ALZHEIMER'S DISEASE-RELATED DEMENTIAS
SUMMIT 2019

MARCH 14-15
2019

ADRD Summit 2019 Report to the National Advisory Neurological Disorders and Stroke Council

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Abstract. This document reports to the NINDS Council the results of the Alzheimer's Disease-Related Dementias (ADRD) Summit 2019, held in Natcher Auditorium on the NIH campus. The March 14-15, 2019 event complements the National Institute on Aging's (NIA) Alzheimer's Disease (AD) 2012, 2015, and 2018 Research Summits, as well as the 2017 Dementia Care Summit, and follows the ADRD Conference 2013 and the ADRD Summit 2016 held by NINDS in collaboration with NIA. These triennial conferences (the AD, ADRD, and Care Summits) are coordinated planning efforts that respond to the National Plan to Address Alzheimer's Disease ("National Plan"), first released in 2012 and now updated annually. The conferences set national research recommendations with timelines that reflect critical scientific priorities for research on AD and ADRD (AD/ADRD). As for the previous summits, the ADRD Summit 2019 steering committee solicited input from nationally and internationally recognized dementia-science experts, as well as from public and private stakeholders, to update and further develop prioritized recommendations to guide ADRD research for the next several years. The report, if approved by the NINDS 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 2019 recommendations in the next annual update of the National Plan, thus refining, revising, and adding to the previously included ADRD 2016 recommendations. The research recommendations reported herein will help guide 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 conveys substantial health and financial costs, affecting about 50 million people worldwide. Alzheimer's disease alone, as one dementia disorder, affects 5.8 million people in the 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) and signed into law in 2011, plans, coordinates, and integrates federal and non-federal (private and state-level) activities to overcome AD and ADRD including through research, clinical care, and long-term services and support. Among the goals of the National Plan, perhaps the most ambitious is Goal 1, a research goal to prevent and effectively treat AD/ADRD by 2025. The Plan also includes several specific strategies to accelerate our pace towards this goal – one strategy is to review the latest science and identify and update 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 National Plan. These 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 Summit 2016 established initial, detailed ADRD-specific research priorities in the National Plan, including those related to dementia health disparities (HD). As follow-up to the ADRD Conference 2013 and the ADRD Summit 2016, NINDS held the third ADRD Summit, the subject of this report to Council, on March 14-15, 2019.

The clinical syndrome of AD, which typically includes characteristic AD brain pathology, i.e. beta-amyloid (plaques) and tau (tangles), is the most frequently assigned dementia diagnosis and accounts for about two-thirds of dementia cases in the United States. Though plaques and tangles are the most common brain pathologies observed in individuals with dementia, other brain pathologies also co-occur with cognitive decline and dementia in neurodegenerative diseases, including in more than half of individuals with clinically diagnosed AD. Several pathologies, e.g., tau, beta-amyloid, alpha-synuclein, TDP-43 and cerebrovascular-related injury, occur or are thought to occur in all (beta-amyloid plaques and tau tangles) or in a subset of clinical AD cases, and these pathologies also contribute via other diagnoses to the overall burden of dementia. Therefore, there is a clear need for deeper understanding of disease mechanisms that affect cognition across diagnoses that span the dementia spectrum (**Figure 1**).

