) Define genetic and molecular modifiers of FTD (including in diverse populations). AD+ADRD Research Implementation Milestone Database (6.I) https://www.nia.nih.gov/research/milestones/translational-clinical-research-pharmacological/milestone-6-i	In-progress	RFA-NS-17-017 RFA-NS-21-003 PAR-22-029 PAR-23-212 PAR-24-148

ADRD Summit 2022 Session 3: Vascular Contributions to Cognitive Impairment and Dementia (VCID)		
Milestone # (Priority Level) Milestone Text	**7/2025 Status**	**Response**
1(1) Basic Mechanisms and Experimental Models: Establish and refine experimental models and technologies to identify disease-relevant mechanisms underlying VCID. AD+ADRD Research Implementation Milestone Database (4.R) https://www.nia.nih.gov/research/milestones/enabling-infrastructure/milestone-4-r	In-progress	RFA-NS-19-027 PAR-19-167 RFA-NS-21-005 NOT-NS-21-038 NOT-NS-21-039 PAR-22-026 PAR-23-154 RFA-NS-24-032
2(3) Basic Mechanisms and Experimental Models: Study the neurovascular unit structure and function to establish how it is impacted by VCID. AD+ADRD Research Implementation Milestone Database (2.Q) https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-q	In-progress	RFA-AG-15-010 RFA-NS-16-021 PAR-18-413 RFA-NS-19-039 RFA-NS-20-004 NOT-NS-21-039 PAR-22-026 PAR-23-140 PAR-24-196 PAR-24-198
3(4) Basic Mechanisms and Experimental Models: Use experimental models to investigate how aging, cerebrovascular and cardiovascular disease impact myelin, white matter degeneration and neurodegeneration. AD+ADRD Research Implementation Milestone Database (2.R) https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-r	In-progress	RFA-NS-16-021 PAR-18-413 RFA-NS-20-013 created DiverseVCID NOT-NS-21-038 NOT-NS-21-039 PAR-22-023 PAR-22-029 PAR-22-037 PAR-24-196 RFA-NS-24-027 created VCID CWOW

4(1) Human Studies: Develop and validate markers of VCID in diverse populations using 1) cognitive, physical, or other functional assessments, and 2) biomarkers of key vascular processes, including in the most common scenario where VCID is accompanied by AD in human studies. AD+ADRD Research Implementation Milestone Database (9.R) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-r	In-progress	RFA-NS-16-020 & RFA-NS-16-019, MarkVCID RFA-NS-21-004, RFA-NS-21-005, & RFA-NS-22-017, MarkVCID2 NOT-NS-21-038 RFA-NS-24-001
5(2) Human Studies: Identify and apply 1) interventions (medication, lifestyle or a combination of these) that reduce cardiovascular and cerebrovascular risk and 2) care models to test their efficacy for prevention and treatment of VCID across the spectrum of severity and in diverse populations. AD+ADRD Research Implementation Milestone Database (8.E) https://www.nia.nih.gov/research/milestones/translational-clinical-research/non-pharmacological/milestone-8-e	In-progress	RFA-NS-20-012 NOT-NS-21-038 RFA-NS-23-001 RFA-NS-24-013
6(4) Human Studies: Understand the impact on VCID of other known dementia risk factors (e.g., aging, genetics) and co-morbid neurodegeneration along the life-course in diverse populations to establish VCID interactions with other dementia disease processes. AD+ADRD Research Implementation Milestone Database (2.S) https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-s	Achieved	RFA-NS-17-012 created DetectCID RFA-NS-21-004, RFA-NS-21-005, & RFA-NS-22-017, MarkVCID2 NOT-NS-21-038 RFA-NS-22-006 PAR-22-026
7(2) Translational Studies: Incorporate VCID mechanisms derived from basic science animal/human studies into the design of human trials targeting prevention or treatment of dementia/mild cognitive impairment. AD+ADRD Research Implementation Milestone Database (4.U) https://www.nia.nih.gov/research/milestones/research-resources/milestone-4-u	In-progress	RFA-NS-16-020 & RFA-NS-16-019 MarkVCID RFA-NS-20-012 RFA-NS-21-004, RFA-NS-21-005, & RFA-NS-22-017 MarkVCID2 RFA-NS-22-006 RFA-NS-23-001 RFA-NS-24-013

8(3) Translational Studies: Validate hypothesized mechanisms of VCID in large-scale, including community-based diverse, human studies leveraging existing and in-process biospecimens, genomics, and imaging data. AD+ADRD Research Implementation Milestone Database (4.T) https://www.nia.nih.gov/research/milestones/research-resources/milestone-4-t	In-progress	RFA-NS-16-020 & RFA-NS-16-019 MarkVCID RFA-NS-20-012 RFA-NS-21-004, RFA-NS-21-005, & RFA-NS-22-017 MarkVCID2 NOT-NS-21-039 RFA-NS-22-006 RFA-NS-23-001 RFA-NS-24-013 RFA-NS-24-027 created VCID CWOW

