# ADRD Summit 2022 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 2022 that was held on March 22-23, 2022 via an all virtual platform, due to the global COVID-19 pandemic. The Summit addresses research priorities for ADRD and complements the National Institute on Aging's (NIA) Alzheimer's Disease (AD) Research Summits and National Research Summits on Care, Services, and Supports for Persons with Dementia and Their Caregivers. The ADRD Summit 2022 follows the ADRD Conference 2013, ADRD Summit 2016 and ADRD Summit 2019 led by the National Institute of Neurological Disorders and Stroke (NINDS) in collaboration with NIA. Together, these triennial summits on AD, ADRD, and Care are coordinated planning efforts that respond to the National Plan to Address Alzheimer's Disease ("National Plan") 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 public and private stakeholders. 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) Council. The NAPA Council will then consider including the ADRD Summit 2022 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, the annual professional judgment budget that NIH prepares and submits to the President for review and transmittal to Congress each year.

## Introduction

Dementia carries substantial health and financial costs, affecting about 55 million people worldwide. AD alone, as one dementia diagnosis, affects 6.2 million people in the United States (U.S.). The toll on individuals, caregivers, and society is enormous and is expected to increase as the population ages. The National Plan to Address Alzheimer's Disease—launched by the National Alzheimer's Project Act (NAPA) that was signed into law in 2011—plans, coordinates, and integrates federal and non-federal (private and state-level) activities to overcome AD and ADRD. This includes research and communication on topics such as risk factors, clinical care, and long-term services and support. Among the goals of the National Plan is the first and perhaps most ambitious—Goal 1: to prevent and effectively treat AD/ADRD by 2025. The Plan includes several specific strategies to accelerate pace towards this goal, instructing review of the latest science and identification and updating of AD/ADRD research priorities regularly through research summits. Therefore, to help achieve Goal 1, and as a federal action specified in the National Plan, periodic summits are held that set and refine ADRD research priorities in the Plan. ADRD summits are led by NINDS, in collaboration with NIA, and with input from federal, national, and international partners. The ADRD Conference 2013 and the ADRD Summits in 2016 and 2019 established initial, detailed ADRD-specific research priorities in the National Plan, including those related to dementia health disparities and equity. On March 22-23, 2022, NINDS held the fourth ADRD Summit, the subject of this report to Council.

Over the first decade of the National Plan to Address Alzheimer's disease, there has been a data-driven shift in both our understanding of the relationship between AD and ADRD, as well as the landscape of mechanistic drivers of dementia overall—and thus, the most likely pathways to successful intervention. The shift is that new data have made it clear that there is not a one-to-one relationship between the type of brain pathology present and the clinically assigned dementia diagnosis in most individuals. Indeed, many non-AD dementia diagnoses are now known to be associated with classic AD pathology (beta-amyloid plaques and tau tangles). Similarly, brain pathologies often associated with one or more ADRD diagnoses (e.g., vascular, Lewy bodies, TAR DNA-binding protein [TDP]-43 proteinopathy) are also frequently associated with clinically diagnosed AD. Therefore, these relationships, between clinical diagnoses and pathologies, are not as straightforward as once thought. However, for most researchers, caregivers, and members of the public, there remains an expectation, explicit or implicit, that a single type of brain pathology causes a single type of clinical dementia. These traditional ideas have impeded scientific rigor and narrowed the scope of clinical considerations as well as mechanistic, translational, and clinical studies that are critically needed to advance successful future interventions. Therefore, to accelerate progress toward Goal 1 of the National Plan, including for diverse populations as well as precision medicine approaches, there is a clear need for deeper understanding of disease mechanisms that affect cognition across diagnoses, over the lifespan, and throughout the dementia spectrum (Figure 1).

Thus, the National Plan addresses several other clinical dementias (defined as ADRD) with pathologies that also occur in at least a substantial subset of clinically diagnosed AD. These disorders include frontotemporal dementias (FTD), Lewy body dementias (LBD), vascular contributions to cognitive impairment and dementia (VCID), and multiple etiology (sometimes referred to as mixed etiology) dementias (MED). There is a critical need for clear mechanistic understanding and improved clinical detection of ADRD in our aging population, as well as more knowledge about the presence and significance of co-morbid brain pathologies in individuals diagnosed with the clinical syndrome of AD. Clarification will emerge from multiple sources: pathological findings, clinical characterization, biomarkers that differentiate among dementia syndromes, disease mechanisms including targets and justifications for intervention, and, ultimately, both pragmatic and therapeutic approaches that leverage advances to prevent, treat, stop, delay, or reverse disease pathogenesis and thus reduce dementia burden.

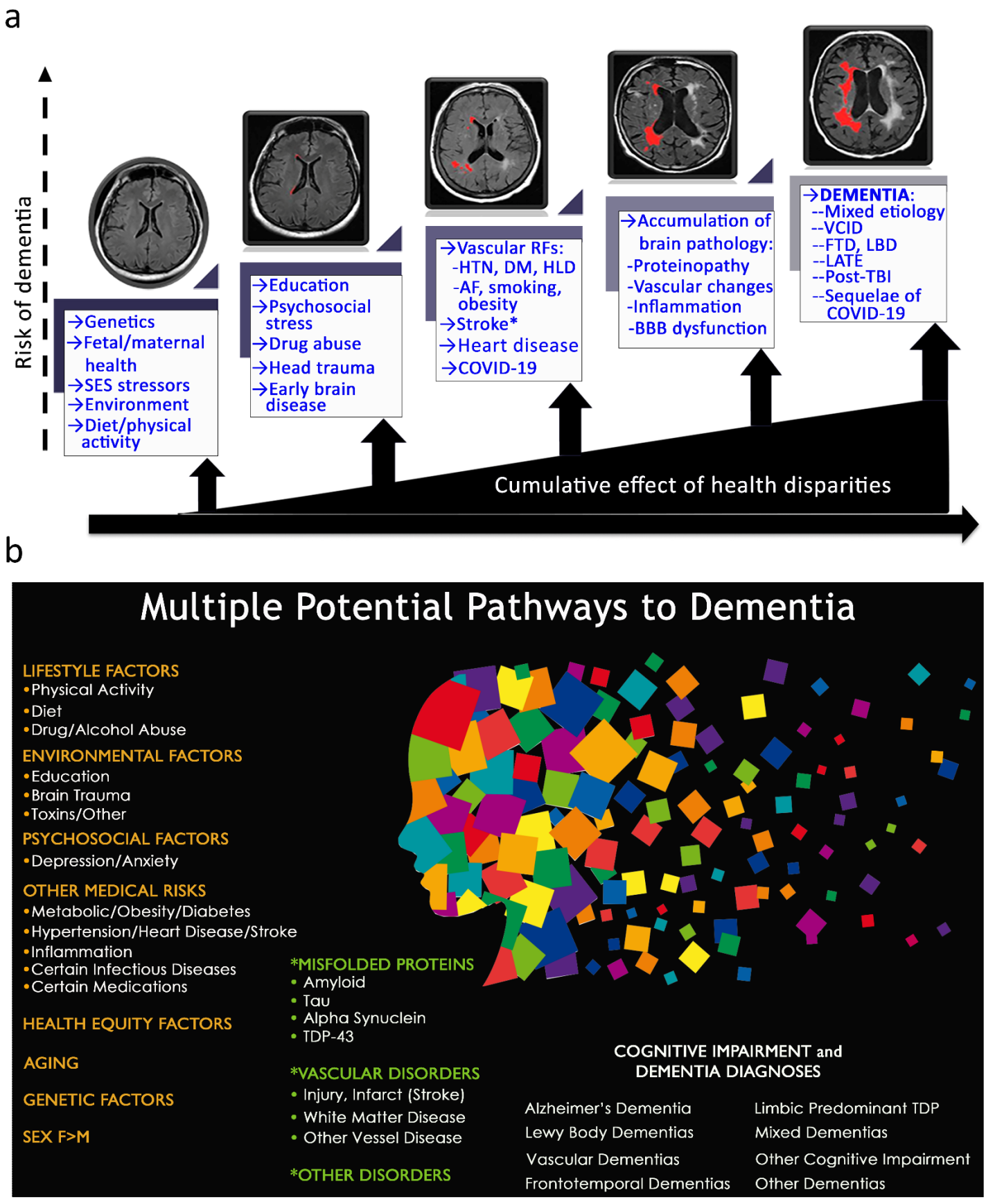


*Figure 1a, b. Multiple risk factors and potential pathways to brain pathologies and clinical diagnoses of dementia.*

The AD Summit, ADRD Summit, and the National Research Summit on Care, Services, and Supports for Persons with Dementia and their Caregivers are key components of the NIH response to NAPA. These planning efforts generate recommendations and milestones for the U.S. and international research communities. At the NIH, the recommendations and milestones inform development of the annual NIH AD/ADRD bypass budget proposals mandated in the Consolidated and Further Continuing Appropriations Act of 2015. The annual bypass budgets estimate the *additional* funds above the NIH base for increased investigator-initiated research and AD/ADRD initiatives needed to achieve the NAPA goals. The annual AD/ADRD bypass budgets are transmitted to Congress separately from the typical federal budget process. Since 2015, recognizing the necessity of addressing AD/ADRD aggressively as the nation ages, there has been more than five-fold increase in NIH funding for AD/ADRD research. A significant part of this increase is due to increased appropriations to NIA that are intended for AD/ADRD research, and by the fact that NIA has shared, via collaboration with NINDS and other NIH institutes, implementation of research priorities identified by NIH-led AD/ADRD planning efforts. NINDS has pursued ADRD research priorities set in 2013, 2016, and 2019 by funding ADRD-relevant investigator-initiated research grants within the NINDS pay line, and outside the pay line through a high program priority process, as well as by launching new funding opportunities as indicated in Appendix 1 and Appendix 2 of this Report.

The goals of the 2022 ADRD Summit were to: 1) review and assess progress on the research recommendations developed by the ADRD Summits in 2013, 2016 and 2019, 2) refine and add new recommendations based on recent scientific discoveries, 3) solicit input from stakeholders, and 4) update priorities and timelines for addressing ADRD. These revised and new recommendations, once approved by the NINDS and NAPA Advisory Councils, will become part of the National Plan and inform future AD/ADRD bypass budgets. The 2022 Summit brought together a broad representation of stakeholders in a "bottom-up approach" to assess and manage ADRD research via a collaborative, cross-sector forum. As in prior years, the ADRD Summit addressed, via dedicated sessions, special research priorities for FTD, LBD, VCID, and MED. This year, Health Disparities in AD/ADRD, which has been part of the ADRD Summits since the start in 2013, was included under the more comprehensive topic of Health Equity in AD/ADRD research. This change reflects the forward-facing NINDS vision regarding the future of research and medicine. The 2022 Summit also included updates on the MED special topics from the 2019 Summit, LATE (TDP-43 in Common Late-Onset Dementias) and Post-Traumatic Brain Injury (TBI) AD/ADRD, as well as new special topic session on the Impact of COVID-19 on AD/ADRD Risk and Outcomes.

Planning and execution of the 2022 ADRD Summit generally followed the successful strategy developed for the 2013 2016, and 2019 ADRD Summits. However, due to the global COVID-19 pandemic, the ADRD Summit 2022 was held in a remote format using an electronic platform with live participation from all speakers and attendees that was recorded for archival purposes and future viewing. The Summit process included regular pre-summit, summit, and post-summit video calls to update and further develop draft prioritized research recommendations, which were presented at the Summit for public input that informed final deliverables (ADRD Summit 2022 Prioritized Recommendations). A critical feature of the ADRD Summits is open and transparent engagement with stakeholders, including members of the public, with significant time dedicated to open microphone question, answer, and comment periods. In prior years, this was achieved in part through highly interactive question and answer sessions that would lead into "hallway" conversations during breaks. In the virtual format, the interactive elements of the Summit were achieved by utilizing the Q&A function of the virtual platform as a proxy for the open microphone. The Summit participants had the option to speak or ask a question during the live, open question time and were instructed to enter their name only in the Q&A feature that served as a platform for the queue. In keeping with the goal of openness and interactions that would most closely replicate those during an in-person meeting, the attendees were asked not to write out their question but rather just their name and wait until they could be brought onto the virtual stage live with their camera and microphone on to address the speakers and panels directly. There was a total of 210 minutes of open microphone time in the ADRD Summit 2022. A summary of other major activities in advance preparation, the Summit itself, and follow-up, appears below.

**Advance Preparation for the 2022 ADRD Summit.** Pre-summit efforts began in August of 2021 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 the National Plan (MED, Health Equity, VCID, LBD, and FTD), and for two MED subtopic sessions (TDP-43 and TBI in Common Dementias, respectively) established in the ADRD Summit 2019. In addition, the Scientific Chair proposed a new MED special topic session on the Impact of COVID-19 on AD/ADRD Risk and Outcomes. This proposal was viewed as timely, relevant, and was accepted unanimously. 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 scientific members (Tables 2 and 3) tasked with developing recommendations (MED special topic of impact of COVID-19 on AD/ADRD risk and outcomes) or, for other topic areas, 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 2021 and March 2022. NIH staff provided the committees with responses to a joint NINDS/NIA Request for Information (NOT-NS-22-032) 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.

Each session committee considered proposing up to eight recommendations (four each for MED special topics) with priority ranking such that there could be up to two #1, #2, #3, and #4 priority recommendations, where the highest priority recommendation has the designation #1. The timelines indicated were determined by each committee estimating the number of years needed to complete or fully implement each recommendation once the activity is started.

Resulting from this preparatory process, the 2022 ADRD Summit agenda and draft recommendations were posted online before the Summit and presented for public input at the Summit.

**Summit.** The primary goal of the 2022 ADRD Summit was to solicit input and feedback from a wide range of ADRD stakeholders 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 1,527 individuals registered for the virtual meeting, with 400-700 attending most sessions. The Summit was recorded and made available for archival viewing on the NIH VideoCast (Day 1, Day 2). A breadth of stakeholders – academic, clinical, government, industry, non-profit and public - registered and participating in the virtual Summit. Structurally, the Summit was divided up into 8 scientific sessions occurring over 2 days with 128 panelists and 44 individual talks. During each session, following a topic overview, the session's chairs presented a summary of scientific progress that had occurred since 2019 and then proposed updates and refinements to draft research recommendations for public input. A special video testimonial, "Voices of AD/ADRD," was introduced on Day 2 to raise awareness of the disease burden on patients with AD/ADRD and their caregivers. Furthermore, broad public input was received, including strong presence of patients and caregivers throughout the Summit. The public portion of the Summit concluded March 23 with a review of all suggested additions, revisions, and further opportunity for input from all participants. Immediately following the summit proceedings, NINDS led a closed session during which session chairs, NIH and other federal officials, Working Group members, and the Scientific Chair reviewed the proposed revisions, edited the draft recommendations as agreed upon by the Steering Committee, and assigned duties to complete final revisions of 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 2022 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 2022 ADRD Summit session committees appears in Tables 1-3. In addition to federal representation from the NINDS, NIA participation included Drs. Eliezer Masliah, Cerise Elliot, Mack Mackiewicz, Damali Martin, Lisa Opanashuk, Nina Silverberg, Keenan Walker and Austin Yang. The National Heart, Lung and Blood Institute (NHLBI) participation included Drs. Marishka Brown, Selenia Catania, Lawrence Fine and George Sopko. 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 Summit, there was a consensus that great progress has been made since 2019; however, more progress is needed to accelerate clinical translation of the emerging science. A number of cross-cutting themes emerged in scientific presentations and discussions that followed, including:

- Health equity in AD/ADRD as a major imperative and continuing unmet need
- The need for research and implementation of pragmatic approaches and solutions in AD/ADRD, including pragmatic clinical trials
- The urgent need for precise biomarkers to identify underlying disease processes in healthy individuals and those with diagnosed AD/ADRD or prodromal syndromes
- Innovative approaches to personalized prevention and treatment that address health equity and diverse populations by design
- In clinical research, prevention, pre-symptomatic vigilance, and concerted efforts to support the immediate needs of individuals living with cognitive impairment and dementia
- In basic research, needs include novel strategies and tools (e.g., models, biology paradigms) and/or seeking synergies, maximizing divergence in disease pathways.

Below are highlights of the key takeaways from presentations on the recommendations and discussions that took place during the Summit.

## Health Equity in AD/ADRD (Co-Chairs: Hector González, PhD and Julie Zissimopoulos, PhD)

The topic of health disparities in AD/ADRD has been part of the ADRD Summits since the beginning in 2013; however, given the preponderance of evidence with regards to cumulative effect of health disparities on life-time risk and outcomes of ADRD (Figure 2), this year it was included under the more comprehensive topic of Health Equity in AD/ADRD research.

The highest priority recommendations in AD/ADRD health equity center on: (1) inclusion of underrepresented populations in research to improve representative sampling and retention of diverse communities; and (2) increase of training support and capacity of the AD/ADRD workforce of persons historically underrepresented in biomedical, behavioral, and social sciences. Following a vigorous discussion on this topic, general themes emerged that encompassed several key areas of relevance to health equity in AD/ADRD: a) the need for assessment tools, including biomarkers, to understand ADRD in diverse populations via dedicated studies of minoritized populations, covering the entire life-span, b) developing research studies that go “wide and deep”, highlighting multiple approaches, breaking the barriers to recruitment of diverse populations, c) improving access to clinical trials, especially to ensure equity, and with free of cost participation, d) addressing gene-environment interaction through inclusion of health disparity factors that are related to life-course of environmental exposures (e.g., nutrition, lifestyle, and toxicities), e) the need for novel models (e.g., organelles) to thoroughly account for the variability and specifics of diverse environments, f) the urgent need to encourage and expand biospecimen and tissue collection with special focus on brain donation for discovery, g)

encouraging transparency in communication with caregivers regarding diagnosis and prognosis, and h) building a strong foundation for developing diverse workforce via retention and support of mentors at all stages of their career span.

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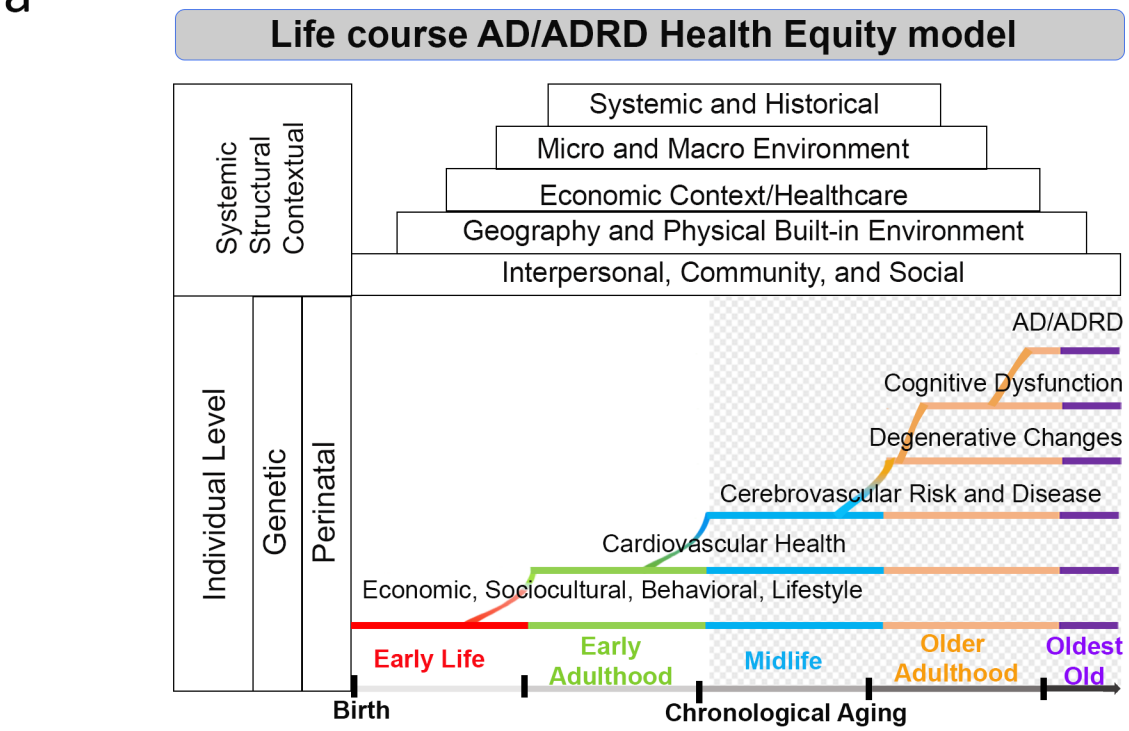


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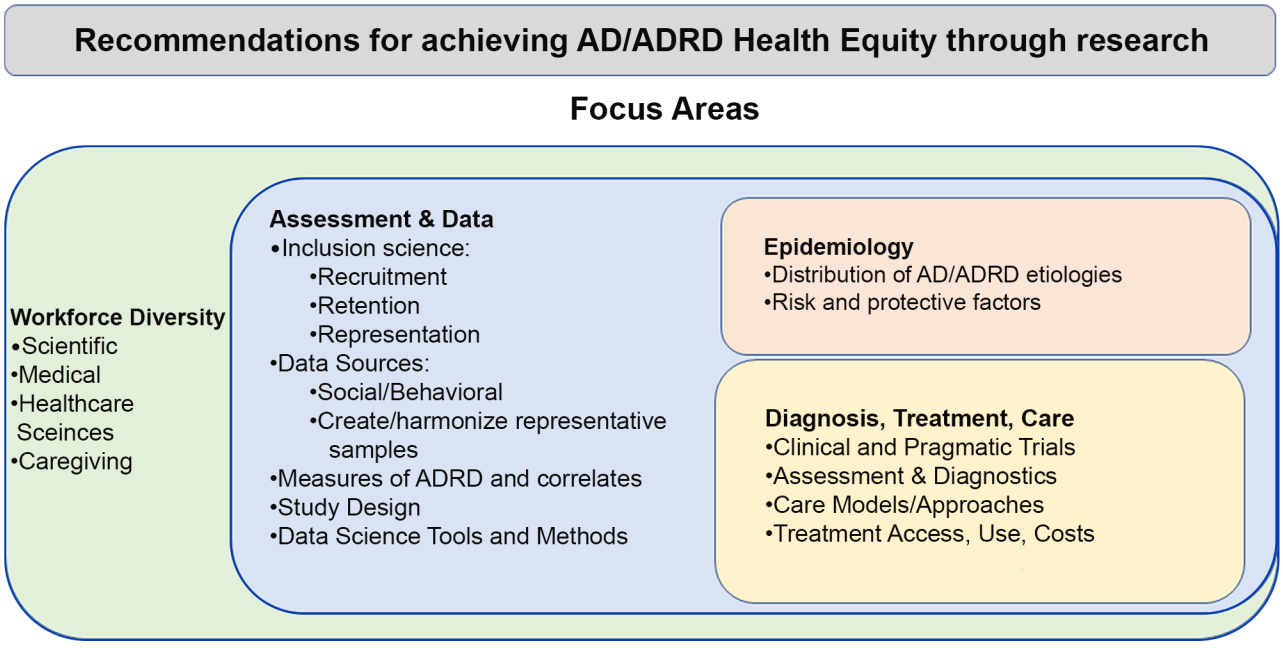


*Figure 2 a) There are multiple components of health disparities that have a cumulative effect on life-course and outcomes of AD/ADRD. These components are two broad categories (i) systemic, structural, and contextual (ii) individual, genetic, and perinatal level. Modified from González et al 2019 (PMID: 31759880). b) Health equity session committee recommendation for achieving AD/ADRD health equity through research by following focus areas. These focus areas include workforce diversity, assessment and data, epidemiology and diagnosis, treatment, and care.*

## Frontotemporal Dementia (FTD) (Co-Chairs: Adam Boxer, MD, PhD and Celeste Karch, PhD)

Previous ADRD Summits underscored rapid progress in FTD research with highlights including the discovery of repeat expansions in the *C9orf72* gene as a frequent cause of ALS and FTD in 2011, and in 2022 the FTD session included discussion of the first disease modifying agent trials for genetic FTD better understanding of genetic modifiers of FTD onset. FTD recommendations had been reprioritized over time based on progress, including the addition of a 2019 recognition of a need to improve the development of FTD biomarkers and expand genotyping efforts to enable new disease modifying agent clinical trials for FTD. Over the past several years, rapid progress in structural biology using cryo-electron microscopy has identified unique structures of tau protein aggregates in FTD syndromes as compared to in pathologically confirmed clinical AD, and aggregates of the lysosomal protein TMEM106B as a possible contributor to FTD pathology. Through the efforts of ALLFTD and related programs, increased availability of genetic, biomarker and clinical data has enabled the construction of detailed disease progression models on which new clinical trial designs and endpoints are being developed. Improvements in the early and accurate diagnosis of sporadic FTD syndromes are now being realized through the application of AD blood biomarker technology FTD cohorts and increasing numbers of clinical trials are underway in genetic FTD syndromes with many employing FTD specific biomarkers to demonstrate biological proof of concept in early-stage studies.