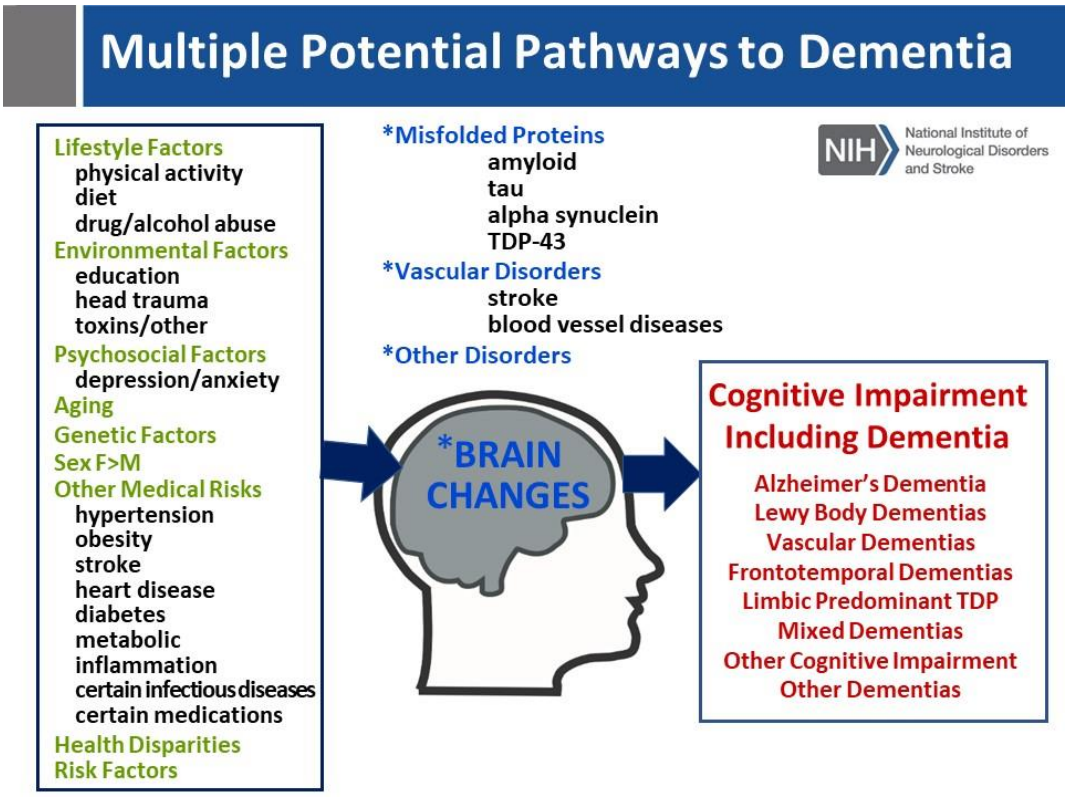

Figure 1. There are multiple risk factors and pathways to brain pathologies and ultimately to clinical diagnoses of cognitive impairment of dementia. These include lifestyle factors, environmental factors, psychosocial factors, aging, genetic factors, sex, other medical factors including hypertension, metabolic disorders, and immune factors, and risk factors associated with health disparities. Figure by Julie Schneider, MD, MS, Rush University, and Roderick A. Corriveau, PhD, NINDS.

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 degeneration (FTD), Lewy body dementias (LBD), vascular contributions to cognitive impairment and dementia (VCID) and multiple etiology (sometimes referred to as mixed) dementias. 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, therapeutic approaches that leverage these advances to stop, delay, or even reverse disease pathogenesis and dementia burden.

The ADRD Summits, together with NIA's AD and Dementia Care Summits, are pivotal components of NIH's NAPA responsiveness. These planning efforts and the resulting recommendations and milestones are used to develop the annual NIH AD/ADRD bypass budget proposal. 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 initiatives needed to prevent and effectively treat AD/ADRD by 2025. The annual AD/ADRD bypass budgets are directly transmitted to the President and subsequently to Congress without modification through the normal federal budget process. Recognizing the necessity of addressing AD/ADRD aggressively as the nation ages, there has been an approximately four-fold increase in NIH funding for AD/ADRD research since 2011. This is due in

significant part 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 for implementing research priorities identified by NIH-led AD/ADRD planning efforts. NINDS has pursued ADRD research priorities set in 2013 and 2016 by funding ADRD-relevant investigator-initiated research grants within the NINDS payline, and outside the payline through a high program priority process, as well as by launching new funding opportunities as outlined in the **Session Highlights** section below (page 6). Please see **Appendix 1** for the NIH ADRD research funding opportunities that have been created since ADRD 2015 based on the ADRD Research Milestones (Appendix 1, List of Funding Opportunity Announcements on pages 49-51).