ADRD Summit 2022 Session 4: Lewy Body Dementias (LBD)		
Milestone # (Priority Level) Milestone Text	**11/2024 Status**	**Response**
1(1) Clinical Characterization and Intervention: Prepare for and initiate clinical trials that aim to alleviate or slow the course of LBD symptoms, and delay or prevent the onset of disease. AD+ADRD Research Implementation Milestone Database (5.D) https://www.nia.nih.gov/research/milestones/translational-clinical-research-pharmacological/milestone-5-d	In-progress	RFA-NS-18-017 RFA-NS-19-015 PAS-19-210 RFA-NS-21-008 NOT-NS-21-040 RFA-NS-22-056 RFA-NS-25-010
2(2) Clinical Characterization and Intervention: Develop and refine neuroimaging biomarkers that track progression, assist in differential diagnosis, provide therapeutic target engagement, and relate to pathology. AD+ADRD Research Implementation Milestone Database (9.O) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-o	In-progress	RFA-NS-16-022 RFA-NS-17-016 RFA-NS-18-024 RFA-NS-19-013 created LBD CWOW RFA-NS-19-014 created CW2IP2 PAR-19-170 PAS-19-210 NOT-NS-21-001 RFA-NS-22-001 RFA-NS-24-001
3(3) Clinical Characterization and Intervention: Develop and refine biomarkers for diagnosis, prediction, and prognosis utilizing biofluids, tissues, and digital and electrophysiological methods. AD+ADRD Research Implementation Milestone Database (9.P) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-p	In-progress	RFA-NS-16-022 PAR-17-054 RFA-NS-19-014 RFA-NS-20-014 NOT-NS-21-001 RFA-NS-22-001 RFA-NS-24-001 RFA-NS-24-026
4(4) Clinical Characterization and Intervention: Expand existing and develop new longitudinal LBD study cohorts, including diverse populations, from pre-symptomatic disease to autopsy to support diagnostic, epidemiologic, and therapeutic studies. AD+ADRD Research Implementation Milestone Database (9.J) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-j	In-progress	RFA-NS-17-016 PAR-18-661 PAR-19-170 PAS-19-210 NOT-NS-21-001 RFA-NS-22-001 PAR-22-029 RFA-NS-25-010

5(1) Pathogenesis and Mechanisms of Toxicity: Delineate genetic loci and their functions contributing to the onset and progression of LBDs using genetic, transcriptomic, epigenetic, and environmental characterization analyses. AD+ADRD Research Implementation Milestone Database (1.L) https://www.nia.nih.gov/research/milestones/epidemiology-population-studies/milestone-1-l	In-progress	RFA-NS-19-015 RFA-NS-21-007 PAR-22-048 PAR-24-249 PAR-24-270
6(2) Pathogenesis and Mechanisms of Toxicity: Enhance and standardize the techniques for neuropathologic characterization of LBD and the use of LBD pathology cohorts including more diverse cohorts. AD+ADRD Research Implementation Milestone Database (1.K) https://www.nia.nih.gov/research/milestones/population-studies-precision-medicine-health-disparities/milestone-1-k	In-progress	RFA-NS-17-016 RFA-NS-18-017 RFA-NS-20-014 NOT-NS-21-001 RFA-NS-21-007 PAR-22-029
7(3) Pathogenesis and Mechanisms of Toxicity: Develop models to understand the pathophysiology and normal molecular and cellular functions of á-synuclein to support drug discovery. AD+ADRD Research Implementation Milestone Database (2.T) https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-t	In-progress	PAR-19-167 RFA-NS-21-006 RFA-NS-21-007 PAR-22-029 PAR-22-037 PAR-22-059 PAR-23-154 RFA-NS-24-032
8(4) Pathogenesis and Mechanisms of Toxicity: Identify mechanisms of selective vulnerability, disease heterogeneity, disease spread/propagation, and interaction with other age-related pathologies as therapeutic targets. AD+ADRD Research Implementation Milestone Database (2.M) https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-m	In-progress	PAS-19-210 RFA-NS-21-006 RFA-NS-21-007 PAR-22-029 PAR-22-037 PAR-22-059 PAR-24-249