Reflecting the rapid research evolution and considering the committees assessment of challenges and barriers to FTD research the highest priority recommendations for the FTD session in 2022 have shifted to understanding FTD epidemiology and genetics, especially in diverse populations, including how socioeconomic and ethnocultural status affects disease risk and manifestations, and 2) advancing FTD science and identify therapeutic targets through the creation, validation, and use of pre-clinical and translational tools and resources was also given highest priority. During the discussion, the urgent need for biomarkers was highlighted, particularly as related to pre-symptomatic disease, and focusing on accelerating the course of clinical translation of already existing biomarkers of neurodegeneration (e.g., Neurofilament light chain [NfL]) and developing novel ones for disease progression monitoring. Furthermore, this discussion emphasized developing novel endpoints that capture the broad spectrum of clinical FTD. With a robust input from patients and caregivers, a particular focus on prevention and the need to support those living with FTD as well as delay in diagnosis and “single diagnosis box” were discussed. Other aspects of discussion covered risk and resilience factors characterization, the need for quantitative data beyond the “omics” level, e.g., at the level of protein biology and other precision methods of molecular disease characterization.

### CHALLENGES AND OPPORTUNITIES IN FTD RESEARCH

*Lack of Diversity*

- Little is known about FTD in African American, Latinx, Asian, Native American, Pacific Islander populations
- Most natural history studies include less than 5% African American and Latinx individuals, despite extensive recruitment efforts
- FTD genetics may vary across different populations (*MAPT* H2 allele, *GRN*, *C9orf72*, *TMEM106B*, *CHCHD10*, etc.)

*FTD syndromes are rare diseases*

- Insufficient numbers of *GRN*, *MAPT* mutation carriers to conduct multiple clinical trials using standard designs and methods
- Increasing numbers of promising therapeutic approaches and companies interested in FTD therapeutic development

*Few informative biomarkers*

- Limited ability to conduct prevention trials in familial FTD, limited power in symptomatic individuals
- Late diagnosis of sporadic FTD syndromes (bvFTD, CBD, PSP); Preclinical diagnosis challenging
- Accurate molecular diagnosis of sporadic bvFTD (Tau vs. TDP vs. FUS) challenging during life

*Difficulty of in person assessments*

- Geographically dispersed population; travel often necessary for research, but burdensome
- Local resources may limit access to technologies such as PET, MRI, LP etc., particularly in other countries

## Vascular contributions to Cognitive Impairment and Dementia (VCID) (Co-Chairs: Donna Wilcock, PhD and Ron Petersen, MD, PhD)

Vascular contributions to cognitive impairment and dementia (VCID) encompass all types of cerebrovascular and cardiovascular disease that are related to cognitive decline. The VCID working group approached recommendations in three categories of research: basic, human and translational. Within this framework, the top priorities are focused on: (1) establishing and refining the experimental models and technologies to identify disease-relevant mechanisms underlying VCID and (2) developing and validating markers of VCID in diverse populations using cognitive, physical, or other functional assessments, as well as biomarkers of key vascular processes, including in the most common scenario where VCID is accompanied by AD in human studies. In discussion that followed presentation, VCID was identified as an area of clear intersection of science offering countless opportunities to explore novel pathways and fine-tune existing models. Some of the areas of intersect include dementia and disorders of sleep through amyloid accumulation and loss of normal glymphatics function via perivascular spaces. The argument was made for novel approaches including non-ischemic mechanisms of VCID, e.g., impaired fluid-based clearance mechanisms as opposed to traditional "ischemic" models, as well as the nuanced models accounting for diversity in cell types involved in vascular pathological processes, regional blood flow, and vascular reactivity contributing to the biology of disease related to cognitive decline. These models must be prioritized based on reproducibility and repeatability of their performance at every stage of research including design, data collection, and data sharing. The group discussed a concept of VCID as "systemic disease" and the role of circulating biomarkers and emerging imaging technologies that may prove advantageous in future investigations (Figure 3).

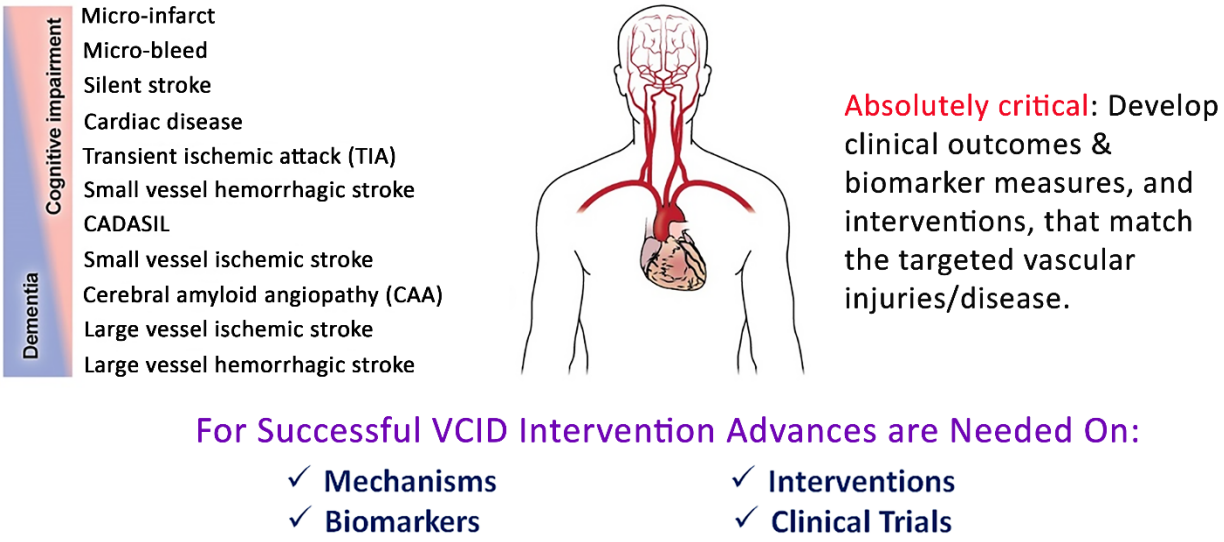


*Figure 3. There are multiple factors associated with vascular cognitive impairment and dementia (VCID), including, Micro-infarct, micro-bleed, cardiac disease, stroke, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). For successful VCID intervention, there is a critical requirement to develop clinical outcomes and biomarker measures along with advancing the disease mechanism and clinical trials.*

## Lewy Body Dementias (LBD) (Co-Chairs: James Leverenz, MD and Kejal Kantarci, MD)

LBD includes Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). The LBD committee highlighted advances demonstrating that underlying pathologies associated with dementia diagnoses, including LBD, are ultimately complex and can reflect contributions from co-morbidities and multiple pathological pathways (Figure 4). The updated recommendations are divided into two broad categories: clinical science, and pathologic processes of toxicity. The top priority for clinical science is to 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, as part of the overarching clinical characterization and

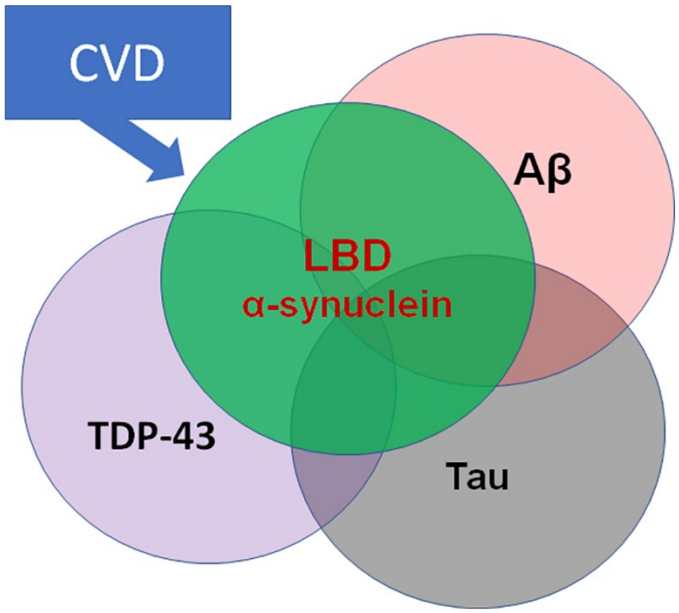


*Figure 4. There is overlap among different misfolded proteins, as well as cerebrovascular diseases (CVD), associated with clinical LBD.*

intervention theme. For pathology, the priority of delineating genetic loci and their functions that contribute to the onset and progression of LBDs using genetic, transcriptomic, epigenetic, and environmental characterization analyses encompassed key pathogenesis and mechanisms of toxicity considerations. Some of the most engaging discussion points regarding LBD recommendations included: a) the imperative of sharing of information across the disease entities, b) increasing access to ongoing scientific dialogue to the public in order to foster research collaborations, c) improving access to clinical trials across the spectrum of LBD, especially as diagnostic precision evolves and patients seek new opportunities, d) the urgent need for biomarkers at every stage of disease including pre-symptomatic, preclinical diagnostic, and prognostic, e) growing focus on disease heterogeneity – both clinical and precision characterization and the need for "breaking the siloes," and f) developing opportunities for disease modification and symptoms control in patients living with LBDs.

## Multiple Etiology Dementias (MED) (Chair: Katherine Possin, PhD)

Autopsy studies looking at the brains of people who had dementia suggest that most of those age 80 and older (which represents most people with dementia) have pathology associated with multiple neurodegenerative diseases linked to dementia symptoms. Thus, multiple, or mixed, etiology of dementias (MED) has a prominent presence among the ADRD. In the 2022 recommendations, research as well as cross-cutting themes that apply to all AD/ADRD were considered. There are five broad categories: Detection and Diagnosis of Cognitive Impairment and MED, Basic Research in MED, Interventions and Treatments for MED, Dementia Capable Workforce, and Data Harmonization (Figure 5).

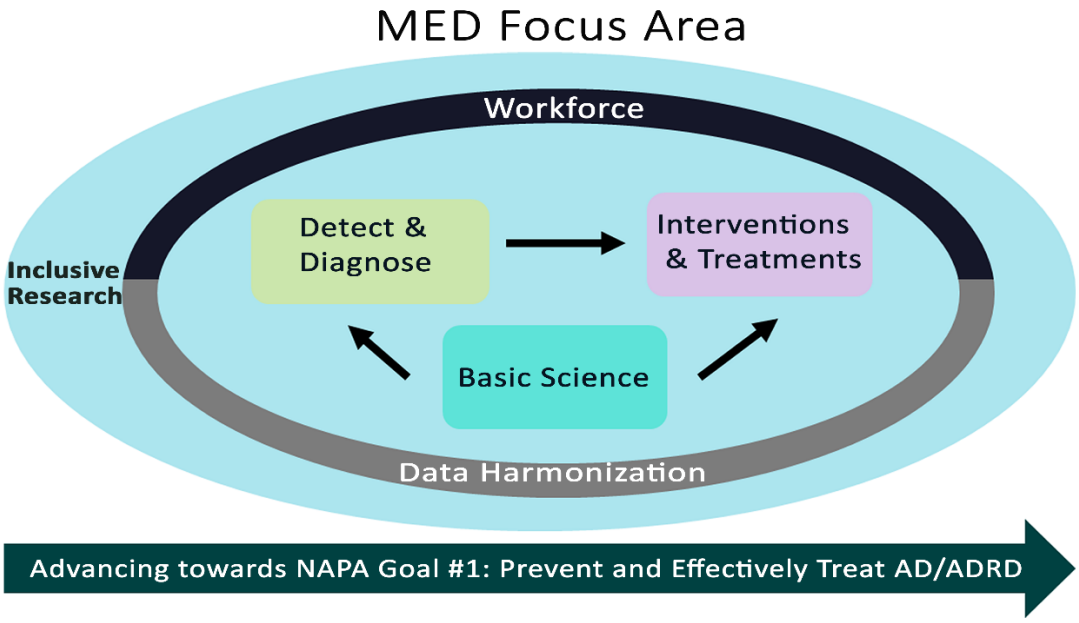


*Figure 5. There are five broad categories for MED focus areas: Detection and Diagnosis of Cognitive Impairment for MED, Basic Science Research in MED, Interventions and Treatments for MED, Dementia Capable Workforce, and Data Harmonization. Within those categories, the top recommendations are on the detection of cognitive impairment and clinical studies on promising interventions and treatments.*

The top MED priorities presented at the Summit included: 1) evaluation of 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 and 2) conducting clinical studies on approved or promising interventions and treatments to mitigate risk for cognitive decline. During the robust discussion that included significant input from the public, the importance of engaging caregivers and incorporating their input was emphasized. Consensus was reached that it is a high priority to advance research on detection and diagnosis that is clinically actionable, culturally appropriate, and tied to compassionate disclosure. It is also critical to consider healthcare provider burden and well-being that contribute to the quality of care and support that they are ultimately able to provide. The need for research on cultural aspects of risk/benefit perception and policy research into economic impact of screening and early detection on diverse populations were highlighted, as well as the need to understand how to broadly implement effective dementia care. Furthermore, opportunities to amplify effectiveness of multiple approaches to research via harmonization across MED have been proposed. Finally, the importance of care partners input from research concept to execution could not be underestimated.

For scientific reasons and for organizational purposes, the special topics from 2019 and 2022 are considered as subsets of the MED session, as indicated below.

### MED Special Topic: Post-TBI AD/ADRD (Chair: Kristen Dams-O'Connor, PhD)

Population-based studies suggest as many as 10 million people in the U.S. living with some type of TBI-related disability. TBI symptoms can overlap with many different dementia diagnoses, and TBI is a widely recognized risk factor for AD/ADRD. However, quantifying group-level risk elevation is neither informative nor actionable: extant literature largely obscures critical distinctions about individual and injury characteristics and their associations with distinct clinical dementia phenotypes and underlying pathological processes. Traditional methods and existing data pose significant limitations to better understanding the relationship between TBI and AD/ADRD outcomes. Epidemiological studies relying on electronic health records underestimate TBI exposure and lifetime head trauma exposure is difficult to quantify. The top priority in the 2022 post-TBI AD/ADRD recommendations is to promote collaboration among TBI and dementia researchers through working groups, retrospective and prospective data and measurement harmonization across longitudinal studies, investments in post-TBI AD/ADRD research infrastructure, and interdisciplinary collaboration. In discussion, the topics that have been emphasized included: a) the central role of multimodal biomarker arrays to understand the clinical heterogeneity of post-TBI AD/ADRD, and the need for longitudinal prospective study designs with detailed exposure history characterization and autopsy endpoints, b) the need to differentiate acute injury vs. chronic symptoms to distinguish chronic stable post-TBI symptoms vs. post-traumatic neurodegeneration (see Figure 6) and to clarify the relationship of post-TBI AD/ADRD to chronic traumatic encephalopathy, c) the imperative of standardization and prioritization of translational models of TBI through expanding and aligning ongoing collaborations between Veterans Affairs, Department of Defense and NIH, and d) the importance of including stakeholders in research and expanding the availability and accessibility of public-facing education regarding post-TBI AD/ADRD.

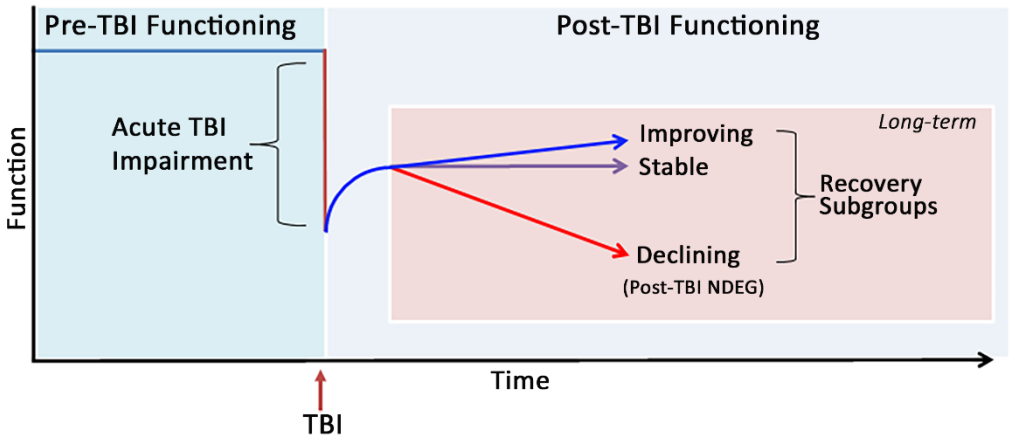


*Figure 6. History of traumatic brain injury (TBI) is considered a risk factor for AD/ADRD. Recovery for patients with clinically significant TBI can be classified in three subgroups: an improving subgroup, a stable subgroup, and a declining subgroup at greatest risk for dementia.*

## MED Special Topic: LATE (TDP-43 in Common Late-Onset Dementias) (Chair: Julie Schneider, MD, MS)

TDP-43 (transactive response DNA binding protein of 43 kDa) is a protein that helps regulate gene expression in the brain and other tissues. Previous studies have shown that misfolded forms of this protein play a causative role in rare diseases such as amyotrophic lateral sclerosis (ALS) and FTLD, but new studies indicate that misfolded TDP-43 is also commonly found in older people's brains with and without AD pathology, and in 90% of people with hippocampal sclerosis. During the 2019 ADRD Summit, the new term for a disease was used by the TDP-43 Session co-chairs, "Limbic predominant Age-related TDP-43 Encephalopathy" or LATE (Figure 7). While LATE can be a mimic of clinical AD, there is emerging evidence that LATE can occur together with or as a separate entity from clinical AD, and that it is linked to hippocampal sclerosis. The top priority presented at this Summit is to 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. In robust discussion that followed, the need for: a) harmonization of data and sample collection for the benefit of related fields, b) investigations into LATE/VCID interactions, hippocampal sclerosis, and senescent changes, including but not limited to the role of clearance mechanisms and sleep disruptions c) clinical diagnosis readiness including biomarkers and clinical criteria needed to validate prospectively and to provide options to patients and families, and d) consideration of "health span" of disease, i.e. the primacy of quality of life and actionable detection/diagnosis option.