The goals of the ADRD Summit 2019 were to review and assess progress on the research recommendations developed by the ADRD 2013 and 2016 Summits, to refine and add new recommendations based on recent scientific discoveries, to solicit input from stakeholders, and to 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 2019 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 2013 and 2019, the ADRD Summit 2016 addressed, via dedicated sessions, special research priorities for FTD, LBD, VCID, and mixed dementias, and continued to prioritize and develop recommendations for health disparities in AD/ADRD research. In 2019, at the suggestion of the Scientific Chair, NINDS also included an emerging topics session that covered the science of TDP-43 neuropathology and traumatic brain injuries (TBI) as contributors to common clinical cognitive impairment and dementia diagnoses along the spectrum of AD/ADRD syndromes.

Planning and execution of the ADRD Summit 2019 followed the successful strategy developed for the 2013 ADRD Conference. Activities included pre-summit, summit, and post-summit teleconference 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 2019 Prioritized Recommendations**, page 13-42). A brief outline of major activities in advance preparation, the Summit itself, and follow-up, appears below.

Advance Preparation for 2019 Summit. Pre-summit efforts began in late summer 2018, when NINDS and NIA leadership and staff convened with the ADRD Summit 2019 Scientific Chair to develop an overall strategy. Areas of focus included defining topic areas corresponding to the seven summit sessions and selecting scientific chairs for each session. The session chairs, together with NIH session leads, then formed committees by selecting a roster of experts for each topic area. Committees thus consisted of 7 to 19 scientific members (**Table 1; page 42**) tasked with assessing progress on the 2016 ADRD research recommendations (Corriveau et al., 2017; ADRD Summit 2016), as well as with updating, refining, adding to and prioritizing draft recommendations for formal consideration by the NINDS and NAPA Councils, respectively. Each committee met several times via teleconference between October 2018 and March 2019. NIH staff provided the committees with responses to a joint NINDS/NIA RFI that solicited public input on updating the ADRD research priorities, as well as an analysis of progress made on the 2016 ADRD milestones (**Appendix 2 ADRD Milestone Progress and Implementation** on pages 52-58). Cross-committee coordination occurred through a monthly teleconference of the Summit Organizing Committee consisting of: session committee scientific chairs (as listed in **Table 1 on page 42**); the Summit Scientific Chair (Dr. Julie Schneider); NIH and other federal officials (**Table 2; page 47**), including NINDS/NIH Summit lead Dr. Roderick Corriveau; and the Steering Committee (Dr. Corriveau, Dr. Walter Koroshetz, Dr. Eliezer Masliah from NIA; Dr. Laura Gitlin, Chair of the NAPA Council; Dr. Tom Montine, 2013 ADRD Scientific Chair; Dr. David Holtzman, 2016 ADRD Summit Scientific Chair; and NINDS Council

member Ms. Susan Dickinson). Dr. Aaron Gitler, also a member of the NINDS Council, served on emerging scientific topics committee.

As in 2013 and 2016, the highest priorities have been designated #1 by the session committees (see full recommendations below, page 13-42). Each session committee had the option of proposing up to eight recommendations, designating up to two #1, #2, #3, and #4 recommendations in different focus areas. As for previous ADRD summits, each committee estimated the number of years needed to complete or fully implement each recommendation.

As a result of this preparatory work, the ADRD Summit 2019 agenda and draft recommendations were posted online before the Summit, distributed to meeting registrants as hard copies, and presented at the Summit to gather input from all stakeholders present in person or via webcast.

Summit. The ADRD Summit 2019 was advertised broadly to the scientific community, government agencies, and NGOs, resulting in 810 registrants. Of these, 481 individuals joined in person and there were more than 1,200 additional views online during the conference, and 791 views to date after the Summit concluded. As with the 2016 ADRD Conference (Day 1 and Day 2), the primary goal of the 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. Following a general overview, each session's chairs presented a summary of scientific progress that had occurred since 2016 and then proposed updated and refined research recommendations for public input. The Emerging Topics session, which was new in 2019, presented draft recommendations for TDP-43 neuropathology in common dementias and for TBI as a risk factor for common dementias. Each of the seven topic sessions included ample time for discussion and exchange with attendees. The public portion of the Summit concluded March 15 with a review of all suggested additions and revisions and further opportunity for input from all participants. Directly after the summit proceedings, NINDS led a closed executive session during which session chairs, NIH and other federal officials, Steering Committee members, and the Scientific Chair reviewed the proposed revisions, edited the draft recommendations as agreed upon by the Executive Committee, and assigned duties to complete the work.