ADRD Summit 2022 Session 5: Multiple Etiology Dementias (MED)		
Milestone # (Priority Level) Milestone Text	**11/2024 Status**	**Response**
MED1(1) Detection and Diagnosis of Cognitive Impairment and MED: Evaluate pragmatic approaches to objectively detect cognitive impairment and link to quality care when a patient, care partner, or clinician reports cognitive, behavioral or functional changes. AD+ADRD Research Implementation Milestone Database (9.K) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-k	In-progress	RFA-NS-17-012 created DetectCID RFA-NS-19-030 RFA-NS-20-013 RFA-NS-22-006 RFA-NS-22-009
2(4) Detection and Diagnosis of Cognitive Impairment and MED: Evaluate the benefits, burdens, and harms of screening for cognitive impairment in older adults in the absence of a patient, care partner or clinician report of cognitive, behavioral or functional changes. AD+ADRD Research Implementation Milestone Database (9.N) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-n	To Be Initiated	
3(3) Detection and Diagnosis of Cognitive Impairment and MED: Conduct multimodal clinical and translational research to support the identification of multiple etiologies in diverse populations. AD+ADRD Research Implementation Milestone Database (9.L) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-l	In-progress	RFA-NS-17-012 created DetectCID RFA-NS-22-009 RFA-NS-24-001 RFA-NS-24-026

4(2) Basic Research in MED: Advance basic research on the common and interacting risk factors and mechanisms of multiple etiology cognitive impairment and dementia in diverse populations. AD+ADRD Research Implementation Milestone Database (2.L) https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-l	In-progress	PAS-17-028 PAR-18-661 RFA-NS-19-026 RFA-NS-19-027 RFA-NS-19-030 PAR-19-167 RFA-NS-20-005 PAR-22-029 PAR-22-037 PAR-22-059 PAR-23-211 PAR-23-212 PAR-24-147 PAR-24-148 PAR-24-203 RFA-NS-24-003 RFA-NS-24-024
5(1) Interventions and Treatments for MED: Conduct clinical studies on approved or promising interventions and treatments to mitigate risk for cognitive decline. AD+ADRD Research Implementation Milestone Database (11.L) https://www.nia.nih.gov/research/milestones/diagnosis-assessment-and-disease-monitoring/milestone-11-l	In-progress	RFA-NS-23-001 RFA-NS-24-013 RFA-NS-25-010 RFA-NS-25-013
6(4) Interventions and Treatments for MED: Implement and evaluate outcomes for effective dementia care programs that support persons living with dementia and their caregivers, including those of socially, ethnically and racially diverse populations. AD+ADRD Research Implementation Milestone Database (13.L) https://www.nia.nih.gov/research/milestones/care-caregiver-support/milestone-13-l	In-progress	RFA-NS-17-012 created DetectCID RFA-NS-22-009 RFA-NS-25-013

7(2) Dementia Capable Workforce: Promote education and training on multiple etiology cognitive impairment and dementia to increase the dementia capable workforce, advance researchers including from groups underrepresented in science, and foster inclusive research practices. AD+ADRD Research Implementation Milestone Database (11.J) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-11-j	In-progress	PAR-17-072 NOT-NS-19-003 NOT-NS-20-089 NOT-NS-21-047 PAR-22-021 PAR-22-022 RFA-NS-22-061 PAR-24-212 NOT-NS-24-071
8(3) Data Harmonization: Conduct research to improve pre- and post-data collection harmonization and sharing practices across multiple etiology cognitive impairment and dementia studies. AD+ADRD Research Implementation Milestone Database (3.I) https://www.nia.nih.gov/research/milestones/research-resources/med-best-practices-adrd-research-data-sharing	In-progress	RFA-NS-22-006 RFA-NS-22-062 RFA-NS-23-002

ADRD Summit 2022 Session 6: MED Special Topic: Post-TBI AD/ADRD		
Milestone # (Priority Level) Milestone Text	**11/2024 Status**	**Response**
1(1) Promote collaboration among TBI and dementia researchers through working groups, retrospective and prospective data and measurement harmonization, and interdisciplinary research. AD+ADRD Research Implementation Milestone Database (1.N) https://www.nia.nih.gov/research/milestones/population-studies-precision-medicine-health-disparities/milestone-1-n-0	In-progress	RFA-NS-19-026 RFA-NS-19-030 NOT-NS-22-002 PAR-22-024 RFA-NS-24-003
2(2) Characterize the heterogeneous clinical and biological phenotypes and time course of progressive dementia following varied TBI exposure histories by developing biomarkers and methods to quantify lifetime head trauma exposure and diagnose post-TBI dementias. AD+ADRD Research Implementation Milestone Database (11.K) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-11-k	In-progress	RFA-NS-19-026 RFA-NS-19-030 NOT-NS-22-002 PAR-22-024 RFA-NS-23-002 RFA-NS-24-003
3(3) Establish research infrastructure, including multimodal longitudinal studies with autopsy endpoints that employ standardized CDEs and methodologies, to study post-TBI AD/ADRD. AD+ADRD Research Implementation Milestone Database (1.O) https://www.nia.nih.gov/research/milestones/population-studies-precision-medicine-health-disparities/milestone-1-o-0	In-progress	RFA-NS-19-026 RFA-NS-19-030 NOT-NS-22-002 PAR-22-024 PAR-23-218 RFA-NS-24-003
4(4) Basic and translational research to elucidate the mechanistic pathways, development, and progression of post-TBI AD/ADRD neuro-pathologies to better understand clinical symptom expression. AD+ADRD Research Implementation Milestone Database (2.W) https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-w-0	In-progress	RFA-NS-19-030 NOT-NS-22-002 PAR-22-024 PAR-23-218 RFA-NS-24-003