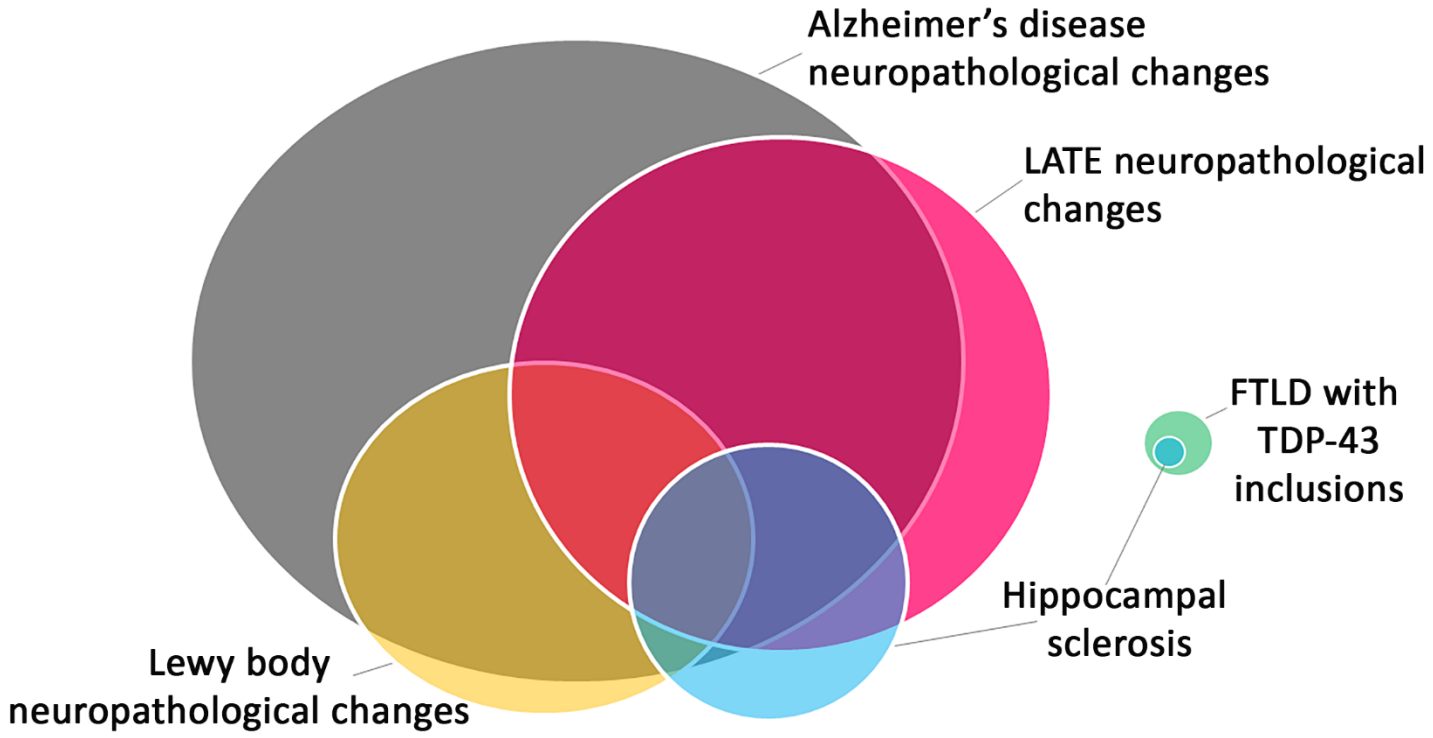


*Figure 7. There is emerging evidence that Limbic predominant Age-related TDP-43 Encephalopathy (LATE) neuropathological changes (NC) can occur together with or as a separate entity from Alzheimer's disease neuropathological changes (AD-NC), and that it is often linked to hippocampal sclerosis (HS) and Lewy body disease (LBD). LATE and FTLD-TDP (which can also be associated with HS) appear separately in this schematic, consistent with the scientific view of the committee. Therefore, the top priority presented at this Summit was to 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.*

## MED Special Topic: Impact of COVID-19 on AD/ADRD Risk and Outcomes (Co-Chairs: Natalia Rost, MD, MPH and Sudha Seshadri, MD)

The COVID-19 pandemic continues to have drastic impact on the U.S. and worldwide (Figure 8). While some initial studies have clearly described the acute impact of SARS-CoV-2 virus on the brain, the long-term impact of COVID-19 on risk for AD/ADRD outcomes is not yet fully known. Neuropsychiatric and cognitive complaints such as 'brain fog' are common among survivors. However, the unique impact of SARS-CoV-2 infection on the brain described to date suggests propensity for long-term neurological consequences including cerebrovascular effects with endothelial injury and loss of blood brain barrier integrity, neurotropism, and early evidence of neuroinflammation as seen in neuroimaging and neuropathological studies. Because these pathogenic factors may influence neurodegeneration pathways, the impact of COVID-19 on AD/ADRD is expected but should be carefully studied as an explicit endeavor and hypothesis. Potential detrimental effects related to risk of AD/ADRD in survivors of SARS-CoV-2 infection include but are not limited to: 1) increase in incidence of cognitive impairment/dementia cases, 2) accelerated course of cognitive decline among already diagnosed cognitive impairment/dementia cases, 3) accelerated course of neurodegeneration and brain vascular pathology among already diagnosed cognitive impairment/dementia cases, 4) shift in the population timeline of cognitive impairment/dementia clinical onset toward younger ages (and increased incidence in early-onset dementias), and 5) increased mortality among individuals with advanced dementia. The top priority proposed by this special topic workgroup is to 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. Other priorities for this emerging topic included: a) characterization of the clinical phenotype and development of diagnostic criteria for neurocognitive impairment and dementia associated with COVID-19, b) investigation into interaction between social, structural, and systemic inequalities, comorbidities and interventions and risk/neurocognitive sequelae of COVID-19, and c) advancement of current understanding of basic mechanisms underlying neurocognitive impairment/dementia due to COVID-19 with the goal of developing biomarkers, risk profiles, and foundation for early interventional trials.

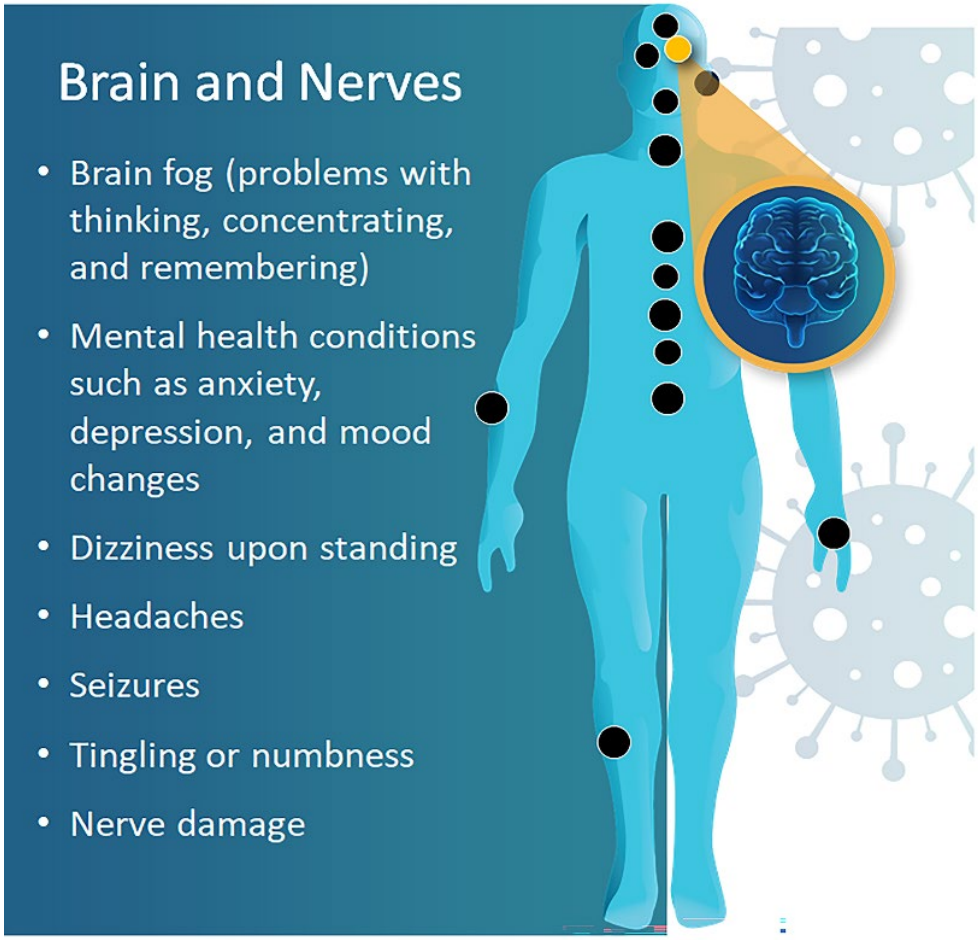


*Figure 8. Symptoms associated with long COVID have similarities to ADRD symptoms. https://covid19.nih.gov/covid-19-topics/long-covid*

The recommendations in this Report, which have been approved by the NANDS Working Group of Council (Table 1), represent national priorities that will inform future NIH AD/ADRD bypass budgets and, as congressionally appropriated funds become available, corresponding funding of ADRD research activities. All recommendations stand independently as written, with bullet points below each providing context and further insight into conversations and the thinking of the consensus process that resulted in them. The recommendations in this report all represent important research goals. Each session committee was required to assign rank priorities and for a research recommendation to be included in this report, it must be among the top priorities in its respective field. Timelines described after the recommendation text do not reflect prioritization, but rather serve to guide planning and implementation logistics. Finally, note that the ordering of sessions in no way reflects prioritization – all sessions (Health Equity, FTD, VCID, LBD, MED, MED Special Topics) are of equally high priority.

As Scientific Chair of the ADRD Summit 2022, I respectfully submit this Report to the NINDS Council on behalf of all committee co-chairs and members.

Sincerely,

Natalia S. Rost, MD

Natalia S. Rost, MD, MPH, FAAN, FAHA

Scientific Chair, ADRD Summit 2022
Chief, Stroke Division, Massachusetts General Hospital
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# ADRD Summit 2022
# PRIORITIZED RECOMMENDATIONS

## Health Equity in AD/ADRD

### Recommendation 1 - Priority 1. Advance equity in AD/ADRD research via inclusion science to improve representative sampling and retention of diverse communities. (5 - 7 years)

- Increase the awareness and visibility of the science of recruitment.
- Establish AD/ADRD diversity recruitment and retention centers.
- Build accountability mechanisms for recruitment goals within existing networks.
- Prioritize initiation of 2-3 lifespan cohort studies.

### Recommendation 2 - Priority 1. Increase training support and capacity of an AD/ADRD scientific workforce of persons historically under-represented in biomedical, behavioral, and social sciences. (1 - 3 years)

- Workforce diversity is critical to all aspects of science of AD/ADRD – from neurons to nations – as it affects the quality of the data collected, the knowledge accumulated, and the representativeness of future research and the workforce pipeline.
- Create an inclusive and diverse workforce that brings additional perspectives and broadens research scope, which is a critical and essential component for conducting AD/ADRD research with minoritized populations.
- Ensure a representative workforce that aligns with diverse communities to facilitate better communication with community participants and partners, enabling greater data validity.
- Leverage existing diverse AD/ADRD health equity research groups and organizations to further attract, train, and retool a competent workforce, especially individuals under-represented in science.
- Partner with relevant stakeholders to identify and invest in promising trainees early in the pipeline, including as early as high school.
- Enhance existing systems for tracking and monitoring progress in the diversification of the AD/ADRD scientific workforce, including incorporating metrics for barriers to recruitment and retention of diverse scholars.
- Implement a robust mentorship and sponsorship system for AD/ADRD trainees that prioritizes mentors and institutions to train under-represented scholars.
- Expand the availability of targeted training mechanisms, writing workshops, and other career development resources to support under-represented scholars in obtaining AD/ADRD training, beginning in college and through their advanced research training.

### Recommendation 3 - Priority 2. Promote career development of biomedical, behavioral, and social scientists conducting AD/ADRD health equity research. (1 - 3 years)

- Retooling and expanding the knowledge base on conducting inclusive science of midcareer and senior scientists attracted to the field of AD/ADRD is essential if progress is to occur in successfully retaining an inclusive and competent research workforce.

- Develop an iterative training framework for AD/ADRD health equity research at various training and career stages.
- Require training and education in health equity principles, as through Responsible Conduct of Research training, for all scholars, regardless of their background or level.
- Provide training and education in health equity research to all grant reviewers and increase participation in the study section of scientists with expertise in health equity research, including individuals who are members of under-represented populations. A knowledgeable reviewer pool is essential to achieve the goals of increasing the inclusion of populations facing inequities in research and increasing research focused on health equity.
- Increase opportunities for participation in high-level decision-making committees and opportunities for mid-career and senior under-represented scholars.

### Recommendation 4 - Priority 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. (3 - 5 years)

- Conduct research on how insurance benefit design and payment and reimbursement policies impact assessment and diagnosis of dementia in diverse populations.
- Determine generalizable population effects of provider-specific and health system factors on likelihood, quality, and validity of assessment and diagnosis in diverse populations. This may include access to dementia specialists, the role of ethnic/racial concordance, provider and practice-level organization, and diagnostic resources.
- 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 equitable assessment and diagnosis.
- Develop new research on the effects of assessment, detection, diagnosis, and referrals on health, social, and economic outcomes.

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

Cognitive Assessment:

- Consider specific recommendations to develop novel and unbiased normative methods development as well as recommendations/guidelines/possible white paper guidance on when to use and when not to use race or ethnic-based norms for biomarkers and cognitive data.
- Prioritize establishing 2-3 studies to harmonize cognitive assessment across diverse populations.

Biomarkers:

- Increase biomarkers availability and development of resources to address the fundamental questions of biomarkers utility in distinct race/ ethnic groups. Existing frameworks may not apply well in diverse populations given the lack of consideration of vascular disease; biomarkers may have different meanings and values in non-White populations.
- Prioritize dedicated biomarker studies of ethnic/racial persons across the lifespan with a special focus on increasing brain and other nervous tissue donation for discovery and validation studies.
- Enhance inclusion of digital “biomarkers” (e.g., blood pressure, heart rate, sleep data) in existing and large prospective cohort studies of diverse populations.

-Omics:

- Prioritize studies that characterize genetic risk factors in the context of environmental and other (non-genetic) factors. Genetic discoveries need to be examined in the context of environmental, behavioral, socioeconomic, and cultural factors. Increase investigations of how genetic risk shapes downstream multisystem factors; that inform and enable lifestyle interventions tailored to those who would benefit most; and reduce stigmatization of individuals or groups at high genetic risk.

- Expand the scope of data collection, including multi-omics and other biomarkers of exposures in diverse populations is needed; Prioritize 2-3 large life-course studies of cognitively well-characterized populations that are severely under-represented in -omics (GWAS, WGS, epigenetic and other -omics approaches).
- Prioritize establishing 2-3 studies geared towards the development of methods for analyzing large-scale multidimensional data generated from diverse populations.

### Recommendation 6 - Priority 3. Apply existing and novel surveillance methods to assess inequities, including trends in inequities, in AD/ADRD prevalence, incidence, diagnosis, treatment, and care. (3 - 5 years)

- Documenting inequities by surveilling trends in inequities in AD/ADRD prevalence, incidence, and related outcomes is integral to achieving health equity in AD/ADRD because it informs public health priorities, prevention, and treatment strategies.
- Recent studies suggest that dementia incidence rates may be declining, but most of this evidence is based on White persons in Europe and the U.S. Therefore, data are needed to surveil trends in dementia incidence among under-represented ethnic/racial minority populations regionally within the U.S. and internationally.
- Document and monitor inequities in AD/ADRD prevalence, incidence, diagnosis, and treatment across a range of social determinants of health, including but not limited to race/ethnicity, nativity, primary language, income and wealth, cultural context, educational background, gender identity and sexual orientation, and neighborhood environment.
- Direct attention to the impact of historical and contemporary policies (e.g., education policy, economic policy, health care policy, urban planning policy) and events (e.g., economic recessions, COVID-19 pandemic) to enable mitigation of AD/ADRD inequities and to achieve AD/ADRD equities.
- Establish new cohorts/registries to accurately estimate the prevalence, incidence, and clinical course of AD/ADRD phenotypes (e.g., Lewy Body, VCID, frontotemporal dementia, early onset dementia) in populations under-represented in research. Adapt innovative methods for determining prevalence and incidence, particularly of rare dementias from other fields.
- Develop novel approaches to identify and address determinants of ethnic/racial minority under-inclusion in AD/ADRD cohorts, registries, and clinical trials (e.g., high screen failures), which are a major source of data on inequities and trends in inequities (see Recommendation 1). These determinants might include but are not limited to: recruitment and retention practices, economic barriers and discrimination that reduce access to and quality of healthcare, misinterpretation of early signs of dementia and underdiagnosis by health care providers, and stigma within communities facing inequities.
- Develop valid estimates of AD/ADRD health inequities from samples that are representative of the U.S. population or oversample to adequately power informative research on groups under-represented in research.

### Recommendation 7 - Priority 4. Identify life course and multi-level mechanisms of and pathways to AD/ADRD inequities and use the discoveries to reduce these inequities. (5 - 7 years)

- Establish as a standard practice in research on determinants of racial/ethnic and other inequities in AD/ADRD; a conceptual model that describes the underlying drivers of those inequities.
- Measure whole person risk factors (both established and novel) over the life course and across generations, focusing on appropriate risk periods and associations of these factors with AD/ADRD, including cognitive, pathologic, behavioral, and functional outcomes among populations facing inequity in AD/ADRD, and/or inequity in the determinants of AD/ADRD.
- Establish new rigorous and adequately powered AD/ADRD cohort studies or harmonization efforts to augment ongoing cohort studies that evaluate the influence of and interaction between social, environmental, and biological mechanisms in producing AD/ADRD inequities. These mechanisms include, but are not limited to:
    - Structural and policy-level factors (e.g., racism in banking and lending, housing, education, occupation, legal/penal system, politics; economic policies present and past)

    - Early-life exposures (e.g., perinatal health, adverse childhood circumstances, and events) and epigenetics
    - Exposures to toxicants in the environment (e.g., air/water pollutants)
    - Other characteristics of the neighborhood, housing, schools (e.g., disorder, safety, segregation)
    - Occupational features (e.g., hazards, job security, income)
    - Psychosocial trauma (e.g., interpersonal discrimination, micro/macro-aggressions)
    - Psychosocial exposures and conditions (e.g., stress, depression) and their -omics biomarkers
    - Deep vascular, metabolic, and other systems phenotyping
    - Polygenic risk plus other -omics, including whole genome sequencing, epigenetics, transcriptomics, metabolomics, and proteomics
    - 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
- Develop studies aiming to examine intersectionality (e.g., race and gender, or race and income) in excess risk for an AD/ADRD outcome should entail sufficiently large subpopulations. This may require over-sampling rather than representative sampling alone.
- Apply methods to translate scientific discoveries to the under-represented groups and region(s) from which they are drawn.

### Recommendation 8 - Priority 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. (5 - 7 years)

- Develop and review national definition/standards for dementia ‘costs’ and ‘health outcomes’ relevant for the U.S. population and populations experiencing health inequities.
- 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 and data needs and establish a national database for dementia equity research on social, economic, and health-related factors as drivers of inequities in dementia treatment and high-quality dementia care and their impact on health and non-health outcomes.
- Expand research on the drivers of inequities in pharmacological, non-pharmacological, and medical and social service care interventions used in routine clinical care for AD/ADRD and its 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 diverse populations.
- Conduct new research on the role of supply-side factors, such as health system ownership of physician practices and health insurance offerings for achieving equity in AD/ADRD treatments and care.
- Catalog existing and develop advanced health economics models of pharmacological, non-pharmacological, and health care intervention access, costs, and outcomes on important and objective outcomes in diverse populations.
- Increase research on the role of sociocultural, behavioral, physical/built environment, economic, and health care system factors on equitable access to and use of different care models and pharmaceutical treatments for the cognitive and behavioral symptoms of dementia.
- Identify the impact of adopting telemedicine and mobile healthcare on ADRD outcomes among underrepresented minority populations vulnerable to health inequities by reducing financial, communication, structural barriers to accessing medical and unpaid care. Examine the impact of improved access to quality care through remote monitoring and data collection, remote specialist feedback, and remote provider-provider decision support from a professional network.

## Frontotemporal Degeneration (FTD)

### Recommendation 1 – Priority 1. Understand FTD epidemiology and genetics in diverse populations, including how socioeconomic and ethnocultural status affects disease risk and manifestations. (1 - 5 years)

- The majority of existing FTD clinical research and genetic data are from non-latin/a/o/x white individuals, but increasingly, studies from non-U.S. international cohorts suggest that FTD genetics in these cohorts are significantly different from those documented in current U.S. and European Union cohorts. Because little is known about FTD in diverse populations, it is possible that the incidence, prevalence, range of clinical phenotypes, and types of symptoms may be different in diverse populations than in non-latin/a/o/x white and may provide important insight for these and other populations.
- Moreover, unlike AD, FTD is a rare disease with an overall much lower prevalence, early age of onset, and initial symptoms that may be less likely to be recognized as part of a neurodegenerative disease. For these reasons, traditional approaches to improving diverse population participation in AD/ADRD research may not be applicable to FTD, and new approaches to diverse population recruitment and clinical research are needed specifically for FTD.
- Conduct studies to determine the prevalence, incidence, risk, and resilience factors for FTD in African American, Latin/a/ox, Asian, Native American, Pacific Islander, and other diverse populations in North America, as well as other diverse populations worldwide. Given the complexity and multiple subgroups within each population, oversampling for data collection should be employed.
- Develop culturally tailored and linguistically appropriate education and outreach tools to both support studies in diverse population and to reduce inequity in access to diagnosis. Such tools should be deliverable via online, mobile device, print, and in-person interactions. Clinicians/scientists from diverse populations should be engaged in these efforts.
- Develop and deploy new clinical assessment tools to identify and characterize FTD in diverse populations. These may include surveys, digital biomarkers, and health records reviews. Tools must be sensitive to psychiatric/behavioral symptoms, motor (Parkinsonism, motor neuron disease), cognitive, and speech/language symptoms of FTD.
- Develop and deploy new biomarkers that can be collected remotely and assessed in geographically remote, resource-limited, and diverse populations.
- Understand the role of socioeconomic, environmental, psychological factors, and comorbidities in the etiology of frontotemporal dementia syndromes.
- Develop educational tools and infrastructure to encourage and support brain and biosample donations from diverse populations. Encourage community outreach programs and partnerships with primary care and community health clinics.
- Develop methods to identify FTD in psychiatric settings and homeless individuals, as well as in people involved with the legal system, such as prisoners and individuals on parole. FTD may be misdiagnosed as a psychiatric disease and may lead to chronic homelessness or arrest for criminal behaviors, so this will be important to understand the epidemiology of this disease.

### Recommendation 2 – Priority 2. Develop an array of FTD biomarkers for diagnosis, prediction, disease monitoring, target engagement, and patient stratification for clinical trials. (2 - 7 years)

- Diagnosing people with FTD accurately and early in disease progression remains a major challenge for patient care and identification of participants for suitable clinical trials and potential treatments. This need is amplified for diverse populations, who may not have access to certain paradigms used in diagnosis, such as PET. In addition, being able to monitor disease progression, target engagement, and surrogate measures of clinical benefits of investigational therapies remain major barriers to developing effective treatments. Given the diversity of pathogenic mechanisms in FTD, it is possible that a given molecularly targeted therapy may only

benefit a subset of patients or may only benefit patients at a particular stage of disease progression. Thus, patient stratification based on target engagement, disease stage, and predictive biomarkers may be critical for effective and efficient clinical trials.

- Increase emphasis on developing easily accessible biomarkers, including those that can measure clinical and physiologic status and could be derived from remote collection, such as blood, peripheral tissue-based biomarkers, and digital biomarkers/tools to measure clinical and physiologic status.
- Develop diagnostic biomarkers to differentiate and characterize different forms of FTD, including FTLD-tau, FTLD-TDP, and FTLD-FUS. Given the recent identification of different conformations of these proteins in different clinical presentations, it may be necessary to characterize different forms of the same protein (such as tau in Progressive Supranuclear Palsy (PSP) vs. in behavioral variant of FTD (bvFTD), or in sporadic vs. inherited forms, etc. using structural biology approaches including cryo-Electron Microscopy) to best meet the goals of this recommendation.
- Develop biomarkers (fluid- or molecular imaging-based) for establishing target engagement for emerging treatments directed against tau, TDP-43, and other targets.
- Develop biomarkers (fluid- or molecular imaging-based) for stratifying participants into groups that are more likely to respond to emerging therapies under investigation.
- Investigate and validate biomarkers in cross-sectional cohorts (for group comparisons). Investigate changes over time, as well as predictive value in longitudinal cohorts.
- Develop machine learning approaches and other data-driven approaches to use existing datasets and integrate biomarker data to develop prediction algorithms or other tools to facilitate FTD diagnosis, disease progression modelling, and treatment response/clinical trial simulators.

### Recommendation 3 – Priority 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. (1 - 5 years)

- Given the diversity 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. Travel requirements for standard clinical research designs are burdensome and often restrict research participation to participants either in proximity to the specialist sites or with the financial resources, comfort level, and physical fitness for long-distance travel.
- Advance novel clinical trial designs for FTD to increase power, reduce placebo exposure, increase inclusivity to more patient populations (including diverse populations), 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 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 diverse 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.