Post-Summit Follow-Up. Post-summit efforts included a Steering Committee teleconference and several meetings among the session committees to further refine ADRD research recommendations content, prioritization, and proposed timelines and timeframes. These activities resulted in the ADRD Summit 2019 Prioritized Recommendations that we submit for approval in this Report. Upon acceptance by the National Advisory Neurological Disorders and Stroke Council and the NAPA Council, the research recommendations become ADRD milestones that will be included as part of the National Plan and inform the development of future AD/ADRD bypass budgets and new AD/ADRD funding opportunities at NIH.

Organizing Participants and Sponsorship. Full membership of the ADRD Summit 2019 session committees appears in **Tables 1** and **2**. NIA participation complemented NINDS' efforts through the efforts of Dr. Richard Hodes, Dr. Eliezer Masliah, and Dr. Cerise Elliot from the NIA, as well as Dr. Jue Chen from the NHLBI. Additional Summit sponsors included the NIH Office of Disease Prevention, the Foundation for the National Institutes of Health with support from their contributors: Alzheimer's Association; GHR Foundation; Biogen; Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) Coalition; Alzheimer's Drug Discovery Foundation; American Stroke Association, a division of the American Heart Association; CurePSP; EIP Pharma; The John A. Hartford Foundation; and the WellMed Charitable Foundation.

Session Highlights. At the summit the seven topic area sessions each included a brief introduction followed by presentations of the draft recommendations, their rationale, and finally public input during open microphone discussions. Sessions also included an overview of progress made since 2016 that informed the 2019 draft recommendations, and/or perspectives from the research community, healthcare providers, and people affected by AD/ADRD. Below are session highlights of the key takeaways from recommendations, on-going efforts in the recommended areas, and discussions that took place during the open mic time. Note that the format of the 48 2019 prioritized research recommendations (page 13-42) is not uniform across all seven topic areas: this was a deliberate decision intended to enable flexibility of optimal prioritization within each topic area. Timelines, however, reflect time to completion or to achieve fully operational status for the recommendation after work is initiated.

As was the case with the 2013 ADRD Conference and the 2016 ADRD Summit proceedings, all recommendations in this report represent very important research goals. Each topic committee was required to assign rank priorities starting at #1. However, for a research recommendation to be included in this report, it must be among the top priorities in its respective field. In addition, timelines do not in any way reflect prioritization, but rather serve to guide planning and implementation logistics. Finally, ordering of sessions in no way reflects prioritization – all sessions (MED, HD, LBD, FTLD, VCID, Emerging Topics, and Nomenclature) are of equally high priority.

Topic 1: Multiple Etiology Dementias (MED) (Chairs: David Knopman, MD; Kate Possin, PhD)

Based on the recommendations from ADRD 2016, NIH established in 2017 a national Consortium for Detecting Cognitive Impairment, Including Dementia (DetectCID), which consists of three teams across the U.S. that are developing and validating easy-to-use cognitive impairment detection tools for use in primary care settings. There have also been several NIH funding opportunities to dissect and investigate common mechanisms of AD/ADRD and to develop novel cell and animal models to enable further studies on the topic (e.g., PAS-17-028, RFA-NS-19-027, PAR-19-167, etc.)

In 2019, the top priorities for MED remain the same as in 2016: increasing accurate detection of cognitive impairment through development of better tools and effective clinical pathways from detection to referral to confirmed diagnosis; and advancing basic and clinical research on common mechanisms of multi-etiology cognitive impairment and dementia. For increasing accurate and early detection, there was a suggestion to focus more efforts on even earlier, preclinical diagnosis during prodromal phase or prior to complaints, but it was recognized that this would be an area to improve only after further progress has first been made on increasing detection and follow-up of individuals that can be clinically diagnosed. The MED Committee also noted that the recommendation is not to perform screening of patients but to detect impairment only when there is a concern voiced by a patient, care partner (e.g. family member), clinician, or other caregiver – these detection tools might include self-administered assessments and tests in various settings (e.g., home, every day clinical settings, online, etc.) for diverse populations.