ADRD Summit 2022 Session 7: MED Special Topic: TDP-43 Pathology in Common, Late-Onset Dementias (LATE)		
Milestone # (Priority Level) Milestone Text	**11/2024 Status**	**Response**
1(1) Define LATE (pathologic, clinical, genetic, molecular) classification and diagnostic boundaries across FTLD-TDP, AD and other dementia related pathologies and their syndromes to enhance diagnosis, research, and awareness assuring diversity, inclusion and equity. AD+ADRD Research Implementation Milestone Database (11.M) https://www.nia.nih.gov/research/milestones/diagnosis-assessment-and-disease-monitoring/med-late-differential-diagnosis	In-progress	PAR-23-212 PAR-24-148
2(2) Develop biomarkers, classifiers, and risk profiles to establish in-vivo diagnostic criteria for LATE in persons without cognitive symptoms and in persons with amnestic or other relevant late-life dementia syndromes, assuring diversity, inclusion and equity. AD+ADRD Research Implementation Milestone Database (9.T) https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-t	In-progress	RFA-NS-19-014 created Center without Walls for Imaging Proteinopathies with PET (CW2IP2) RFA-NS-22-006 PAR-22-029 RFA-NS-24-001
3(3) Build new experimental models that incorporate aging with behavioral, pathologic, and molecular phenotypes of TDP-43 proteinopathy or hippocampal sclerosis, to advance knowledge and enable testing of therapeutics. AD+ADRD Research Implementation Milestone Database (4.V) https://www.nia.nih.gov/research/milestones/enabling-infrastructure/milestone-4-v	In-progress	RFA-NS-19-027 PAR-19-167 RFA-NS-20-005 RFA-NS-21-003 NOT-NS-21-041 PAR-23-154 RFA-NS-24-032

4(4) Study the intersection of hippocampal sclerosis (HS) and LATE-NC, within and across all disciplines (clinical, pathologic, diagnostic, genetic, molecular, etc.) and consider the roles of vasculopathy, senescence, and other potential contributing factors, assuring diversity, inclusion and equity. AD+ADRD Research Implementation Milestone Database (2.BB) https://www.nia.nih.gov/research/milestones/disease-mechanisms/med-late-understanding-mechanisms-and-relationships-other	In-progress	RFA-NS-20-005 PAR-23-212 PAR-24-148

ADRD Summit 2022 Session 8: MED Special Topic: Impact of COVID-19 on AD/ADRD Risk and Outcomes		
Milestone # (Priority Level) Milestone Text	**11/2024 Status**	**Response**
1(1) Establish research infrastructure enabling clinical, epidemiological and basic research studies of COVID-19 impact on AD/ADRD risk and outcomes, prioritizing disproportionally affected populations and clinical trials readiness. AD+ADRD Research Implementation Milestone Database (4.AA) https://www.nia.nih.gov/research/milestones/research-resources/med-covid-19-building-research-infrastructure	In-progress	NOT-NS-23-001 NOT-NS-21-037
2(2) Characterize the clinical phenotype and develop diagnostic criteria for neurocognitive impairment and dementia associated with COVID-19 in those with and without neurocognitive impairment/dementia prior to infection. AD+ADRD Research Implementation Milestone Database (11.N) https://www.nia.nih.gov/research/milestones/diagnosis-assessment-and-disease-monitoring/med-covid-19-understanding-impact	In-progress	PAR-23-214 PAR-24-203
3(3) Explore interaction of social, structural, and systemic inequalities, comorbidities and social and medical interventions with risk and neurocognitive sequelae of COVID-19. AD+ADRD Research Implementation Milestone Database (1.U) https://www.nia.nih.gov/research/milestones/epidemiology-population-studies/med-covid-19-understanding-barriers-health	In-progress	NOT-NS-21-037

4(4) Advance understanding of basic mechanisms underlying neurocognitive impairment and dementia due to COVID-19 in order to develop biomarkers, risk profiles, and the foundation for early interventional trials. AD+ADRD Research Implementation Milestone Database (2.CC) https://www.nia.nih.gov/research/milestones/disease-mechanisms/med-covid-19-understanding-ad-adrd-brain-changes-after-covid	In-progress	PAR-23-214 PAR-24-203