### Recommendation 4 - Priority 4. Identify overlapping pathogenic mechanisms between FTD and other neurodegenerative disorders and syndromes. (2 - 7 years)

- Within FTD and other neurodegenerative disorders, there are single upstream genetic causes (e.g., C9orf72 expansion) and unifying pathologies (e.g., TDP-43 proteinopathy) that manifest in multiple distinct clinical pathologies. What explains the diversity of clinical phenotypes? Elucidating the underlying mechanisms for this divergence of clinical phenotypes will be beneficial for prognostic purposes and likely reveal which therapeutic targets are relevant for which form(s) of FTD.
- Likewise, within the FTD spectrum, there are clinical phenotypes (e.g., behavioral variant FTD) with multiple underlying genetic and pathological causes. Elucidating the underlying mechanisms for this convergence in phenotypes (e.g., network-system-level dysfunction, differences in regional vulnerability) will similarly reveal which therapeutic targets are relevant for which form(s) of FTD. These same questions are relevant for sporadic and inherited/familial forms of FTD.
- Identify distinct and overlapping pathogenic mechanisms between FTD, ALS, AD, HD, and other disorders and syndromes. 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, with potentially different underlying pathologies, including differences (where relevant) between sporadic and inherited/familial forms of disease. For example, determining the common mechanisms leading to an ALS phenotype caused by C9orf72, FUS and TARBP mutations, or a hyperkinetic movement disorder caused by HTT and C9orf72 expansions.
- Conduct multi-disease comparative genetic (including transcriptomic and epigenomic), proteomic, metabolomic and lipidomic analyses of FTD-TDP (with ALS, LATE and other disorders), FTD-tau (including MAPT carriers, corticobasal degeneration (CBD), PSP and others with AD, CTE to determine common risk factors and mechanisms.
- Determine whether genetic variants identified in one FTD subset, such as TMEM106B, confer risk/resilience across the FTD spectrum and across diverse populations.
- 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.

### Recommendation 5 – Priority 1. Advance understanding of FTD and identify therapeutic targets through the creation, validation, and use of pre-clinical and translational tools and resources. (7 - 10 years)

- While the amount of data and number of tools (often in the form of biological models) are increasing in the FTD research field, there is a need to generate more tools and data across disease stages and harmonize these across diverse datasets and disease subtypes, as well as a need to improve tools/models and their validity for disease mechanism characterization, target identification, validation, and drug development.
- Increase clinical resources to expand and broaden the identification and collection of FTD patient cohorts across all stages and clinical presentation of FTD; include representation from diverse populations. Improve bioinformatics infrastructure for capturing phenotype and genotype information and enable data sharing.
- Develop data and resource infrastructures to support management and collaborative analyses of diverse clinical, imaging, genetic, molecular, and biomarker data and resources from FTD basic science and clinical studies. This includes, but is not limited to, data obtained from the use of cell and tissue/fluid resources.
- Create, advertise, and distribute biosamples and data from well-characterized and diverse FTD cohorts, including but not limited to cell models, brain tissue, digital neuropathology, biofluids, neuroimaging, and clinical/cognitive data.

- Enhance molecular characterization of FTDs, including but not limited to proteomics, metabolomics, lipidomics, transcriptomics, and epigenomics in tissues and models. Generating data with single-cell resolution is particularly valuable.
- Harmonize and integrate these various and diverse -omics datasets via computational tools (including through the leveraging of AI) to develop molecular maps of disease pathogenesis, identify disease modifiers, and predict disease progression and/or response to potential interventions via clinical trial simulators.
- Develop cell, animal, and computational models for specific purposes and validate them for these specific purposes. For example, animal models may not be able to perfectly recapitulate all aspects of human disease but can be valuable for modeling perturbations or interventions directed at specific molecular pathways that cannot be conducted in other systems. The type of model and specific purpose should be based on the unique attributes of that type of model, combined with other complementary models where appropriate, and validated against human data whenever possible for the specific purpose/context of use (e.g., translational biomarkers).

### Recommendation 6 – Priority 2. Accelerate pre-clinical disease-modifying and symptomatic therapeutic development in FTD. (2 - 7 years)

- 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.
- Where appropriate, leverage mechanism-agnostic approaches (e.g., high-throughput compound screening) to develop therapies, including those based on disease-relevant readouts in appropriate model systems.
- In addition to pursuing disease-modifying approaches, symptomatic therapies should also be pursued including, but not limited to, electro/magnetic neurostimulation and rehabilitation approaches.

### Recommendation 7 – Priority 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. (3 - 10 years)

- FTD is distinct from AD and other ADRDs in which brain regions and cell types are affected, particularly at the early stages of the disease. Understanding why this may reveal unique and novel therapeutic targets. Moreover, the cells that may be particularly vulnerable to FTD may not have correlated in mouse models.
- Roles for various glial cell types as well as non-CNS components such as inflammation and vasculature are increasingly being identified in FTD, yet much work remains to understand how and to what extent dysfunction in these cell types or systems impacts FTD and particular subtypes.
- Identify, characterize, and recapitulate cell type specificity in FTD, including establishing the cell types most vulnerable in FTD and/or recreating their vulnerability *in vitro* and *in vivo*. Approaches to the model may include examples such as engineering cell types that lack correlates in mouse models and nonhuman primate models.
- Define and characterize mechanisms by which cell-intrinsic processes, such as protein gain and/or loss of function, dysregulated proteostasis, or dysregulated lipid metabolism, lead to cellular vulnerability in FTD.
- Define and characterize mechanisms by which cell-extrinsic processes, such as neuroinflammation, senescence, trans/intercellular spreading of toxic proteins, or vascular dysfunction, contribute to cellular vulnerability in FTD.
- Define mechanisms by which broad organismal processes contribute to FTD, such as aging, and sleep dysfunction, contribute to cellular vulnerability in FTD.

### Recommendation 8 – Priority 4. Define genetic and molecular modifiers of FTD (including in diverse populations). (3 - 10 years)

- While some of the most common autosomal dominant causes of inherited FTD have been identified, rare genetic causes remain uncharacterized and present potential novel insights into disease mechanisms and/or build on to existing pathogenic models.
- In addition, it is a priority to understand the genetic architecture of FTD in diverse populations. Do rare and common variants impact disease risk similarly across populations? Are there variants that confer risk or unique resilience within specific populations?
- Identify and functionally annotate risk/resilience loci in Mendelian and sporadic forms of FTD. This includes leveraging functional genomics to map variants and their effects on specific genes within given loci. Defining the cell-type 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 banking DNA where any researcher can send samples, receive genotype information, or request data/samples from large cohorts.
- 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.

## Vascular Contributions to Cognitive Impairment and Dementia (VCID)

### Recommendation 1 – Priority 1. Basic Mechanisms and Experimental Models: Establish and refine experimental models and technologies to identify disease-relevant mechanisms underlying VCID. (5 - 8 years)

- Establish and refine experimental models so that they: (i) reproduce small vessel disease and other key pathogenic processes thought to result in cognitive impairment; (ii) are easily applicable to both VCID and AD research for advances in mixed etiology dementias; (iii) address vascular contributions to damage of both white matter and grey matter or (iv) include genetic and acquired conditions that are associated with VCID.
- Because of the pathogenic diversity of VCID syndromes, multiple models, each recapitulating key features of a specific human disease process, are needed. In particular, models should be established that reproduce the pathophysiology of small vessel disease and develop clinically relevant manifestations/lesions (examples include microinfarcts, microhemorrhages, superficial siderosis, arteriolosclerosis, atherosclerosis, cerebral amyloid angiopathy, and vascular inflammation).
- Generate novel models that will facilitate the study of white matter degeneration. White matter degeneration is a pathologic process that currently lacks suitable animal models for mechanistic studies.
- Conduct studies that leverage existing models of systemic cardiovascular disease such as cardiac failure, atrial fibrillation, or renal disease to examine the brain for pathological signatures of VCID.
- Consider models that incorporate existing and emerging genetic factors of VCID. Examples include, but are not limited to, ApoE, TREM2, and Collagen IV, among others.
- Develop models of VCID that incorporate common lifestyle, vascular, and metabolic factors associated with aging, including chronic conditions, to investigate the additive effects on pathophysiology. Models should aim to mimic the human condition to the extent possible.
- Incorporate VCID, AD (amyloid plaques and/or neurofibrillary tangles), as well as other neurodegenerative pathologies in animal models to inform interactions of neurodegenerative and VCID pathophysiologies.

- Use in vitro and/or iPSC models to study specific molecular mechanisms that are not feasible in animal models.
- Given that age remains one of the strongest risk factors for the onset of dementia, incorporate age as a biological factor in experimental model studies. Sex as a biological variable also needs to be incorporated to provide translational insights.
- Validate and align existing and new models to human VCID pathologies; incorporate approaches such as multi-omics, neuroimaging, and neuropathology and consider regional specificity.
- Apply and develop methods to VCID research that include next-generation technologies such as cognitive/behavioral assessments, deep multiphoton microscopy to allow imaging of subcortical white matter, higher resolution MRI and CT/PET modalities for live animal imaging, and technologies to obtain spatial proteomic and transcriptomic analyses.

### Recommendation 2 – Priority 3. Basic Mechanisms and Experimental Models: Study the neurovascular unit structure and function to establish how it is impacted by VCID. (4 - 6 years)

- Identify cell-type specific changes within the neurovascular unit with VCID pathologies, including endothelial cells, pericytes, astrocytes, perivascular macrophages / microglia, perivascular fibroblasts, oligodendrocytes, and interneurons, leveraging single-cell and spatial technologies.
- Continue to investigate how the neurovascular unit contributes to regulation of neurovascular coupling and basal blood flow. In particular, studies are encouraged that dissect vascular function and blood flow control across different microvascular zones (arteriole, arteriole-capillary transition/pre-capillary, capillaries, and venules) and how VCID pathology affects each of these zones.
- Undertake studies of the mechanisms underlying loss of blood-brain barrier integrity, and the relationship between blood-brain barrier integrity and blood-based biomarkers for neurodegenerative conditions.
- In addition to controlling blood supply, there is known remodeling of the neurovascular unit with aging and VCID. Conduct critical studies of age and VCID-related changes in capillary angiogenesis, regression, and vascular matrix composition.
- Investigate how the normal function of the neurovascular unit is impacted by risk factors of VCID such as aging, cardiovascular and cerebrovascular disease, and AD pathology and genetics. This will be critical for understanding disease mechanisms.
- Disentangle the relative contributions of clearance mechanisms to VCID, including the possible clearance of metabolic waste across the blood-brain barrier, perivascular clearance, and phagocytic degradation.
- Understand the anatomical pathways and driving forces for perivascular clearance under normal conditions and during VCID. Delineate the relative contributions of peri-arteriolar, peri-venular, and basement membrane compartments to fluid drainage.
- Undertake essential studies establishing the contribution of non-neurovascular unit cells, including myeloid cells, to VCID.
- Establish the impact of normal, biological aging on the neurovascular unit structure and function.

### Recommendation 3 – Priority 4. Basic Mechanisms and Experimental Models: Use experimental models to investigate how aging, cerebrovascular and cardiovascular disease impact myelin, white matter degeneration and neurodegeneration. (5 - 8 years)

- White matter changes are characteristic of some VCID processes, yet oligodendrocyte biology in the context of cerebrovascular and cardiovascular disease remains poorly understood. Therefore, studies are encouraged to establish these mechanisms.
- The high co-morbidity of cerebrovascular disease with AD pathology necessitates the study of these two processes together in experimental models.

- Develop tools to characterize the effects of altered cerebrovascular phenotypic cell changes, as they related to different microvascular zones, brain regions and vascular functioning; A focus on understanding endothelial cell molecular and functional disease changes will be critical.
- Apply multi-omics and sophisticated bioinformatics to elucidate disease mechanisms, and also create the opportunity to share data through centralized systems.

### Recommendation 4 – Priority 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. (3 - 5 years)

- Develop and validate standardized assessments that include cognitive, behavioral, and functional measures, which may also incorporate physical function, non-CNS organ-related (heart, kidney, etc.), and other measures indicating the presence of VCID. This would be an important step toward improving risk assessment, clinical diagnosis, and measurement of clinically meaningful trial outcomes for VCID.
- Identify newer sensitive behavioral and functional outcome measures (e.g., depression, apathy, other behavioral impairments, mild executive dysfunction, and altered gait) for human studies that provide novel information relevant to VCID.
- Discover, develop, and validate the clinical utility of candidate non-invasive, lower-cost, systemic markers (e.g., retinal measures, other neurobehavioral measures, remote digital systemic and cognitive assessments) for detecting the presence and progression of VCID.
- Explore the heterogeneity in cerebrovascular disease by identifying and validating fluid, imaging, and multi-omic biomarkers of individual microvascular markers (e.g., lacunar infarcts, ischemic white matter damage, enlarged perivascular spaces) and processes (e.g., cerebral amyloid angiopathy, BBB dysfunction, impaired neurovascular coupling) related to cognitive/neurologic impairment. These new developments may help refine the understanding of various cerebrovascular disease processes and their contributions to VCID across the lifespan.
- Validate emerging fluid markers, including circulating exosomes. Those identified broadly from VCID and AD/ADRD new basic and translational study data need to be measured: a) use appropriate clinical and population settings; b) in new clinical neuropathology studies; c) to study influences of systemic disease (e.g., kidney and heart function/failure) on the fluid markers; and d) to compare differences in these measures translationally in human compared to animal model endophenotypes, thus providing more detailed cellular-mechanistic information and translational validation.

### Recommendation 5 – Priority 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. (7 - 10 years)

- 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; adoption of user-friendly structures and systems, medical devices; environment/neighborhood modification and behavioral interventions, may be successful pathways for reducing VCID.
- Consider adding brain imaging and cognition to cardiovascular intervention trials to determine how such interventions influence VCID-relevant outcomes. Utilize as default, whenever feasible and appropriate, study designs that incorporate oversampling of minoritized populations at risk of VCID in clinical trials.
- Conduct early phase clinical trials testing novel interventions shown to be vasoactive or that target specific aspects of dysfunction of the neurovascular unit in VCID, leveraging new translational research discoveries.

- Within current and future large randomized and epidemiological cohort studies of AD/ADRD, include ancillary studies that develop, validate, and apply surrogate non-imaging markers of VCID in blood, urine, or CSF for severity of VCID (particularly those that are more strongly associated with persons having both a high cardiovascular and/or cerebrovascular disease burden who also develop dementia). Promote the incorporation of VCID markers in non-VCID trials in aging and neurodegenerative disorders to control for individual differences in VCID.
- Increase the harmonization and open sharing of VCID data, images, and protocols wherever feasible to permit meta-analyses across trials, following current best practices for VCID trials. Where appropriate, incorporate standardized VCID biomarkers developed and standardized recently.
- Extend pragmatic prevention or treatment trials or initiate studies that test the best models for delivering care to persons with ADRD and supporting their caregivers, including policy interventions such as paid family leave.
- Explore VCID treatments in existing studies by determining the possible cause of the emerging trend of lower incidence of age-related dementia reported in North America and Europe and developing better screening methods, and design of effective VCID prevention trials.

### Recommendation 6 – Priority 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. (7 - 10 years)

- Investigate the life-course and progression of VCID biomarkers in VCID, dementia, and aging studies in the context of specific populations with high vascular risk factors and inequalities in cognitive impairment (including race and ethnic populations that have traditionally been excluded from ADRD research and who may be disproportionately affected by VCID) to inform intervention design. Existing birth cohorts such as those found in statewide health systems or national medical systems have utility in understanding life-course factors contributing to later life VCID.
- Conduct life-course epidemiology investigations including: i) studies on VCID, AD/ADRD, and aging in the context of sex differences and specific populations with high vascular risk factors or disease burdens (including disproportionately affected race and ethnic populations); ii) environmental factors associated with increased resilience to vascular disease and cognitive impairment (e.g., Mediterranean diet, education, cognitive engagement, physical fitness, social networks, sleep); iii) factors that increase the risk for VCID based on the presence of monogenic conditions (e.g., CADASIL) or GWAS-identified variants associated with cerebrovascular disease (e.g., HDAC9); iv) functional pathways of GWAS-identified variants; e) potential gene-environment interactions; and v) detailed focus on links between VCID and the genomic loci associated with AD (e.g., PICALM, CLU, APOE, TREM2) that appear to interact with vascular biology or BBB dysfunction. As above, cross-validation of new factors (variables and genes) from basic science needs to be followed closely in clinical-translational research work.
- Conduct studies that address the complex pathways leading from vascular risk factors, cardiovascular disease, and cerebrovascular disease to longitudinal changes in cognition, brain structure, Aβ, tauopathy, and neurodegeneration. Systems-based approaches, multi-omics, and bioinformatics coupled with multi-modal imaging, biochemical, genetic, and clinical markers can help determine whether risk conditions common to AD, cardiovascular, and cerebrovascular disease reflect convergent pathways versus additive effects of independent pathways. Translational cross-validation and detailed evaluation in animal models will be necessary to mechanistically capture critical brain and circulating molecular and cellular phenotypic changes.
- Encourage interaction between scientists working with models of disease and organ system failure (CHF, CKD, microbiome degradation, geroscience) and scientists working with VCID and related forms of AD/ADRD to investigate the links between organ system failure, cardiovascular disease, brain changes, and VCID.
- Ensure rigor and reproducibility using appropriate study designs, adequate sample sizes, and use of statistical models and methods to accommodate the high dimensionality and multimodality of the data with the heterogeneity of VCID in the population to identify new specific and biologically relevant VCID targets.

- Establish the generalizability of the sample to the population through evaluation of selection, attrition, and algorithm bias as well as consistency of effects across sub-populations of interest, including women, race/ethnic underrepresented groups, and other pre-specified subgroups of interest.
- Require, foster, and prioritize the adoption of open data, image, and specimen sharing principles to promote transparency and facilitate reproducibility and collaboration to promote VCID-ADRD science and medicine.

### Recommendation 7 – Priority 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. (5 - 7 years)

- Include in clinical trials outcomes developed in parallel with animal models, while conversely ensuring that animal models include readouts informed by clinically relevant highly valued patient outcomes. This will allow direct ties to be drawn between the results of animal- and human-based interventions.
- Evaluate mechanisms of amyloid-related imaging abnormalities of the edema and hemorrhagic types (ARIA-E and ARIA-H) associated with amyloid-lowering immunotherapies using both human and experimental models. Determine the impact that VCID co-morbidity has on ARIA incidence and establish potential for mitigating therapies / precision medicine approaches to minimize impact of ARIA with newly approved immunotherapies.
- Incorporate VCID biomarkers and cerebrovascular disease in prior, ongoing, and future clinical trials targeting both cardiovascular and neurodegenerative disorders.
- Incorporate the pathologically validated vascular biomarkers in observational clinical studies to determine their progression over time and their association with risk factors, cognitive/neurologic impairment, and cognitive/neurologic decline in human subjects, considering effects of vascular and aging processes across the lifespan-specific relationships in young adult, midlife, old, and oldest-old life stages.

### Recommendation 8 – Priority 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. (4 - 6 years)

- Work translationally to characterize the interrelationships of vascular risk factors and AD biomarkers 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.
- The gut-brain axis is emerging as an important factor in many neurological disorders. Translational studies are encouraged to examine systemic factors including gut-brain axis in relation to VCID.
- Use insights from human studies to guide development of improved models, including cellular, rodent, and non-human primate.
- Undertake studies to examine the fundamental biology underlying CSF and plasma candidate VCID biomarkers to establish their physiological function in the brain and their pathophysiological mechanisms underlying VCID.
- Leverage existing biospecimens and imaging from trials to evaluate mechanisms of action of interventions found to alter VCID-relevant outcomes using experimental models of VCID.
- Develop non-invasive human based techniques that will evaluate clearance of disease-relevant biomolecules from the brain to the peripheral compartments including CSF and plasma.

## Lewy Body Dementias (LBD)

### Recommendation 1 – Priority 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. (1 - 7 years)

- Promote and prepare infrastructure for clinical trials of novel treatments specific to Lewy Body Dementia (LBD). Efforts to develop and test novel therapeutics for LBD must build upon the knowledge base gained from genetic and environmental studies and from systematic profiling of well-characterized human samples that identify underlying disease mechanisms and biomarkers. The long-range goal is to use therapeutic approaches that prevent or alter the disease processes using pharmacologic approaches, gene therapy, regenerative medicine, or surgical interventions, among others, by enhancing 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 reducing inflammation (see also recommendations #7 and #8).
- Clinical trials should include persons with either, or both, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), that is LBD. Trials should also be conducted in both the symptomatic and the pre-dementia disease stages, including mild cognitive impairment of Parkinson's disease (MCI-PD) and mild cognitive impairment with Lewy bodies (MCI-DLB), those at genetic risk (e.g., LRRK2, SNCA or GBA) as well as in persons with isolated rapid eye movement (REM) sleep behavior disorder (RBD) and fully manifest psychosis (hallucinations and delusions). Prodromal disorder/symptoms that could be targeted for symptomatic approaches include RBD, autonomic dysfunction, and depression, clinically significant symptoms that have the greatest impact on patient function and caregiver burden. The participants in trials and the investigators involved in trials will be as inclusive as possible with regards to racial/ethnic, sex, socioeconomic and cultural diversity.
- Promote: 1) therapeutic trial of at least one novel drug targeting known (e.g., α-synuclein, APOE, GBA) or emerging genetic 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 DLB pathology; 3) infrastructure to support preclinical drug development including one or more aspects of the preclinical development pipeline (e.g. screening, confirmation, lead optimization, preclinical efficacy studies, initial tox studies). In the near-term, at least one novel compound strategy (e.g., novel cholinomimetic agents) and at least one already U.S. Food & Drug Administration (FDA)-approved compound (e.g., anti-amyloid antibody) will enter clinical trials over the upcoming 1-3 years. In the longer-term, at least one "disease-pathology-modifying" agent and at least three "symptomatic" agents will enter clinical trials over the upcoming 3-5 years.
- Develop and validate DLB-Specific clinical outcome measures. As part of the development of a clinical trial infrastructure, one or more consensus, sensitive, disease-stage specific clinical outcome measures should be developed over the upcoming 2 years to encompass the complex phenomenology inherent to LBD symptomatology, to include cognitive, neuropsychiatric/behavioral, motor, sleep, autonomic, sensory and other clinical domains. Clinical tools to track cognitive changes via neuropsychological measures or batteries and problematic symptoms (e.g., cognitive fluctuations, autonomic features, etc.) in LBD are urgently needed. Similar or additional tools to track changes in the pre-dementia, prodromal, and at-risk LBD cohorts are also needed (see also recommendations #2 and #3). The goal of any composite measure would be to track change over time and be 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 consensus proposal for development and validation of 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 using these new methods should also be generated. New outcome measures should be developed in consultation and collaboration with global regulatory authorities, including FDA, EMA, and others.
- To meet the above recommendations, it will be necessary to engage existing clinical and research networks, non-governmental organizations, and the pharmaceutical industry to establish new and expand existing

networks for well-characterized cohorts of established or at-risk LBD for treatment trials. These networks will also engage with the LBD patient/caregiver communities that they serve to help define the highest-priority symptoms (i.e., those responsible for the greatest caregiver/patient distress and burden) to target for trials. It is important that cross-site standardization (e.g., common clinical, imaging, and outcome measures) occur to the greatest extent possible (see also recommendations #2, #3, and #4). These efforts will help identify and resolve pre-analytical factors needed to standardize biomarker measurements for use in multicenter clinical trials. Since LBD is clinically and pathologically heterogeneous and several pathologic and genetic factors likely contribute, biomarkers (see also recommendations #2 and #3) should be incorporated into trial design and the required enrollment enriched and with sufficient numbers; or stratified to improve the ability to study more homogenous LBD cohorts in a clinical trial design, thus improving statistical power and likelihood of success. Proposed metrics: 1) develop a robust infrastructure, including consensus protocol elements, for the conduction of numerous multisite LBD clinical trials over the upcoming 2 years (see recommendation #4), and 2) develop one or more working groups of investigators from relevant pharma companies, medical and research community, and general public over the upcoming year 1 to address barriers to clinical trials in LBD.

### Recommendation 2 – Priority 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. (2 - 7 years)

- Develop imaging approaches within the next 3-5 years to: a) enhance the differential diagnostic accuracy of LBD compared to other dementing illnesses and Parkinsonisms; b) detect preclinical and prodromal LBD; c) establish reproducibility and the expected change over time relevant for clinical trials (see recommendation #1); d) characterize and monitor disease progression in natural history and genetic studies (see recommendations #4 and #6) by integrating established and new imaging tools; and e) validate these tools against postmortem neuropathology (see recommendation #5) using both *in vivo* and *ex vivo* imaging.
- Develop at least one α-synuclein tracer within the next 7 years that is sensitive and specific to α-synuclein in the human brain, and that can be measured safely. Establish the biochemical and biophysical features of the tracers as well as safety and efficacy in human trials. Validate α-synuclein tracers against postmortem neuropathology using both in vivo and ex vivo imaging and utilize this technology as the standard to develop assays for measuring α-synuclein in blood and CSF (see recommendation #3). Compare performance of α-synuclein tracers with alternative approaches such as nigrostriatal dopaminergic imaging or myocardial sympathetic innervation imaging in LBD and other neurodegenerative dementias and parkinsonian disorders.
- Repurpose currently available imaging tools for the diagnosis and classification of LBD within the next 5 years. For example, molecular imaging of neurotransmitter receptors can be considered. Emphasis should be placed on imaging modalities demonstrating high reproducibility across 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 feasibility of imaging biomarkers developed in the research setting for use in clinical trials where imaging resources may be limited or heterogeneous across sites. Tools should be accessible in diverse settings, including historically underserved populations, and imaging tools should be evaluated in racially and ethnically diverse cohorts, incorporating sex differences.
- Determine the feasibility of emerging technologies or analytical approaches through *in vivo* and *ex vivo* imaging for value added to natural history studies and multicenter therapeutic trials within the next 5 years. Utilize a multicenter approach to determine scalability of techniques and prepare for Phase 3 trials. Incorporate multimodal analyses, including EEG, systems-level biomarkers, or biofluid biomarkers, to enhance accuracy of diagnosis and reliability of prediction of disease progression. Establish large datasets to enable machine learning and artificial intelligence approaches. For these approaches to be successful, protocol harmonization and data sharing are essential (see recommendation #4); however, post-acquisition harmonization of legacy data should also be considered.
- Investigate imaging biomarkers' potential for sensitivity/specificity to the contributions of α-synuclein, beta-amyloid, TDP-43, tau, and other protein deposits as well as vascular disease lesions to LBD disease heterogeneity

and clinical phenotypes within the next 5 years. Determine pathophysiologic underpinnings of core clinical features of LBD with imaging biomarkers. Utilize established and new imaging tools to determine the evolution of the multi-proteinopathy, including synergistic interactions of proteins across brain regions and across 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 disease. Safety is a priority in terms of radiotracer research.

### Recommendation 3 – Priority 3. Clinical Characterization and Intervention: Develop and refine biomarkers for diagnosis, prediction, and prognosis utilizing biofluids, tissues, and digital and electrophysiological methods. (2 - 7 years)

- Develop biomarkers by capitalizing on existing or new cross-sectional, case-control and longitudinal studies of individuals throughout the course of LBD (including prodromal stages), in which symptoms of cognitive and/or motor decline, neuropsychiatric and autonomic changes are tracked (see also recommendation #4). Building on and extending existing cohort studies and establishing new cohorts will support these aspects of biomarker discovery and validation portfolio over the next 5-7 years.
- A panel of biomarkers should reflect pathophysiological changes related to LBD (e.g., synaptic, lysosomal, and other processes related to a-synuclein pathology) as well as changes due to other proteinopathies (such as amyloid, tau, and TDP43) and vascular pathology. During biomarker development, the context of use should be defined and validated, such as diagnosis (including prodromal disease), prediction and prognosis, or use in clinical trials, including stratification and enrichment, monitoring response to therapies, and measuring outcomes (see recommendation #1 & #4). Normative data for biomarkers should be obtained on well-phenotyped and demographically comparable control subjects and/or appropriate disease controls, with attention to race/ethnicity. At least one panel of biomarkers reflecting the multiple proteinopathies and vascular changes in LBD will undergo validation as having diagnostic and/or predictive/prognostic value. Prioritize studies of biomarkers and panels with the goal of eventual CLIA and FDA approval within 2-7 years.
- Where appropriate, carry out biomarker discovery and evaluation in multiple tissues (e.g., skin, colon, salivary gland, PBMCs, others) and biofluids (e.g., whole blood, plasma, CSF, urine, saliva, tears, microbiome samples, others). Novel biomarkers or biomarkers in different tissues should be compared to gold standards wherever possible. Targeted as well as -omic approaches to biomarker discovery and development should be pursued. Collection and biomarker analysis of samples from at least CSF, blood, and skin biopsies from participants of at least two cohorts need to be accomplished. A catalog and database of cohorts and samples available at government and non-government organizations should be developed (1-2 years, see also recommendations #1 and #4), and biomarker data generated will be deposited into this database to allow sharing of well-curated samples and data.
- For validated biomarkers, study approaches to disclosure of results in symptomatic and at-risk populations and consequences of revealing this information. Studies of disclosure can be initiated in 1-5 years.
- Efforts should be made to develop comparable biomarkers in model systems (e.g., transgenic animals; iPSC-derived models, etc.) to those biomarkers identified in human studies; this process may be bidirectional and accomplished within 2-5 years.
- Develop and validate digital and electrophysiological approaches to biomarkers, including wearables, electroencephalogram, and polysomnography, computerized testing, home-based monitoring of lifestyle, behavior, cognition, neuropsychiatric symptoms, autonomic function, activity, and 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, acceptability of methods to participants, and compliance is essential. Defining the psychometric properties and validating these approaches for diagnosis and to track progression is critical. Quantitative approaches should be adapted for telehealth and clinical trials. At least two electrophysiological studies (EEG and sleep) are initiated in early stage or prodromal LBD cohorts; at least one digital biomarker study is initiated in 2-5 years. Workshops should develop metrics of feasibility, acceptability and compliance 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.

- Harmonize protocols and common data elements to facilitate analyses of biomarkers in relation to genetic and environmental risk factors, clinical measures, sex differences, medical comorbidity, and phenotypes of DLB vs PDD (discussed in recommendation #4). While detailed phenotyping through the DLB module is carried out in some studies, harmonization of key phenotypic domains will support larger-scale integration of data. Imaging and neuropathology data should be incorporated, where available, to help to interpret and validate biomarkers. A workshop to harmonize definitions and approaches to common data elements (CDEs) should be held within 1-2 years. One or more integrative studies of biomarkers with an investigative team requiring multidisciplinary teams of investigators (clinical, biomarker, biology, statistician and others) will be initiated in 2-5 years.

### Recommendation 4 – Priority 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. (1 – 7 years)

- Virtually all of the LBD recommendations require access to well-characterized and deeply phenotyped LBD subjects and their associated imaging, biofluid biomarker, genetic, and neuropathologic characterization. This includes recruitment to clinical trials, biospecimens, and data for biofluid biomarkers, imaging, genetic and neuropathologic investigation, and for translational research. Thus, continued prioritization is needed for efforts to expand longitudinal LBD cohorts with deep phenotyping, uploading of clinical, genetic, biofluid biomarker, and imaging data into a central database, and biofluids into a biofluid repository to allow for broad utilization by the LBD research community. Deep phenotyping would include characterization of cognitive, motor, and behavioral change over time, quality of life and function, comorbid health conditions, and risk factors. Utilization of digital biomarkers would assist with phenotyping across diverse subject cohorts (see also Recommendation #3). Double current or proposed cohorts' sizes and associated clinical characterization, including imaging, biofluid collection, and support of autopsy data.
- An imperative for Recommendation #4 is a focus on increasing diversity of participants in LBD research cohorts to allow investigation and validity across racial, cultural, and sex differences. Twenty percent of subject cohorts fulfilling criteria for diverse populations or female sex is desired.
- Sufficiently large longitudinal and compatible cohorts are needed to allow for the development of predictive models for clinical conversion, rate of decline, and clinical heterogeneity in LBD. This effort would be enhanced by common phenotyping, imaging, and biofluid collection methods across cohorts, including diverse populations and non-U.S. based LBD research-based programs. To accomplish this goal, we recommend the development of the potential to harmonize and merge datasets across existing and future study cohorts, including normal aging and AD/ADRD cohorts (both U.S. and non-U.S.-based programs). Data sets should contain cognitive, behavioral, motor, and biomarker characteristics. It is recommended to convene a meeting to develop and publish common data elements and collection protocols (see also proposals from other recommendations) that allow for collaboration and utilization of data and biological specimens across sites.

### Recommendation 5 – Priority 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. (1 - 7 years)

- Discover and replicate genetic variants associated with LBDs within the next 3 years. Initial success has been achieved with the execution of large-scale association studies. Systematic identification of novel genetic, epigenetic, and environmental determinants associated with risk for LBDs; or with core clinical or neuropathological features of LBDs remains a major goal. This goal will require genome-wide cross-sectional and longitudinal association studies, whole-genome sequencing, genome-wide methylation mapping, and expression studies. This recommendation also includes the identification of genetic and epigenetic factors influencing the risk of developing LBDs in patients with pre-existing PD or other prodromal LBDs syndromes. There is a related

need to develop polygenic scores for longitudinal prediction of risk of LBDs and for clinical trials; (e.g., for enrichment and stratification). Examination of gene-environment interactions is also important.

- To advance this research, large cross-sectional and longitudinal cohorts and LBDs families are needed (see recommendation #4). This includes expanding follow-up, recruitment, or phenotyping for existing cohorts; and establishing new cohorts. Some cohorts could span the prodromal to terminal disease stages. Cohorts should emphasize harmonized, longitudinal clinical, molecular and biomarker characterizations, environmental factors, and include diverse populations. Promote inclusive participation, transparency, and diversity in all aspects of this endeavor.
- Translate LBD-associated genetic variants into mechanisms, therapeutic targets, and biomarkers. This should emphasize analyses of specific types of brain cells and single brain cells from human autopsy brains using single-cell multi-omics approaches. Clarifying the putative causal variants underlying genetic association signals is also important. Proposed metric: the functional mechanism of at least one novel genetic locus linked to risk of LBDs will be established over the upcoming 5 years (see recommendation #7).
- Clarify the divergences and convergences in the genetic, molecular, neuropathological, and clinical landscape of LBDs and related neurodegenerative diseases, including the basis of sex differences. LBDs are clinically and neuropathologically heterogeneous (e.g., showing Lewy bodies, amyloid plaques, tangles, etc.), and there is a need to identify aspects of the genetic architecture that may be shared with or different from other neurodegenerative diseases and dementias. This requires innovative analytical approaches and existing and new data sets suitable for these analyses across LBDs and related neurodegenerative diseases.
- Prioritize innovative data analytics and data platforms. Although progress has been made on central knowledge, there remains a need to expand on existing platforms; develop new solutions for easier and more user-friendly data platforms and analytics. There is a need to facilitate data sharing, to generate and harmonize high-dimensional data sets, to visualize complex data, and to create a framework for comparative analyses between LBD and molecularly closely related neurodegenerative diseases.

### Recommendation 6 – Priority 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. (2 - 7 years)

- Within the next 4 years, develop best practices for neuropathologic evaluation of LBD as well as standardization of neuropathologic methods (e.g., minimal sampling schemes and staining methods) and data collection (e.g., quantitative and semiquantitative data). This should include emerging digital image analysis and open-source deep learning techniques to detect and quantify histopathological features for clinicopathological correlation and diagnosis (see recommendations #1 through #4). Techniques should be tested for scalability, feasibility, and generalizability across multiple cohorts, anatomical areas, and histologic methods.
- Within the next 3 years, develop tissue processing and sampling strategies for LBD-associated pathologies 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 REM sleep behavior disorder, cognitive fluctuations, and visual hallucinations (see recommendations #2 and #3 for validation of imaging and biofluid measures).
- Within the next 5 years, develop cost-effective scalable methods to assess integrity and quality of human tissue samples across multiple cohorts used in molecular, neurochemical, and genetic research (see recommendations #7 and #8).
- Encourage and enhance infrastructure for collection of peripheral tissue samples (fixed and frozen) from autopsies, including skin, salivary gland, gastrointestinal, and solid organ tissues outside the central nervous system for detection of non-CNS α-synuclein. Analysis of central and peripheral tissues would include emerging seeding aggregation assays (see recommendation #3).
- Within the next 5 years, increase autopsies on subjects at-risk for LBD, including those currently enrolled in prospective longitudinal studies who have standardized collection of demographic and clinical data (see

recommendation #4). Autopsies should be sought of 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, and Parkinsonism.

- Provide outreach and education to underrepresented groups, including studies on barriers to autopsy, importance of brain donation, as well as logistical support and resources necessary to facilitate brain donations. This would include individuals who may not be included in formal research studies of LBD or prodromal LBD. Increase autopsies on subjects from diverse backgrounds representative of the diversity of the US, including minority groups (Native American, Asian, Hispanic/Latino, and African American).
- Within the next 3 years, create a publicly available portal linking scientists or other investigators to LBD tissue resources (see recommendation #4). Integrate a universal unique identifying number (e.g., GUID) to provide a link between molecular (e.g., genomic, transcriptomic, and proteomic) data and the specific autopsy samples with these 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 antemortem biomarkers in the networked repositories (discussed in recommendation #4).

### Recommendation 7 – Priority 3. Pathogenesis and Mechanisms of Toxicity: Develop models to understand the pathophysiology and normal molecular and cellular functions of α-synuclein to support drug discovery. (5 - 7 years)

- Encourage studies that inform current clinical therapeutic development by identifying potential safety concerns and new targets. The fundamental biology of α-synuclein has been extensively studied in many experimental paradigms, particularly in the context of motor systems, while the normal function and misfolding of this protein in areas vulnerable to the broader set of LBDs remains underexplored. It is unknown if small molecule therapies targeting motor systems will have meaningful effects on non-motor systems (e.g., cognition). Improve our knowledge of the normal function of α-synuclein and role of α-synuclein in non-motor systems.
- Improve knowledge on pathological α-synuclein by isolating Lewy Bodies from LBD, PD, and PDD patients and characterizing them biochemically and biophysically to determine if unique features of specific LB α-synuclein strains exist. Understanding the fundamental biology of α-synuclein in the context of the broadest numbers of neurons vulnerable to LBD will be important. Questions to be asked, mainly using animal models that mimic key clinical and/or pathophysiological components of bona fide disease, will relate to cellular, regional physiology, and pathophysiology of neurons when α-synuclein expression is modified. Identifying sequelae of α-synuclein removal from mature brain across multiple regions, in terms of neuronal health and function, is an important component and will guide therapeutic development. Promote the discovery of at least one novel target to preserve or restore synaptic function in circuits damaged by α-synuclein and associated pathology.
- Additional areas of focus should include *in-vitro* models utilizing human-derived materials, such as induced pluripotent stem cells, integrating genetic discoveries from human population studies that have identified pathways relevant to LBD risk and progression with the directed goal of identifying biological pathways and networks that ultimately regulate gene expression and other disease risk factors hypothesized to be causative of LBD. These models can be used to screen and identify potential therapeutic agents. Consider both Mendelian alleles and non-mendelian pathways, such as genetic risk scores.
- Understand the regulation of α-synuclein protein levels and its aggregation, as a product of both regulation of expression, misfolding, and clearance. In addition, post-transcriptional regulation within cells, will be important to provide tractable hypotheses relevant to LBD genetic risk. This recommendation should also be considered in the context of the aging human brain. This consideration should improve thinking about which human subjects might benefit from α-synuclein modification, or other targets, in LBDs and may inform clinical action around measurement of target engagement. Studies are encouraged to examine lysosomal function and glucocerebrosidase (GBA) genetics/function with α-synuclein accumulation and spread. These can inform the development and implementation of emerging therapeutics targeting GBA/autophagy in GBA carriers and potentially sporadic disease.

- It is clear that aging contributes substantially, and critically, to LBD risk. The role of aging should be interrogated further using LBD-relevant model systems that allow for modeling this risk factor and also in analyses of available resources such as high volume 'omics' datasets, including novel methods such as mRNA expression, proteomics, metabolomics, etc.
- Identify biological mechanisms explaining both sex differences and resilience in LBD across numerous demographic backgrounds (i.e., diverse cohorts), as identified in human pathological studies. Inclusion of samples from all genders/sex at appropriate numbers to support well-powered analyses of all groups is required.
- Overall, the overarching goal of the pre-clinical basic science and translational work in this recommendation is to prioritize the discovery of at least one novel drug targeting known (e.g., α-synuclein, APOE, GBA) or emerging genetic or neuropathological targets and mechanisms implicated in LBD.

### Recommendation 8 – Priority 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. (5-7 years)

- A major recent conceptual framework for how we think about neurodegenerative diseases is the proposal that many of these disease proteins can undergo cell-to-cell spread between brain regions in wild-type animal models in the context of LBD, and some human studies even suggest they may spread to the peripheral nervous system. Thus, roles of genetic risk factors from genome-wide association and exome sequencing studies can be interrogated in animal models where the levels of these genetic risk factors are manipulated. Whether α-synuclein has the ability to spread in general or only across certain types of cells is unknown. Further, the molecular mechanisms for the uptake, intracellular trafficking, degradation, and release of α-synuclein preformed fibrils versus LB and -GCI α-synuclein strains in neurons and oligodendrocytes are unknown, as well as brain vs. periphery. It is also unclear whether α-synuclein directly interacts with other proteins that are known to aggregate (e.g., β-amyloid, TDP-43, tau) and/or vascular pathology to trigger LBD pathology. Research to understand how LBD pathology develops and progresses is critical for the development of LBD-specific animal models and therapeutics. These studies would move forward new mechanistically tractable targets that could be engaged for clinical studies.
- Develop more complete animal and cellular models of the molecular pathology and symptomatology of LBDs. New models are needed that identify key processes involved in neuronal damage, vascular changes, and protein deposition (see recommendation 1) having synergistic translatability to human studies on LBD. Such models will need to be able to identify the key pathways mediating the propagation of toxic protein assemblies between cells in an appropriate, physiologically relevant context.
- Develop a more complete understanding of why some neurons are vulnerable to toxicity evoked by α-synuclein assemblies while others remain resistant (i.e., selective vulnerability) is needed. Studies should identify the anatomical, biochemical, and molecular underpinnings of brain regional differences in LB pathology associated with variable behavioral outputs in the human brain as well as animal models that are relevant to human clinical phenotypes. Where feasible, biospecimens and data from humans, including PDD and DLB patients, should be used for validation of findings (see recommendations #1, #2, and #3) for important preclinical work in therapeutic development.
- Identify mechanisms by which α-synuclein, tau, and β-amyloid pathologies interact in the intact brain is a critical step towards a fuller picture of the complex pathophysiology of LBDs. Prioritize the development of LBD models in which more than one pathology is present either within the same cells or in proximate cell populations. These studies should also account for potential interaction and/or additional independent association of aging and related factors (see recommendation #2). This preclinical work will inform the potential role for therapeutic strategies targeting multiple pathologies in LBD.
- Studies of genetic and molecular interactions of α-synuclein and tau cross-seeding and resultant spread patterns of both pathologies will inform selective vulnerability in the human brain. (See recommendation #6)

- Contributions of immune-mediated mechanisms and inflammation in LBD pathogenesis and cellular vulnerability should be investigated, and agents that alter or reduce central inflammation should be tested in the model systems described in this section.
- There is a need to use one or more preclinical models to explore potential efficacy of newly discovered and developed compounds, including systems based on human neurons and/or organoids derived from patient stem cells and suitable animal model systems that mimic the multi-proteinopathy substrate of the LBD spectrum.
- There is also a need for enhancing and leveraging infrastructure for scalable, efficient means to support preclinical drug development that arises from these mechanistic studies, This infrastructure that includes screening, confirmation, lead optimization, efficiency and/or toxicology evaluations should be designed to account for the selective vulnerability, disease heterogeneity, disease spread/propagation, and/or interaction with other age-related pathologies that encompass the full spectrum of LBD.

## Multiple Etiology Dementias (MED)

### Recommendation 1 – Priority 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. (3 - 5 years)

- Conduct pragmatic trials to improve the timely, accurate, compassionate, and actionable detection of cognitive impairment, including mild cognitive impairment and dementia. Approaches should focus on the detection and characterization of cognitive impairment syndromes but not, for the purposes of this specific recommendation, differential (etiological) diagnosis. Paradigms being studied should be practical (e.g., time efficient and with easy-to-interpret results) and may use existing or new neuropsychological and functional assessment tools. Trials must also include methodology to ensure that cognitive impairment detection is linked to quality care, including, but not limited to, diagnostic services, specialty referrals, and caregiver support. While most studies should be conducted in primary care, evaluation of detection paradigms may also be conducted in other clinical or home and community-based settings where there is a high prevalence of undetected cognitive impairment, and where improved detection is likely to have benefits for patients and their families. Trials must be adequately powered and include populations with known health disparities as a central focus.
- Develop and evaluate interventions that expand the capacity of primary care and home and community-based service organizations to improve care during and immediately after a diagnosis is made in primary care. Interventions may include electronic health record (EHR) decision support for the diagnosing provider, clinical services designed to fill gaps in diagnostic care (e.g., involving consultation to the family by a nurse, social worker, or community health worker), and primary care education that improves basic diagnostic and management skills regarding later-life cognitive disorders.
- Conduct research to identify and address structural barriers to the timely detection, diagnosis and care for populations experiencing health disparities and for individuals with pre-existing conditions that may alter performance on brief assessments (e.g., brain injury, Down syndrome, serious mental illness, sensory impairment). In addition, conduct research on the social and cultural differences across populations that can inform how best to detect, diagnose, and support individuals and families.

### Recommendation 2 – Priority 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. (5 - 7 years)

- Evaluate the impact of screening community-dwelling older adults without recognized signs or symptoms of cognitive impairment during the Annual Wellness Visit or other clinical encounters on outcomes that matter to patients, caregivers, providers, health systems, and payers. These outcomes may include: psychological well-being of the patient and caregiver, advance care planning, specialist access, clinical trial participation, stigma,

loss of privileges (e.g., driving, employment, capacity, insurance), provider satisfaction and burden, and healthcare costs and utilization.

- Among studies evaluating the impact of screening, include methodology to ensure that patients who screen positive receive compassionate disclosure and are linked to diagnostic services and quality care. Studies should compare the impact of different diagnosis and care strategies on outcomes (benefits, burdens, and harms).
- Conduct trials that could help determine which populations optimally benefit from screening, as well as those who may be more likely to experience harm, including a comparison of adults with and without report of cognitive/behavioral/functional changes.
- Whenever possible, include primary or secondary outcomes from family members, caregivers, health care providers, health care systems, payers, and other stakeholders in screening studies to evaluate the breadth and diversity of impact on population screening for cognitive impairment.
- Conduct validation studies on brief cognitive assessments in primary care and home and community-based settings that minimize the referral biases inherent in validation studies conducted in specialist and other referred settings. The tools selected for these studies must have strong evidence for accurate early detection (e.g., mild cognitive impairment) in diverse populations, and clear feasibility for primary care workflows.

### Recommendation 3 – Priority 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. (5 - 7 years)

- Promote observational studies with deep phenotyping in diverse populations to characterize the status of the common pathobiologies of later life underlying cognitive impairment, including their combinations, and to map novel pathobiological entities using neuropathological studies.
- Conduct studies to identify risk factors (including infectious disease, metabolic disorders, and TBI), prevalence estimates, sex-specific mechanisms, genetic ancestry, and clinical phenotypes of each pathobiology as well as their combinations. Life course factors, including social and environmental determinants of health, must be measured systematically and evaluated for their impact on disease risk and prevalence estimates. Studies must preferentially include populations most at risk for AD/ADRD and disparities in diagnosis and care, including racial/ethnic minorities and people with Down syndrome.
- Validate multi-biomarker approaches to obtain a full antemortem etiological profile of persons with cognitive impairment that also incorporates genetic modifiers, the effects of sex, and social, environmental, and behavioral factors.
- Develop and implement clinical pathways that identify clinically actionable signs and symptoms of multiple etiologies, incorporate cognitive testing and blood-based biomarkers, prioritize the early and appropriate identification and stratification of patients for disease-specific therapies and clinical trials, facilitate access to differential diagnosis for non-AD dementias, including prion disorders, and track progression over time. Advance ethical best practices for what and how to disclose biomarker results in diverse populations. Prioritize clinical pathways with potential for scale and to reduce inequities in access to diagnosis in AD/ADRD for racial and ethnic minority populations that are at higher risk, particularly populations that are underrepresented in research, for example, on the basis of race/ethnicity, disability or rural locale. Studies must engage community partners and may be primarily based in community settings to foster inclusive enrollment but are also encouraged to prioritize participation in deep phenotyping (e.g., multimodal imaging, neuropathological examinations, and other diagnostic tests) that may only be available at specialist centers. The economic impact of earlier differential diagnosis should be evaluated.

### Recommendation 4 – Priority 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. (3 - 7 years)

- Define interactions at the molecular and cellular level of the common and newly identified pathobiologies of later-life cognitive impairment, including proteinopathies, inflamm-aging, immunosenescence, prion-like seeding/spreading, and other factors that lead to cognitive decline (e.g., psychiatric disorders, substance abuse, TBI, metabolic disorders, sleep abnormalities, social disadvantage, and more) in diverse populations.
- Define molecular signatures of vulnerable vs. resilient neuronal populations as an approach to inform on mechanisms of cell vulnerability.
- Prioritize innovation to address technological gaps that represent barriers to progress in basic research on common mechanisms of MED (e.g., human iPSCs).
- Prioritize creation of multi-disciplinary, multi-sector, multi-career stage teams to address both the heterogeneity and common mechanism questions of MED.

### Recommendation 5 – Priority 1. Interventions and Treatments for MED: Conduct clinical studies on approved or promising interventions and treatments to mitigate risk for cognitive decline. (5 - 10 years)

- Conduct inclusive and pragmatic clinical trials in hospital and community-based settings where risk factors for cognitive decline can be appropriately targeted for intervention. Interventions may target, but are not limited to, exercise, cardiovascular risk reduction, sleep disorders, use of anti-cholinergic medications, treatment of hearing loss, prevention of delirium, allostatic load, and treatment of mood disorders. Studies should include participants at high risk for cognitive decline as well as individuals at earlier phases of risk, from health disparities populations, and Medicare beneficiaries. Studies should elucidate the types of patients most likely to decline and also to benefit from the interventions.
- Prioritize the development of practice-based research networks to facilitate the translation of effective assessment and intervention strategies into practice at a large scale, to achieve greater diversity in research participation, to target communities with the highest prevalence of risk factors, and to generate research results that are more generalizable to the real-world.
- Evaluate the health risk and effectiveness of AD therapeutics in MED (e.g., anti-amyloid therapies) among patients with diverse cultural and socioeconomic backgrounds, accounting for genetics and comorbidities.

### Recommendation 6 – Priority 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. (3 - 7 years)

- Identify barriers and facilitators to widespread diffusion and sustainability of interventions with demonstrated benefit for persons with dementia, caregivers, and payers. Test methods to address barriers, leverage facilitators, foster community engagement, achieve greater health equity, evaluate care quality, and impact outcomes that are identified as most important by people and families living with dementia and with attention to distinct social and cultural populations.
- Conduct implementation studies in multiple and varied real-world settings that draw upon science-based models of widespread diffusion or successful examples of health practice change. Sustainability in current payment structures must be tested. Trial designs should be dynamic and guided by input from people living with cognitive impairment, care partners, clinicians, health system administrators, and payers. Studies must explicitly identify and address sex and gender differences and the unique needs of populations experiencing health disparities.
- Develop and evaluate payment models that will promote dissemination and sustainability of effective dementia care programs in fee-for-service Medicare, Medicare Advantage, and Alternative Payment Models, including provision of needed services by community-based organizations.

- Develop and evaluate core components of culturally sensitive collaborative dementia care models that deliver high-quality care.

### Recommendation 7 – Priority 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. (5 - 10 years)

- Develop, implement, and evaluate training programs in different dementia syndromes for the current and emerging generation of all healthcare professionals who work with older adults, with the goal of increasing the dementia-capable workforce across disciplines. Training programs should deepen understanding in the heterogeneity of cognitive impairment and dementia and its distinct causes.
- Prioritize mentorship and provide research opportunities in multiple etiology cognitive impairment and dementia for the current and emerging generation of researchers, including from groups underrepresented in science, in ways that promote their integration and inclusion into a multicultural educational setting.
- Promote education of researchers in recruiting and retaining diverse research participants from populations that experience health disparities into research studies on multiple etiologies.

### Recommendation 8 - Priority 3. Data Harmonization: Conduct research to improve pre- and post-data collection harmonization and sharing practices across multiple etiology cognitive impairment and dementia studies. (5 - 10 years)

- Develop and evaluate common data elements and standardized consent language required for multiple etiology dementia for inclusion in ongoing and future studies. Development should synergize with other ongoing efforts, such as in TBI.
- Identify barriers and facilitators to widespread incorporation of common data element usage and sharing of data and findings to the broader community, including EHR, CMS, and other real-world data on AD/ADRD.
- Promote incorporation of common data elements into data collection for observation and intervention studies that incorporate phenotypic data. Document and promote neuroimaging acquisition protocols. Promote biospecimen processing and storage protocols to align data capture across studies, as appropriate, including sample processing, sample storage, and assays. Promote inclusion of forms, instruction manuals, and data dictionaries to accompany any data sharing/ centralized reporting of data. Examine pragmatic, streamlined tools that protect participant rights and privacy while enabling the tracking of research participation of individuals across centers and studies.
- Use harmonized data to investigate differences in dementia risk factors, dementia phenotypes, and dementia outcomes in clinic- and community-based studies and with a focus on multiple etiologies.
- Develop and evaluate training opportunities to promote methodologically rigorous and efficient data-sharing for current and emerging generations of researchers, focused on foundational and advanced data harmonization methods to promote the use of shared data to generate new insights and findings across multiple etiology dementia.

## MED Special Topic: Post-TBI AD/ADRD

### Recommendation 1 – Priority 1. Promote collaboration among TBI and dementia researchers through working groups, retrospective and prospective data and measurement harmonization, and interdisciplinary research. (1 - 3 years)

- Convene a working group of stakeholders from the TBI & multiple-etiology dementia communities to evaluate the extent to which current knowledge (e.g., mechanistic pathways, environmental and genetic risk factors, independent and interactive effects of multiple proteinopathies on pathological proliferation and AD/ADRD

clinical manifestation) in AD/ADRD can be applied to the study of dementia after TBI, and how TBI (an AD/ADRD risk factor with a "time zero") contributes to AD/ADRD.

- Harmonize existing data across longitudinal TBI outcome studies and TBI-AD/ADRD studies using data harmonization and advanced psychometric methods; improve data annotation in existing studies to facilitate cross-study comparisons.
- Maximize measurement harmonization across longitudinal TBI and dementia clinical cohort studies by establishing and prospectively collecting common data elements (CDEs; clinical, psychometric, neuroimaging, fluid biomarkers) to facilitate comparisons and data sharing.
- Encourage collaboration between community stakeholders, clinical researchers, biostatisticians, epidemiologists, data scientists, and implementation scientists to incorporate multidimensional/multimodal data, employ causal inference methodologies, and maximize clinical translatability in the study of TBI-AD/ADRD.

### Recommendation 2 – Priority 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. (1 - 10 years)

- Establish and validate a quantitative index of lifetime head trauma exposure.
- Establish and validate a provisional clinical definition of post-TBI dementia(s) that distinguishes chronic static TBI-related symptoms from a progressive neurodegenerative disease as measured by clinical decline and changes in clinically accessible biofluid and imaging biomarkers.
- Conduct longitudinal studies to characterize the clinical phenotype, phenotypic heterogeneity, clinical course, environmental and genetic protective factors, and effect modifiers (e.g., post-traumatic stress disorder, sleep disorders, etc.) of post-TBI AD/ADRDs in samples of men and women from diverse backgrounds with distinct and varied lifetime exposure histories, as characterized by age at injury, severity, mechanism, and chronicity.
- Develop and validate TBI-AD/ADRD biomarkers (e.g., psychometric, wearable sensors, imaging, and biofluid) to non-invasively identify progressive post-TBI AD/ADRD pathologies, monitor disease progression over time, elucidate pathological substrates of domain-specific clinical decline, and predict resilience to cognitive decline and to behavioral disorders.

### Recommendation 3 – Priority 3. Establish research infrastructure, including multimodal longitudinal studies with autopsy endpoints that employ standardized CDEs and methodologies, to study post-TBI AD/ADRD. (1 - 3 years)

- Enrich the design of longitudinal TBI studies to include multimodal clinical and biological/biochemical endpoints relevant to neurodegenerative diseases and incident dementia diagnostics. Similarly, enrich AD/ADRD studies with expanded lifetime TBI ascertainment methods.
- Establish clinic- and community-based prospective studies of individuals with diverse head trauma exposure histories (e.g., single TBI, repetitive head trauma in the contexts of contact sports, military service, domestic violence, and intimate partner violence [IPV]) for longitudinal study using multimodal clinical evaluations and neuroimaging and neuropathological endpoints to inform clinically actionable diagnostics for post-TBI AD/ADRD.
- Expand efforts to build and enhance existing brain biorepositories to include optimally preserved tissues from individuals with diverse head trauma exposure histories (e.g., a history of participation in contact sports or military service, single or repetitive TBI of all severities) and clinical and/or postmortem neuroimaging, medical records, and CDE structured postmortem interview data.
- Launch nationwide inter-agency efforts to expand and standardize the use of NINDS CDEs for Human Neuropathological Studies in TBI for harmonized neuropathological evaluation and postmortem clinical characterization across tissue banking centers. Promote tissue sharing and develop digital pathology infrastructure to facilitate research across tissue banks.

### Recommendation 4 – Priority 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. (7 - 10 years)

- Accelerate the development, standardization, and validation of clinically relevant experimental models of aspects of TBI that accommodate diversity of injury mechanisms and biomechanics; and accurately reproduce their distinct and interactive acute and chronic neuropathological and behavioral sequelae. Collaborate with clinical researchers to refine models as knowledge of human TBI neuropathology evolves.
- Deploy traditional, quantitative, and/or molecular (omics) approaches to deeply characterize post-TBI neuropathologies, identify selectively vulnerable/resilient cells/regions, and determine underlying pathological mechanisms common with, or unique from, other multi-etiology dementias and neurodegenerative disorders.
- Determine how the relative extent, distribution, and temporal progression of individual neuropathologies (and their potential interactions) contribute to the clinical manifestation of dementia following TBI. Identify how TBI exposure history (e.g., mechanism and severity of injury, number of exposures etc.) influences the nature and evolution of autonomic and central nervous system pathologies in humans and experimental models.
- Identify intrinsic (e.g., genetic, proteomic) and environmental (e.g., socioeconomic, educational, lifestyle) factors that confer resilience to cognitive decline and behavioral disorders after TBI and during aging.

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

### Recommendation 1 – Priority 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. (2 - 7 years)

- Develop definitions and classification for distinguishing LATE from other TDP-43 proteinopathy-related disorders, including FTLD-TDP.
    - Using data-driven methods, define the pathologic boundaries to aid disease classification and to enhance basic and translational research.
    - Unravel the clinical spectrum of LATE to refine clinical boundaries relative to other TDP-43 disorders (e.g., bvFTD, semantic dementia, primary progressive aphasia [PPA]).
    - Develop LATE biomarkers that can specifically refine clinical boundaries.
    - Contrast TDP-43 disorders through clinical, pathological, and basic science studies to determine commonalities/differences across TDP43 proteinopathy disorders.
    - Study clinical and pathologic intersections (including known pathologies such as ADNC and vascular disease) across differing TDP-43 proteinopathy diseases.
    - Study ultrastructure to determine TDP-43 proteinopathy conformations/alterations that differ between disorders.
    - Investigate genetic variants and molecular changes associated with LATE-neuropathologic change (LATE-NC) (e.g., GWAS, differential gene expression).
    - Compare disease classes using genetics and other -omic studies (including systems biology/computational approaches) to provide insights on the classification/boundaries across TDP-43 proteinopathy diseases.
- Define the relationships between LATE and non-TDP43 dementia pathologies including, ADNC, Lewy body disease, and cerebrovascular disease, using multiple avenues, including -omics (e.g., systems biology/computational approaches), molecular, epidemiologic, pathologic, and clinical.
    - Identify shared and distinct features of LATE and AD (e.g., investigate determinants of comorbid LATE-ND in individuals with AD neuropathologic change)
    - Clarify the relationship of LATE with LBD (e.g., interface of TDP-43 and α-synuclein)

    - Clarify the interface of LATE/VCID (e.g., role of arteriolosclerosis, clearance, and sleep-related mechanisms)
- Increase awareness of LATE across both research and clinical practice including, trials and basic patient management.
    - Increase awareness of LATE with respect to clinical and pathologic AD
    - Study the impact on quality of life of LATE diagnosis in persons with LATE and their social network. Encourage both human and other disease models to inform one another about the clinical and biological features of LATE.

### Recommendation 2 – Priority 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. (2 - 7 years)

- Develop, harmonize and expand community and other cohorts combining neuroimaging, biofluids, and genetics with autopsy to promote clinical-pathological studies that will better establish phenotypic patterns associated with LATE-NC.
- Identify distinguishing cognitive and behavioral features associated with LATE-NC alone or in the presence of co-pathology.
- Develop clinical criteria for LATE and distinguish it from other late-life dementia syndromes, and test for the accuracy (validation) using pathology.
- Define and incorporate genetic associations of LATE/LATE-NC in the setting of LATE-NC alone or with co-pathology in risk models and/or classifiers.
- Ultimately develop biofluid (e.g., blood or CSF) or neuroimaging (e.g., MRI, PET) biomarkers that show good discrimination of the molecular pathology of LATE-NC (i.e., TDP-43).

### Recommendation 3 – Priority 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. (5 - 8 years)

- Develop and characterize models that incorporate aging designed to simulate LATE-NC, i.e., TDP-43-dependent, clinical, pathological, and molecular phenotypes in common dementias. This may include:
    - Virally transduced animal models using aged animals
    - Knock-in, gene-edited, or stress-induced models
    - Transgenic animal models that express wild-type or mutant TDP-43 or develop hippocampal sclerosis. Consider using inducible promoters to drive transgene expression in the disease-relevant cell type(s) with attention to the appropriate time of life of the animal
    - Vascular contributions to TDP-43 proteinopathy and/or hippocampal sclerosis
    - Interaction between TDP-43 and tau, α-synuclein, amyloid proteinopathies, and other pathologic proteins
    - Glial/neuron inflammatory contributions to TDP-43 proteinopathy, specifically in aging
- Study prion-like transmission of pathological TDP-43 species that simulate anatomical progression of LATE-NC and TDP-43 pathology in common dementias.
- Develop translationally actionable cellular and animal models to enable preclinical therapeutic development and testing pipelines in LATE-NC.

### Recommendation 4 – Priority 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. (2 - 7 years)

- Develop a clear definition and consensus-based protocol for pathological categorization of HS (because of important association with LATE-NC) to provide “gold standard” for pathologic categorization and a rigorous foundation for future study of HS via genetics, clinical-pathologic, and imaging studies.
- Study LATE with versus without HS via clinical-pathological and genetic correlations.
- Develop standardized biomarkers/risk profiles to identify HS clinically.
    - For a clinical biomarker, antemortem and postmortem imaging studies may link specific MTL MRI changes (shape, signal, texture) with HS.
    - Biomarker/risk profiles for HS should be compared with other pathologically confirmed causes of MTL pathology.
    - Risk profiles could include other modalities, including genetic polymorphisms, risk factors, and plasma biomarkers.
- Identify molecular, genetic, clinical, and pathologic drivers of LATE-NC, with versus without HS, and with or without vasculopathy, and the role of senescence.
    - Determine the nature of the small vessel and vessel wall constituent changes seen in LATE+/-HS if this differs from SVD without LATE +/- HS.
    - Explore the mechanism for the common co-occurrence of LATE-NC, SVD, and HS, and determine if TDP-43 proteinopathy promotes vasculopathy "upstream" of HS or vasculopathy promotes both LATE-NC and HS or there is an alternative mechanistic pathway.
    - Study vasculopathy in LATE+HS and its link to aging and senescence mechanisms.
    - Explore common interconnected risk factors for LATE-NC, HS, and vasculopathy.

## MED Special Topic: Impact of COVID-19 on AD/ADRD Risk and Outcomes

### Recommendation 1 – Priority 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. (1 - 3 years)

- Establish new and leverage existing clinical cohorts for longitudinal prospective studies to examine the impact of COVID-19 on AD/ADRD risk and outcomes, prioritizing cohorts that oversample minoritized groups that have been disproportionately affected by both COVID-19 and AD/ADRD, and prepare these cohorts for clinical trials with repurposed or newly developed treatments. Studies should center the experiences of groups that have been historically marginalized and include careful ascertainment of prevalent circulating virus variants in the community at the time of infection.
- Define common data elements (including multilingual), develop a database and data and material sharing avenues, and harmonize collection of social and structural determinants, clinical, neuropsychometric, and imaging data and biosamples (including dried blood spot, plasma, serum, PBMCs, CSF supernatant, CSF cell pellet, saliva, DNA and RNA) using best practices for tissue collection across cohorts to facilitate analyses across various populations.
- Encourage national autopsy, brain donation, and fibroblast collection programs from persons infected with SARS-CoV-2 with and without chronic neuropsychiatric sequelae to study the molecular, pathological, and epigenetic consequences of infection and factors underlying, markers of susceptibility, and resilience.

- Design and validate protocols that (i) examine brain regions and systems known to be especially vulnerable to acute and post-acute sequelae of SARS-CoV-2 (PASC) (e.g. olfactory bulb, autonomic nervous system, cerebral vasculature), (ii) facilitate high-quality research among linguistic, racial, and cultural groups that have been disproportionately affected, incorporating individual and internalized (e.g. coping mechanisms, behavior, genetics) and systemic/structural (e.g. racialized policies and institutions, social supports, access to medical care, vaccines, built environment, occupational exposures) factors, (iii) permit accurate assessment of diagnosis and extent and type of cognitive impairment and brain injury, and iv) consider comorbid symptoms that could impact cognitive assessment such as dyspnea and fatigue.

### Recommendation 2 – Priority 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. (1 - 7 years)

- Evaluate the direct and indirect impact of SARS-CoV-2 infection on brain structure and function utilizing neuroimaging, blood, and CSF biomarkers. We recommend a special emphasis on (i) persistent cognitive, behavioral, and mood impairments, (ii) amplification and acceleration of dementia risk, and (iii) assessment of smell/taste due to high prevalence of persistent hyposmia, anosmia, and dysgeusia in survivors.
- Define and describe the temporal progression of clinical neurocognitive impairment and dementia (CID), including the wide spectrum of acute and delayed objective and subjective neurological manifestations (e.g., “brain fog”), in the presence and absence of other PASC symptoms.
- Determine neuropsychological profiles (e.g., dysexecutive vs. amnestic) as well as stress, behavioral, and mood changes in CID associated with COVID-19 in older adults with AD/ADRD biomarker information.
- Include cognitively unimpaired persons, as well as persons with a prior diagnosis of mild cognitive impairment (MCI) and/or dementia in future studies, since morbidity, mortality, and other impacts may differ between these groups.
- Examine role, if any, of covert and overt (clinically symptomatic) AD/ADRD pathology on modifying the risk and severity of COVID-19 infection (e.g., role of genetic factors underlying susceptibility to both SARS-CoV-2 and ADRD such as APOE4, OAS1, and TMEM106B).
- Examine if type and severity of CID and acceleration of cognitive decline in persons with AD/ADRD (including VCID) relate to the severity of acute illness, vaccination type and status, and treatment.
- Examine role of structural, social, environmental, and behavioral factors on characteristics of CID and risk of AD/ADRD after SARS-CoV-2 infection.

### Recommendation 3 – Priority 3. Explore interaction of social, structural, and systemic inequalities, comorbidities and social and medical interventions with risk and neurocognitive sequelae of COVID-19. (1 - 5 years)

- Prioritize evaluation of structural and social determinants of health and research to understand and eliminate disparities in CID and other neurological sequelae of COVID-19 by race, ethnicity, and gender, with engagement and inclusion of historically marginalized populations at higher risk for COVID-19 infection and sequalae.
- Include careful ascertainment of exposure to SARS-CoV-2, infection, illness and treatment details, access to care, pandemic-related and unrelated barriers to access, social support, and environmental factors in ongoing cohort studies of cardiovascular, cerebrovascular, and other neurological conditions such as brain aging, AD/ADRD, VCID, and stroke.
- Include culturally and linguistically valid, harmonized assessments of neurological, cognitive, and psychiatric consequences in ongoing clinical trials of COVID-19 preventive interventions and treatments.
- Facilitate electronic health record collation and analyses to identify unsuspected, potentially beneficial, or harmful effects of medications administered for other conditions (e.g., ACEI, ARBs) on risk of ADRD in a post-COVID setting.

- Examine the impact of policy interventions such as caregiver support, paid family leaves, access to health care, housing (e.g., rent abatement, eviction protections, household energy insecurity), and non-pharmacological supports on the risk and progression of CID after COVID-19 infection.
- Understand the role of availability, access, uptake, barriers, and effectiveness of innovative health technologies, including telemedicine and artificial intelligence-based solutions, with a focus on reducing racial and geographic disparities in the impact of COVID-19 on AD/ADRD.

### Recommendation 4 – Priority 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. (1 - 7 years)

- Understand the biological pathways implicated in CID, including (i) direct and indirect effects of SARS-CoV-2, (ii) similarities and differences between response to this virus compared to other corona viruses and response to systemic infections and illnesses of comparable severity, and (iii) similarities and differences in pathophysiology of subacute "long COVID" and CID (both elements of PASC).
- Develop model systems corresponding to various clinical presentations of SARS-CoV-2 infection to explore pathophysiology and possible interventions.
- Explore model systems enabling SARS-CoV-2 infection in existing AD/ADRD models to determine direct and indirect effects of viral infection on molecular changes at the cellular and tissue levels and on brain structure, cognitive and behavioral outcomes.
- Conduct long-term studies of COVID-19 survivors from racial, ethnic, economic, and geographic groups who were put at higher risk for COVID-19, and survivors of severity-matched non-COVID illness, to compare and contrast brain injury (as assessed by CSF and blood biomarkers, brain imaging including 3T MRI protocols, MR spectroscopy, and 7T MRI, and PET imaging including for classic AD markers of amyloid/tau and markers of synaptic density and microglial activation for assessment of neuroinflammation, neurodegeneration, blood-brain barrier, endothelial and microvascular injury) and to correlate these markers of brain injuries with sensorimotor, cognitive, behavioral symptoms, either persistent or progressive.
- Explore the age, sex, genetic, biomarker (circulating, multi-omic, imaging), behavioral, psychosocial (including family and social network, occupation, income, access to medical care and support, early life exposures), environmental, immune, vascular, metabolic factors, as well as viral variant, vaccination, treatment, social (neighborhood safety and cohesion, housing and food insecurity, transportation infrastructure, educational quality) and structural (e.g., racism, sexism, classism, homophobia, able-ism) factors and policies that increase or mitigate the risk of CID and subsequent AD/ADRD.
- Develop and study potential interventions against an adverse SARS-CoV-2 impact on AD/ADRD, based on early translational studies, including targeting neuroinflammation, amyloid and/or tau aggregation, viral persistence, and other mechanisms that emerge as the data accumulate.
- Facilitate rapid implementation of candidate drug screening, discovery, and treatment trials to mitigate the impact of COVID-19 on AD/ADRD risk and progression.

# ADRD Summit 2022
# COMMITTEE ROSTERS

## TABLE 1: ADRD Summit 2022 Steering Committee

| NAME, DEGREE(s) | TITLE & AFFILIATION | STEERING COMMITTEE ROLE | |
|---|---|---|---|
| Natalia Rost, MD, MPH (Chair) | Chief, Stroke Division, Dept. of Neurology; Massachusetts General Hospital (MGH); Professor, Harvard Medical School, Boston, MA | Working Group of Council, Chair | Summit Scientific Chair; Session Chair |
| Adam Boxer, MD, PhD | Professor, Dept. of Neurology, University of California, San Francisco (UCSF) | Working Group of Council | Session Chair |
| Cynthia Carlsson, MD, MS | Professor, Dept. of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI | Working Group of Council | NAPA Council Chair |
| S. Thomas Carmichael, MD, PhD | Professor and Chair, Dept. of Neurology, University of California, Los Angeles | Working Group of Council | NANDS Council Representative |
| Kristen Dams-O'Connor, PhD | Professor, Depts. of Rehabilitation & Human Performance and Neurology, Mount Sinai, New York, NY | Working Group of Council | Session Chair |
| Hector González, PhD | Professor, Dept. of Neurosciences, University of California, San Diego | Working Group of Council | Session Chair |
| David Holtzman, MD | Professor, Dept. Neurology, Washington University, St. Louis, MO | Working Group of Council | Past ADRD Summit Chair |
| Kejal Kantarci, MD, MS | Professor, Dept. of Radiology, Mayo Clinic, Rochester, MN | 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 |
| James Leverenz, MD | Director of the Lou Ruvo Center for Brain Health; Endowed Chair for Advanced Neurological Research and Education, Cleveland Clinic, Cleveland, OH | Working Group of Council | Session Chair |
| Thomas Montine, MD, PhD | Professor and Chair, Dept. of Pathology, Stanford University, Stanford, CA | Working Group of Council | Past ADRD Summit Chair |

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| Ronald Petersen, MD, PhD | Professor, Dept. of Neurology, Mayo Clinic, Rochester, MN | Working Group of Council | Session Chair |
| Gina Poe, PhD | Professor, Dept. of Integrative Biology & Physiology, University of California, Los Angeles | Working Group of Council | NANDS Council Representative |
| Katherine Possin, PhD | Professor, Dept. of Neurology, University of California, San Francisco | Working Group of Council | Session Chair |
| Julie Schneider, MD, MS | Professor, Depts. of Pathology and Neurological Sciences, Rush University, Chicago, IL | Working Group of Council | Session Chair, Past ADRD Summit Chair |
| Sudha Seshadri, MD, DM | Professor, Dept. of Neurology; Director, Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health San Antonio | Working Group of Council | Session Chair |
| Donna Wilcock, PhD | Professor, Dept. of Physiology, University of Kentucky, Lexington, KY | Working Group of Council | Session Chair |
| Julie Zissimopoulos, PhD | Associate Professor, Sol Price School of Public Policy, University of Southern California, Los Angeles, CA | Working Group of Council | Session Chair |
| Walter Koroshetz, MD | Director, NINDS | ex-officio | NINDS Director |
| Roderick Corriveau, PhD | Program Director, Division of Neuroscience, NINDS | ex-officio | NIH Summit Lead, NIH Session Lead |
| Keith Whitaker, PhD | Program Manager, NINDS | ex-officio | NIH Summit Administrative Lead, NIH Session Lead |
| 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 |
| Eliezer Masliah, MD | Director, Division of Neuroscience, NIA | ex-officio | NIA Representative |
| Andy Singleton, PhD | Director, Center for Alzheimer's and Related Dementias (CARD), NIH | ex-officio | NIH CARD Representative |

## TABLE 2: ADRD Summit 2022 Non-Federal Committee Members

| SESSION | NAME, DEGREE(S) | TITLE, AFFILIATION |
|---|---|---|
| **Health Equity in AD/ADRD** | Hector González, PhD (Session Chair) | Professor, Dept. of Neurosciences, University of California, San Diego |
| | Julie Zissimopoulos, PhD (Session Chair) | Associate Professor, Sol Price School of Public Policy, University of Southern California, Los Angeles, CA |
| | Toni Antonucci, PhD | Professor of Psychology, College of Literature, Science; Arts and Research Professor, Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor |
| | Lisa Barnes, PhD | Professor, Dept. of Neurological Sciences, Rush Medical College, Chicago, IL |
| | María Corrada-Bravo, ScM, ScD | Professor, Depts. of Neurology and Epidemiology, University of California, Irvine |
| | Shana Dodge, PhD | Director of Research Engagement, The Association for Frontotemporal Degeneration, King of Prussia, PA |
| | Myriam Fornage, PhD | Professor, Center for Human Genetics; Laurence and Johanna Favrot Distinguished Professor in Cardiology, University of Texas Health Science Center at Houston, TX |
| | Paola Gilsanz, ScD | Research Scientist, Epidemiology, Kaiser Permanente, Oakland, CA |
| | Lourdes Guerrero, EdD, MSW | Associate Professor, Dept. of Medicine, University of California, Los Angeles |
| | Carl Hill, PhD, MPH | Chief Diversity, Equity and Inclusion Officer for the Alzheimer's Association, Chicago, IL |
| | Timothy Hughes, PhD | Associate Professor, Dept. of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC |
| | Ara Khachaturian, PhD | Executive Vice-President of the Campaign to Prevent Alzheimer's Disease 2020 (PAD2020), Rockville, MD |
| | Luis Medina, PhD | Assistant Professor, Dept. of Psychology, University of Houston, Houston, TX |

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| | Sid O'Bryant, PhD | Professor and Executive Director, Institute for Translational Research; Professor, Dept. of Pharmacology & Neuroscience, The University of North Texas Health Science Center, Fort Worth, TX |
| | Priya Palta, PhD, MHS | Assistant Professor, Depts. of Medicine and Epidemiology, Columbia University, New York, NY |
| | Alberto Ramos, MD, MSPH, FAASM, FAAN | Professor, Clinical Neurology, University of Miami, Miller School of Medicine, Miami, FL |
| | Wassim Tarraf, PhD | Associate Professor, Institute of Gerontology and the Dept. of Healthcare Sciences, Wayne State University, Detroit, MI |
| | Jacqueline Torres, PhD, MPH | Assistant Professor, Dept. of Epidemiology & Biostatistics, University of California, San Francisco |
| | Jennifer Weuve, MPH, ScD | Associate Professor, Dept. of Epidemiology, Boston University, Boston, MA |
| | Michael Wolf, PhD, MPH, MA | Associate Vice Chair for Research and Professor, Dept. of Medicine; Professor, Dept. of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL |
| **Frontotemporal Degeneration (FTD)** | Adam Boxer, MD, PhD (Session Chair) | Professor, Dept. of Neurology, University of California, San Francisco (UCSF) |
| | Celeste Karch, PhD (Session Chair) | Associate Professor, Dept. of Psychiatry, Washington University School of Medicine, St. Louis, MO |
| | Sami Barmada, MD, PhD | Associate Professor, Dept. of Neurology; Director, Michigan Brain Bank, University of Michigan, Ann Arbor |
| | Alice Chen-Plotkin, MD | Professor, Dept. of Neurology, University of Pennsylvania, Philadelphia, PA |
| | Penny Dacks, PhD | Senior Director of Scientific Initiatives, Association for Frontotemporal Degeneration, King of Prussia, PA |
| | Kristophe Diaz, PhD | Executive Director, Chief Science Officer, CurePSP, New York, NY |
| | Anthony Fitzpatrick, PhD | Assistant Professor, Depts. of Biochemistry and Molecular Biophysics, Columbia University, New York, NY |

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| | Bess Frost, PhD | Associate Professor, Dept. of Cell Systems and Anatomy, University of Texas Health San Antonio |
| | Alison Goate, DPhil | Professor & Chair, Dept. of Genetics and Genomic Sciences; Professor of Neuroscience and Neurology, Icahn School of Medicine at Mount Sinai, New York, NY |
| | David Irwin, MD | Assistant Professor, Dept. of Neurology, University of Pennsylvania, Philadelphia, PA |
| | Peter Nelson, MD, PhD | Professor, Dept. of Pathology and Laboratory Medicine, University of Kentucky, Lexington, KY |
| | Chiadi Onyike, MD | Associate Professor, Dept. of Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD |
| | Leonard Petrucelli, PhD | Professor, Dept. of Neuroscience, Mayo Clinic, Jacksonville, FL |
| | Julie Schneider, MD, MS | Professor, Depts. of Pathology and Neurological Sciences, Rush University, Chicago, IL |
| | Jeffrey Sevigny, MD | Chief Medical Officer, Prevail Therapeutics, New York, NY |
| | Richard Tsai, MD, MBA | Senior Medical Director, Denali Therapeutics, San Francisco, CA |
| **Vascular Contributions to Cognitive Impairment and Dementia (VCID)** | Ronald Petersen, MD, PhD (Session Chair) | Professor, Dept. of Neurology, Mayo Clinic, Rochester, MN |
| | Donna Wilcock, PhD (Session Chair) | Professor, Dept. of Physiology, University of Kentucky, Lexington, KY |
| | Konstantinos Arfanakis, PhD | Professor, Dept. of Diagnostic Radiology and Nuclear Medicine, Rush Medical College, Chicago, IL |
| | Frank Barone, PhD | Professor, Depts. of Neurology and Physiology & Pharmacology, State University of New York (SUNY) Downstate Health Sciences University, Brooklyn, NY |
| | Kristen Dams-O'Connor, PhD | Professor, Depts. of Rehabilitation & Human Performance and Neurology, Mount Sinai, New York, NY |
| | Douglas Gould, PhD | Professor, Dept. of Ophthalmology, University of California, San Francisco |
| | Carl Hill, PhD, MPH | Chief Diversity, Equity and Inclusion Officer for the Alzheimer's Association, Chicago, IL |

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| | Gareth Howell, PhD | Professor and the Diana Davis Spencer Foundation chair for Glaucoma Research, The Jackson Laboratory (JAX), Bar Harbor, ME |
| | Timothy Hughes, PhD | Associate Professor, Dept. of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC |
| | Angela Jefferson, PhD | Professor, Dept. of Neurology; Director, Vanderbilt Memory & Alzheimer's Center, Vanderbilt University, Nashville, TN |
| | Victoria Johnson, MBChB, PhD | Assistant Professor, Dept. of Neurosurgery, University of Pennsylvania, Philadelphia, PA |
| | Anne Leonard, MPH, RN, CCRC, FAHA | Senior Science and Medicine Advisor, American Heart Association, Dallas, TX |
| | Jennifer Manly, PhD | Professor of Neuropsychology, Dept. of Neurology, Columbia University, New York, NY |
| | Melissa Murray, PhD | Associate Professor, Dept. of Neuroscience, Mayo Clinic, Jacksonville, FL |
| | Rema Raman, PhD | Professor, Dept. of Neurology, University of Southern California, Health Sciences Campus, San Diego, CA |
| | Julie Schneider, MD, MS | Professor, Depts. of Pathology and Neurological Sciences, Rush University, Chicago, IL |
| | Sudha Seshadri, MD, DM | Professor, Dept. of Neurology; Director, Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health San Antonio |
| | Andy Shih, PhD | Associate Professor, Depts. of Pediatrics and Bioengineering, University of Washington, Seattle, WA |
| | Eric Smith, MD, MPH, FRCPC | Professor, Dept. of Neurology, University of Calgary, Calgary, Alberta, Canada |
| | William E. Van Nostrand, PhD | Co-Director, George & Anne Ryan Institute for Neuroscience; Professor, Depts. of Neuroscience and Biomedical and Pharmaceutical Sciences, The University of Rhode Island, Kingston, RI |
| | Susanne van Veluw, PhD | Assistant Professor, Dept. of Neurology, Massachusetts General Hospital (MGH) / Harvard Medical School, Boston, MA |

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| | Prashanthi Vemuri, PhD | Professor, Dept. of Radiology, Mayo Clinic Rochester, MN |
| | Cheryl Wellington, PhD | Professor, Dept. of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada |
| **Lewy Body Dementias (LBD)** | James Leverenz, MD (Session Chair) | Director of the Lou Ruvo Center for Brain Health; Endowed Chair for Advanced Neurological Research and Education, Cleveland Clinic, Cleveland, OH |
| | Kejal Kantarci, MD, MS (Session Chair) | Professor, Dept. of Radiology, Mayo Clinic, Rochester, MN |
| | Bradley Boeve, MD | Professor, Dept. of Neurology, Mayo Clinic, Rochester, MN |
| | Jesse Cedarbaum, MD | Neurologist, Professor Adjunct, Yale School of Medicine, Yale University, New Haven, CT |
| | Dennis Dickson, MD | Professor, Dept. of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville, FL |
| | Brittany Dugger, PhD | Assistant Professor, Dept. of Pathology and Laboratory Medicine, University of California, Davis |
| | Douglas Galasko, MD | Professor, Dept. of Neurosciences, University of California San Diego |
| | David Irwin, MD | Assistant Professor, Dept. of Neurology, University of Pennsylvania, Philadelphia, PA |
| | Virginia Lee, PhD | Endowed Professor, Dept. of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA |
| | Karen Marder, MD, MPH | Professor, Dept. of Neurology, Columbia University, New York, NY |
| | Clemens Scherzer, MD | Professor, Dept. of Neurology, Harvard Medical School, Boston, MA |
| | Angela Taylor | Senior Director of Research and Advocacy, Lewy Body Dementia Association, Lilburn, GA |
| | David Vaillancourt, PhD | Professor and Chair, Dept. of Applied Physiology & Kinesiology, University of Florida, Gainesville, FL |
| | David Wolk, MD | Professor, Dept. of Neurology, University of Pennsylvania, Philadelphia, PA |
| **Multiple Etiology** | Katherine Possin, PhD (Session Chair) | Professor, Dept. of Neurology, University of California, San Francisco |

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| **Dementias (MED)** | Jeffrey Burns, MD, MS | Professor, Dept. of Neurology, University of Kansas, Fairway, KS |
| | Penny Dacks, PhD | Senior Director of Scientific Initiatives, Association for Frontotemporal Degeneration, King of Prussia, PA |
| | Peggye Dilworth-Anderson, PhD | Professor, Dept. of Health Policy & Management, University of North Carolina-Chapel Hill |
| | Lea Grinberg, MD, PhD | Professor, Dept. of Neurology, University of California, San Francisco Weill Institute for Neurosciences, San Francisco, CA |
| | Bradley Hyman, MD, PhD | Professor, Dept. of Neurology, Harvard Medical School and Massachusetts General Hospital, Boston, MA |
| | Ozioma Okonkwo, PhD | Associate Professor, Dept. of Medicine; University of Wisconsin-Madison |
| | Heather Snyder, PhD | Vice President, Medical & Scientific Relations, Alzheimer's Association, Chicago, IL |
| | Malú Gámez Tansey, PhD | Professor, Dept. of Neurology, University of Florida, Gainesville, FL |
| | Michael Wolf, PhD, MPH, MA | Associate Vice Chair for Research and Professor, Dept. of Medicine; Professor, Dept. of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL |
| **MED Special Topic: Post-TBI AD/ADRD** | Kristen Dams-O'Connor, PhD (Session Chair) | Professor, Depts. of Rehabilitation & Human Performance and Neurology, Mount Sinai, New York, NY |
| | Victoria Johnson, MBChB, PhD | Assistant Professor, Dept. of Neurosurgery, University of Pennsylvania, Philadelphia, PA |
| | Dirk Keene, MD, PhD | Professor, Dept. of Laboratory Medicine and Pathology, University of Washington, Seattle, WA |
| | Pratik Mukherjee, MD, PhD | Professor, Depts. of Radiology & Biomedical Imaging and Bioengineering, University of California, San Francisco |
| | Mary Jo Pugh, PhD, RN | Professor, Dept. of Internal Medicine, The University of Utah, Salt Lake City, UT |
| | Henrik Zetterberg, MD, PhD | Professor, Dept. of Psychiatry and Neurochemistry, University of Gothenburg, Sweden |

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| **MED Special Topic: LATE (TDP-43 in Common Late-Onset Dementias)** | Julie Schneider, MD, MS (Session Chair) | Professor, Depts. of Pathology and Neurological Sciences, Rush University, Chicago, IL |
| | Konstantinos Arfanakis, PhD | Professor, Dept. of Diagnostic Radiology and Nuclear Medicine, Rush Medical College, Chicago, IL |
| | María Corrada-Bravo, ScM, ScD | Professor, Depts. of Neurology and Epidemiology, University of California, Irvine |
| | Michael Gitcho, PhD | Associate Professor, Dept. of Biological Sciences, Delaware State University, Dover, DE |
| | Brian Kraemer, PhD | Research Professor, Depts. of Medicine, Psychiatry, and Pathology, University of Washington, Seattle WA |
| | Peter Nelson, MD, PhD | Professor, Dept. of Pathology and Laboratory Medicine, University of Kentucky, Lexington, KY |
| | Donna Wilcock, PhD | Professor, Dept. of Physiology, University of Kentucky, Lexington, KY |
| | David Wolk, MD | Professor, Dept. of Neurology, University of Pennsylvania, Philadelphia, PA |
| | Hyun-Sik Yang, MD | Assistant Professor, Dept. of Neurology, Harvard Medical School; Associate Neurologist, Brigham and Women's Hospital, Boston, MA |
| **MED Special Topic: Impact of COVID-19 on AD/ADRD Risk and Outcomes** | Natalia Rost, MD, MPH (Session Chair) | Chief, Stroke Division, Dept. of Neurology; Massachusetts General Hospital (MGH); Professor, Harvard Medical School, Boston, MA |
| | Sudha Seshadri, MD, DM (Session Chair) | Professor, Dept. of Neurology; Director, Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health San Antonio |
| | Carlos Cruchaga, PhD | Professor, Depts. of Psychiatry and Neurology, Washington University School of Medicine, St. Louis, MO |
| | Gabriel de Erausquin, MD, PhD, MSc | Professor, Dept. of Neurology, University of Texas Health, San Antonio |
| | Jason Hinman, MD, PhD | Associate Professor and Vice Chair of Research, Dept. of Neurology, University of California, Los Angeles |
| | Brian Kraemer, PhD | Research Professor, Depts. of Medicine, Psychiatry, and Pathology, University of Washington, Seattle WA |

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| | Jennifer Manly, PhD | Professor of Neuropsychology, Dept. of Neurology, Columbia University, New York, NY |
| | Kumar Rajan, PhD | Section Chief, Community Epidemiology; Professor, Dept. of Internal Medicine; Director, Institute for Aging, Rush Medical College, Chicago, IL |
| | Serena Spudich, MD | Professor, Dept. of Neurology; Chief, Division of Neurological Infections and Global Neurology, Yale University, New Haven, CT |
| | Andrea Troxel, ScD | Director, Division of Biostatistics; Professor, Dept. of Population Health, New York University (NYU), New York, NY |
| | Rong Xu, PhD | Professor, Dept. of Biomedical Informatics, Case Western Reserve University, Cleveland, OH |
| | Hyun-Sik Yang, MD | Assistant Professor, Dept. of Neurology, Harvard Medical School; Associate Neurologist, Brigham and Women's Hospital, Boston, MA |

## TABLE 3: ADRD Summit 2022 Federal Committee Members

| NAME, DEGREE(S) | TITLE, AFFILIATION | ROLE |
|---|---|---|
| Walter Koroshetz, MD | Director, NINDS | Steering Committee, ex-officio |
| Roderick Corriveau, PhD | Program Director, Division of Neuroscience, NINDS | NIH Summit Lead; NIH Session Lead, VCID; Steering Committee, ex-officio |
| Keith Whitaker, PhD | Program Manager, Division of Neuroscience, NINDS | NIH Summit Administrative Lead; NIH Session Lead, MED Special Topic (Impact of COVID-19 on AD/ADRD Risk and Outcomes) |
| Hibah Awwad, PhD | Program Director, Division of Neuroscience, NINDS | Session, MED (Post-TBI AD/ADRD) |
| Debra Babcock, MD, PhD | Program Director, Division of Neuroscience, NINDS | NIH Session Lead, Lewy Body Dementias |
| Richard Benson, MD, PhD | Program Director, Division of Neuroscience, NINDS | NIH Session Lead, Health Equity in AD/ADRD |
| Marishka Brown, PhD | Director of the National Center on Sleep Disorder Research, NHLBI | Organizing Committee |
| Erin Bryant, MJ | Science Writer, Office of Neuroscience Communications and Engagement (ONCE), Media Relations Branch, NINDS | Organizing Committee |
| Selen Catania, PhD | Program Officer, Vascular Biology & Hypertension Branch, NHLBI | Organizing Committee |
| Stacey Chambers, MS | Scientific Project Manager, Division of Clinical Research, NINDS | Organizing Committee |
| Thomas Cheever, PhD | Program Director, Division of Neuroscience, NINDS | NIH Session Lead, Frontotemporal Degeneration |
| Sara Dodson, PhD | Senior Science Policy Analyst, Office of Science Policy & Planning, NINDS | Organizing Committee; Committee: Health Equity in AD/ADRD |
| Lawrence Fine, MD, Dr.PH | Chief of the Branch of Clinical Applications and Prevention, NHLBI | Committee: MED |
| Jordan Gladman, PhD | Senior Advisor for Scientific Management and Operations, Office of the Director, NINDS | Organizing Committee |

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| Rebecca Gottesman, MD, PhD | Senior Investigator and Stroke Branch Chief, Intramural Research, NINDS | Committees: Health Equity in AD/ADRD and MED Special Topic (Impact of COVID-19 on AD/ADRD Risk and Outcomes) |
| Stuart Hoffman, PhD | Scientific Program Manager for Brain Health and Injury, Rehabilitation Research and Development Service, Dept. of Veteran Affairs | Committee: MED Special Topic (Post-TBI AD/ADRD) |
| Helen Lamont, PhD | Director, Director of the Division of Disability and Aging Policy, Office of the Assistant Secretary For Planning and Evaluation (ASPE) | Steering Committee, ex-officio; Committee: MED Special Topic (Impact of COVID-19 on AD/ADRD Risk and Outcomes) |
| Erica Littlejohn, PhD | Health Program Specialist, Division of Clinical Research, NINDS | Committee: Health Equity in AD/ADRD |
| Mack Mackiewicz, PhD | Program Director, Neurobiology of Aging and Neurodegeneration Branch, Division of Neuroscience, NIA | Committee: VCID |
| Demali Martin, PhD | Chief of the Population Studies and Genetics Branch, Division of Neuroscience, NIA | Committee: Health Equity in AD/ADRD |
| Eliezer Masliah, MD | Director, Division of Neuroscience, NIA | Steering Committee, ex-officio; Committee: LBD |
| Amber McCartney, PhD | Health Program Specialist, Division of Neuroscience, NINDS | Organizing Committee |
| Linda McGavern, PhD | Program Director, Division of Neuroscience, NINDS | NIH Session Lead, MED and MED Special Topics |
| Barbara McMakin, MS | Chief, Media Relations, Office of Neuroscience Communications & Engagement, NINDS | Organizing Committee |
| Avindra Nath, MD | Senior Investigator, Section of Infections of the Nervous System, Division of Neuroimmunology & Neurovirology; Clinical Director, Division of Intramural Research, NINDS | Committee: MED Special Topic (Impact of COVID-19 on AD/ADRD Risk and Outcomes) |
| Lisa Opanashuk, PhD | Program Director, Division of Neuroscience, NIA | Committee: MED Special Topic (Post-TBI AD/ADRD) |
| Sonja Scholz, MD, PhD | Lasker Clinical Research Scholar, Investigator, Neurogenetics Branch, Division of Intramural Research, NINDS | Committee: LBD |

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| Nina Silverberg, PhD | Director, Alzheimer's Disease Research Centers Program, Division of Neuroscience, NIA | Committee: MED, MED Special Topic (LATE) |
| Andy Singleton, PhD | Director, Center for Alzheimer's and Related Dementias (CARD), NIH | Steering Committee, ex-officio |
| George Sopko, MD, MPH | Program Director and Medical Officer, Division of Cardiovascular Sciences, NHLBI | Committee: MED Special Topic (Post-TBI AD/ADRD) |
| Nsini Umoh, PhD | Program Director, Division of Neuroscience, NINDS | Committee: MED Special Topic (Post-TBI AD/ADRD) |
| Keenan Walker, PhD | Investigator, Laboratory of Behavioral Neuroscience; Director, Multimodal Imaging of Neurodegenerative Disease (MIND) Unit, Division of Intramural Research, NIA | Committee: VCID |
| J. Austin Yang, PhD | Program Director, Division of Neuroscience, NIA | Committee: FTD |

# Appendix 1: List of Past and Current NINDS Funding Opportunity Announcements

*Lists include all AD/ADRD FOAs in alignment with ADRD research milestones since FY2015, including FOAs with awarded grants and no longer accepting applications, as well as active FOAs.*

**Cross-cutting AD/ADRD Topics**

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)

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

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)

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

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

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

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

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 Equity (HE)**

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-22-022: 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)

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-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)**

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)**

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)

**Limbic-predominant age-related TDP-43 encephalopathy (LATE)**

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

**COVID-19 on AD/ADRD Risk and Outcomes**

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

| ADRD Summit 2019 Session 1: Multiple Etiology Dementias (MED) | | |
|---|---|---|
| **MED Focus Area 1: Improving Detection and Diagnostic Skills in the Community** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response[1]** |
| 1(1) Detect whether cognitive impairment is objectively present when a patient, care partner or clinician reports cognitive, behavioral or functional changes. | In-progress | RFA-NS-17-012 created DetectCID<br>RFA-NS-19-030<br>RFA-NS-20-013 created DiverseVCID<br>RFA-NS-22-006<br>RFA-NS-22-009<br>NIH Reporter link to projects |
| 2(3) Improve differential diagnosis of symptomatic cognitive impairment. | In-progress | PAS-17-028<br>RFA-NS-22-009<br>NIH Reporter link to projects |
| **MED Focus Area 2: Advancing Basic and Clinical Research in MED** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 3(1) Advance basic and clinical research on common mechanisms of multi-etiology cognitive impairment and dementia. | In-progress | PAS-17-028<br>PAR-18-661<br>RFA-NS-19-026<br>RFA-NS-19-027<br>RFA-NS-19-030<br>PAR-19-167<br>RFA-NS-20-005<br>PAR-22-029<br>PAR-22-037<br>PAR-22-059<br>NIH Reporter link to projects |

[1] "Response" in this Appendix includes NINDS led Funding Opportunity Announcements (FOAs) and hyperlinks to published FOAs. Additionally, links are provided to online resources with information about large programs funded under these FOAs, as well as a link to an NIH Reporter (https://reporter.nih.gov/) search result that includes a comprehensive list of awards under these FOAs. Cross-cutting ADRD FOAs invite applications to any ADRD and may be relevant to multiple milestones.

| MED Focus Area 3: Increasing the Dementia Capable Workforce | | |
|---|---|---|
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 4(2) Increase education and training of health professionals and researchers focused on cognitive impairment and dementia. | In-progress | PAR-17-072<br>NOT-NS-19-003<br>NOT-NS-20-089<br>NOT-NS-21-047<br>PAR-22-021<br>PAR-22-022<br>NIH Reporter link to projects |
| **MED Focus Area 4: Intervention Studies to Mitigate Reversible Causes of Dementia** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 5(2) Conduct intervention studies to mitigate reversible causes of cognitive dysfunction in persons with or at-risk for cognitive impairment and dementia of aging where etiology may be uncertain or where multiple etiologies appear likely. | In-progress | RFA-NS-19-012 created DISCOVERY<br>NIH Reporter link to projects |
| **MED Focus Area 5: Research to Implement Effective Dementia Care** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 6(3) Bridge the science-practice gap by conducting implementation research with the goal of better and more widespread implementation of proven dementia care programs that effectively support persons with dementia and their caregivers. | In-progress | RFA-NS-17-012 created DetectCID;<br>RFA-NS-22-009<br>NIH Reporter link to projects |

| ADRD Summit 2019 Session 2: Health Disparities (HD) in AD/ADRD | | |
|---|---|---|
| **HD Focus Area 1: Assessment** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 1(1) Generate and/or improve cognitive assessment tools for populations facing AD/ADRD health disparities. | In-progress | RFA-NS-17-012 created DetectCID<br>RFA-NS-19-012 created DISCOVERY<br>RFA-NS-20-013 created DiverseVCID<br>RFA-NS-22-009<br>NIH Reporter link to projects |

| | | |
|---|---|---|
| 2(1) Increase availability and utilization of harmonized culturally- and linguistically valid assessment tools within ongoing and newly generated studies of AD/ADRD and cognitive health intervention trials. | In-progress | RFA-NS-17-012 created DetectCID<br>RFA-NS-19-012 created DISCOVERY<br>RFA-NS-20-013 created DiverseVCID<br>RFA-NS-22-009<br>PAR-22-029<br>NIH Reporter link to projects |
| **HD Focus Area 2: Resolve AD/ADRD Health Disparities by Discovering Culturally Appropriate Pathways to Effective Prevention and Treatments** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 3(2) Test early mechanistic pathways of multiple etiologies that may account for AD/ADRD health disparities and scientifically move forward potential opportunities for precision medicine. | In-progress | RFA-NS-19-012 created DISCOVERY<br>RFA-NS-20-013 created DiverseVCID<br>NOT-NS-21-047<br>RFA-NS-22-009<br>NIH Reporter link to projects |
| 4(2) Implement culturally tailored multimodal intervention trials and drug therapy trials to reduce AD/ADRD burden in populations facing disparities. | In-progress | NOT-NS-21-047<br>RFA-NS-22-009<br>RFA-NS-22-017<br>PAR-22-022<br>NIH Reporter link to projects |
| **HD Focus Area 3: Monitoring Changes in AD/ADRD Disparities** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 5(3) Clarify the epidemiology of health disparities in AD/ADRD prevalence and incidence by documenting and monitoring trends in health disparities in AD/ADRD prevalence and incidence over time. | In-progress | REGARDS (Reporter link)<br>PAR-15-349<br>PAR-15-350<br>RFA-NS-17-012 created DetectCID<br>RFA-NS-19-012<br>NOT-NS-21-047<br>RFA-NS-22-009<br>RFA-NS-22-017<br>PAR-22-022<br>NIH Reporter link to projects |
| 6(3) Increase policy-relevant research on disparities in access to care, awareness and stigma, and costs of care for persons living with AD/ADRD and their families and caregivers. | In-progress | Allofus.nih.gov<br>NOT-NS-21-047<br>RFA-NS-22-009<br>RFA-NS-22-017<br>PAR-22-022<br>NIH Reporter link to projects |

| HD Focus Area 4: A Diverse and Inclusive AD/ADRD Workforce | | |
|---|---|---|
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 7(4) Improve and increase training, including for individuals who are members of under-represented populations, and of different career levels of scholars who conduct health disparities research in AD/ADRD. | In-progress | NOT-NS-21-047<br>PAR-22-022<br>NIH Reporter link to projects |
| 8(4) Leverage ongoing initiatives on the science of inclusion to facilitate community engagement, understanding, recruitment, and long-term retention of populations experiencing AD/ADRD health disparities. | Achieved | NOT-NS-21-047<br>RFA-NS-22-009<br>RFA-NS-22-017<br>PAR-22-022<br>NIH Reporter link to projects |

| ADRD Summit 2019 Session 3: Dementia Nomenclature | | |
|---|---|---|
| **Nomenclature Focus Area 1: Dementia Nomenclature Working Groups** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 1(1) Form research, clinical practice and public stakeholder dementia nomenclature working groups. | Achieved | Dementia Nomenclature Initiative (DeNomI) |
| **Nomenclature Focus Area 2: Integration and Interoperability of Dementia Nomenclature** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 2(1) Integrate and refine recommendations from the Research, Clinical Practice, and Public Stakeholder Working Groups into standardized, acceptable and accurate nomenclature that works across the spectrum of stakeholders. | In-progress | Dementia Nomenclature Initiative (DeNomI) |

| ADRD Summit 2019 Session 4: Lewy Body Dementias (LBD) | | |
|---|---|---|
| **LBD Focus Area 1: Clinical Science** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 1(1) 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. | In-progress | RFA-NS-18-017<br>RFA-NS-19-015<br>PAS-19-210<br>RFA-NS-21-008<br>NOT-NS-21-040<br>NIH Reporter link to projects |

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|---|---|---|
| 2(2) Longitudinal antemortem LBD characterization. | In-progress | PAR-19-170<br>PAS-19-210<br>NOT-NS-21-001<br>RFA-NS-22-001<br>NIH Reporter link to projects |
| 3(3) Neuroimaging characterization of LBD. | In-progress | RFA-NS-19-014<br>RFA-NS-22-001<br>NOT-NS-21-001<br>NIH Reporter link to projects |
| 4(4) Neuropathologic characterization of LBD and use of LBD pathology cohorts. | In-progress | NOT-NS-21-001<br>PAR-22-029<br>NIH Reporter link to projects |
| **LBD Focus Area 2: Basic Science** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 5(1) Biomarker development. | In-progress | RFA-NS-20-014<br>RFA-NS-22-001<br>NIH Reporter link to projects |
| 6(2) Genetic, epigenetic, and environmental characterization. | In-progress | RFA-NS-19-015<br>RFA-NS-21-007<br>NOT-NS-21-037<br>PAR-22-048<br>NIH Reporter link to projects |
| 7(3) Understanding the molecular, cellular and pathophysiology of α-synuclein in the context of non-motor brain areas. | In-progress | PAR-19-167<br>RFA-NS-21-006<br>RFA-NS-21-007<br>PAR-22-029<br>PAR-22-037<br>PAR-22-059<br>NIH Reporter link to projects |
| 8(4) Identify mechanisms by which Lewy body diseases may spread between and affect different brain regions and how Lewy bodies interact with other pathologies. | In-progress | RFA-NS-21-006<br>RFA-NS-21-007<br>PAR-22-029<br>PAR-22-037<br>PAR-22-059<br>NIH Reporter link to projects |

## ADRD Summit 2019 Session 5: Vascular Contributions to Cognitive Impairment and Dementia (VCID)

### VCID Focus Area 1: Basic Mechanisms and Experimental Models

| Milestone # (Priority Level) Milestone Text | 8/2022 Status | Response |
|---|---|---|
| 1(1) Develop next-generation experimental models and translational imaging methods for VCID. | In-progress | RFA-NS-21-005<br>NOT-NS-21-038<br>NOT-NS-21-039<br>PAR-22-023<br>PAR-22-026<br>NIH Reporter link to projects |
| 2(3) Foster basic science research on neurovascular unit function and how it is impacted by the following: aging, cardiovascular disease, AD pathology and genetics. | In-progress | RFA-NS-16-021<br>PAR-18-413<br>NIH Reporter link to projects |
| 3(4) Encourage basic science research to determine the impact of cardiovascular/ cerebrovascular risk factors and genes on dementia-related brain changes, neurodegeneration and myelin biology. | In-progress | RFA-NS-20-013 created DiverseVCID<br>NOT-NS-21-038<br>NOT-NS-21-039<br>PAR-22-023<br>PAR-22-029<br>PAR-22-037<br>NIH Reporter link to projects |

### VCID Focus Area 2: Human-Based Studies

| Milestone # (Priority Level) Milestone Text | 8/2022 Status | Response |
|---|---|---|
| 4(1) Develop, validate and longitudinally track: (i) cognitive, physical, or other functional assessment components that indicate the presence of VCID, (ii) VCID biomarkers, including when VCID is accompanied by pathological AD. | In-progress | RFA-NS-16-020 & RFA-NS-16-019, MarkVCID<br>RFA-NS-21-004, RFA-NS-21-005, & RFA-NS-22-017, MarkVCID2<br>NOT-NS-21-038<br>NIH Reporter link to projects |
| 5(2) Test for efficacy across the spectrum of VCID severity: (i) interventions proven to reduce cardio- and cerebrovascular risk, (ii) established care models. | In-progress | RFA-NS-20-012<br>NOT-NS-21-038 |

| | | |
|---|---|---|
| 6(4) Determine interrelationships among cerebro- and cardiovascular disease, VCID risk factors, aging, resilience, genetics, amyloid, tau, and neurodegeneration including along the life course. | In-progress | RFA-NS-17-012 created DetectCID<br>RFA-NS-21-004, RFA-NS-21-005, & RFA-NS-22-017, MarkVCID2<br>NOT-NS-21-038<br>RFA-NS-22-006<br>PAR-22-026<br>PAR-22-048<br>NIH Reporter link to projects |
| **VCID Focus Area 3: Translational Studies** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 7(2) Use data and other resources from large-scale clinical research and trials to test hypothesized mechanisms of human VCID in basic science models. | In-progress | PAR-19-167<br>RFA-NS-22-006<br>NIH Reporter link to projects |
| 8(3) Incorporate VCID findings from basic science into the design of clinical research and trials targeting VCID-relevant cognitive impairment and dementia. | In-progress | RFA-NS-16-020 & RFA-NS-16-019 MarkVCID<br>RFA-NS-20-012<br>RFA-NS-21-004, RFA-NS-21-005, & RFA-NS-22-017 MarkVCID2<br>NIH Reporter link to projects |

| **ADRD Summit 2019 Session 6: Frontotemporal Lobar Degeneration (FTD)** | | |
|---|---|---|
| **FTD Focus Area 1: Science of Pathogenesis and Toxicity** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 1(1) Clarify unique and converging cellular mechanisms related to tau pathogenesis, C9orf72 hexanucleotide repeat expansions, GRN mutations, and other targets and pathways contributing to FTD neurodegeneration. | In-progress | RFA-NS-18-015<br>RFA-NS-21-003<br>RFA-NS-21-006<br>RFA-NS-21-007<br>PAR-22-023<br>NIH Reporter link to projects |
| 2(2) Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity. | In-progress | RFA-NS-18-015<br>RFA-NS-20-005<br>RFA-NS-21-003<br>RFA-NS-21-006<br>RFA-NS-21-007<br>PAR-22-059<br>NIH Reporter link to projects |

| | | |
|---|---|---|
| 3(3) Develop data and resource infrastructures to support management and collaborative analysis of diverse clinical, imaging, genetic, molecular, and biomarker data and resources from FTD basic science and clinical studies. | Achieved | National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD); Biospecimen Exchange for Neurological Disorders (BioSEND) (Reporter link)<br>RFA-NS-22-006<br>NIH Reporter link to projects |
| 4(4) Develop better FTD *in vivo* and cell-based model systems. | In-progress | RFA-NS-19-027<br>PAR-19-167<br>NOT-NS-21-041<br>RFA-NS-21-003<br>RFA-NS-21-007<br>NIH Reporter link to projects |
| **FTD Focus Area 2: Clinical Science** | | |
| **Milestone # (Priority Level) Milestone Text** | **8/2022 Status** | **Response** |
| 5(1) Develop FTD biomarkers for diagnosis, prediction, and disease monitoring. | In-progress | PAR-18-661<br>RFA-NS-19-014<br>RFA-NS-21-003<br>RFA-NS-22-006<br>NIH Reporter link to projects |
| 6(2) Advance FTD clinical trial design and execute new prevention and treatment studies. | In-progress | ALLFTD (Reporter link) |
| 7(3) Expand efforts to genotype patients with FTD, identify new risk factor genes and epigenetic modifiers. | In-progress | RFA-NS-17-017<br>RFA-NS-21-003<br>PAR-22-029<br>NIH Reporter link to projects |
| 8(4) Understand phenotypic heterogeneity and natural history including in populations that experience health disparities. | Achieved | NINDS Human Cell and Data Repository (NHCDR) (Reporter link)<br>ALLFTD (Reporter link)<br>ARTFL-LEFFTDS |

## ADRD Summit 2019 Session 7: Emerging Scientific Topics

### Focus Area 1: TDP-43 Pathology in Common Dementias

| Milestone # (Priority Level) Milestone Text | 8/2022 Status | Response |
|---|---|---|
| 1(1) Develop biomarker and risk profiles to establish in-vivo diagnostic criteria for TDP-43 pathology in persons without cognitive symptoms and in persons with amnestic syndromes, e.g. amnestic MCI and AD clinical syndrome. | In-progress | RFA-NS-19-014 created Center without Walls for Imaging Proteinopathies with PET (CW2IP2)<br>NIH Reporter link to projects |
| 2(2) Determine underlying pathobiologic and molecular mechanisms of cellular TDP-43 displacement, post-translational modifications such as phosphorylation, and pathology in pre-symptomatic and manifest common dementias. | In-progress | RFA-NS-20-005<br>RFA-NS-21-003<br>NIH Reporter link to projects |
| 3(3) Examine the pathologic phenotype(s) of TDP-43 pathology in asymptomatic persons and those with common dementias. | In-progress | RFA-NS-20-005<br>PAR-22-029<br>NIH Reporter link to projects |
| 4(4) Build new animal models to advance knowledge about TDP-43 pathology in common dementias, capitalizing on lessons learned from animal models in FTLD/ALS, AD and other diseases. | In-progress | PAR-19-167<br>RFA-NS-20-005<br>RFA-NS-21-003<br>NIH Reporter link to projects |

### Focus Area 2: TBI and AD/ADRD Risk

| Milestone # (Priority Level) Milestone Text | 8/2022 Status | Response |
|---|---|---|
| 5(1) Encourage crosstalk and interdisciplinary collaboration between TBI and dementia researchers. | In-progress | RFA-NS-19-026<br>RFA-NS-19-030<br>PAR-22-024<br>NOT-NS-22-002<br>NIH Reporter link to projects |
| 6(2) Establish infrastructure to study TBI as a risk factor for AD/ADRD. | In-progress | RFA-NS-19-030<br>NOT-NS-22-002<br>PAR-22-024<br>NIH Reporter link to projects |
| 7(3) Promote basic and clinical research examining the development and progression of TBI AD/ADRD neuropathologies and associated clinical symptoms. | In-progress | RFA-NS-19-030<br>NOT-NS-22-002<br>PAR-22-024<br>NIH Reporter link to projects |
| 8(4) Characterize the clinical phenotype of progressive dementia associated with TBI and develop non-invasive diagnostic approaches. | In-progress | RFA-NS-19-026<br>NIH Reporter link to projects |