Feedback received through the Request for Information (RFI) and the MED Session open microphone time emphasized a need to better understand the role of other diseases such as Parkinson's, ALS, prion diseases and how these intersect with AD/ADRD, in addition to improving our understanding of common mechanisms of MED. To build a stronger foundation for achieving these priorities, we also need better education of health professionals and training of researchers, including increasing dementia capable workforce, which was another one of the MED recommendations. A recommendation from ADRD 2016 to determine benefits of cognitive screening was eliminated, but two new areas were added in 2019. One focused on dementia care and the other focused on intervention studies to mitigate reversible

causes of cognitive dysfunction in individuals with or at-risk for cognitive impairment and dementia with uncertain etiology or multiple etiologies.

Topic 2: Health Disparities in AD/ADRD (HD) (Chairs: Lisa Barnes, PhD; Hector González, PhD)

In alignment with one of the top priorities for MED, assessment arose to the top as a major priority area for HD in 2019. This highlighted the importance of generating and/or improving cognitive assessment tools for populations facing AD/ADRD health disparities and increasing the availability and use of assessment tools that are harmonized and culturally- and linguistically valid in on-going or new AD/ADRD clinical studies, both of which is what the NIH-supported DetectCID Consortium is currently aiming to accomplish. Another important area of focus for HD that remained as a second top priority in 2019 was identification and/or clarification of social, environmental, and biological mechanisms that may explain some of the disparities observed in AD/ADRD. Following the 2016 recommendation, a long-standing NINDS cohort study, the REasons for Geographic And Racial Differences in Stroke (REGARDS) includes a component since 2018 to not only measure stroke risk but also cerebro-/cardiovascular risk factors linked to cognitive impairment during follow-up of black and white study participants living within and outside the stroke belt in the U.S. The HD Committee also recommended in parallel there be culturally tailored multi-modal intervention trials to test lifestyle changes, vascular risk factor control, and drug therapies in AD/ADRD health disparities population.

During the open mic discussion, there was a suggestion to do more investigation of very early life factors, such as prenatal conditions, and their role in AD/ADRD since prematurity tends to be more common among underrepresented or disadvantaged populations. A researcher in the audience suggested using admixture to identify ethnic/racial groups. However, it remains unclear when it is scientifically optimal to use genetic admixture, self-identified race/ethnicity, or both, especially when people's self-identification methods vary widely.

The HD Committee recognized some of the progress and on-going efforts since 2016, including a number of AD/ADRD health disparities-focused research projects supported through funding opportunities (e.g., PAR-15-349), establishment of the NIA Health Disparities framework, and publication of the National Strategy for Recruitment and Participation in Alzheimer's and Related Dementias Clinical Research. Thus, the HD Committee build upon this progress by augmenting the ADRD Summit 2016 focus area on community partnerships, recruitment, and retention with a new set of recommendations that focus on nurturing a competent and relevant AD/ADRD health disparities research workforce that is diverse and inclusive. Strategies suggested by the audience included helping women researchers navigate childcare, encouraging and supporting diverse researchers to mentor and serve as role models for emerging AD/ADRD investigators, and encouraging and training more health disparities experts to participate in scientific review panels.

Topic 3: Dementia Nomenclature (Chairs: Ronald Petersen, MD, PhD; Angela Taylor, BMus)

Dementia nomenclature emerged as a priority from both MED and NGO Sessions in 2016. It was recommended that a Nomenclature Working Group be established to come up with a standardized and interoperable set of terms that would address the current challenges that arise from lack of harmonization of dementia terminology used by various communities, including researchers, healthcare providers, government agencies, policymakers, stakeholders, and the public, including individuals and families affected by dementia. Implementing this recommendation in 2018, a nomenclature working group of academic researchers was approved and formed by the NAPA Council. All members of this

group and a few additional members were invited to be on the ADRD 2019 Dementia Nomenclature Session Committee to represent diverse perspectives and provide expertise.

The 2019 Session further delineated how using confounding and inconsistent terms within and across communities become obstacles to advancing dementia research and care, improving public awareness, and reducing stigma associated with dementia. The main challenge for researchers was in lack of clear distinction between disease etiology vs. clinical syndromes. Once the research terms are standardized, ideal terms for use in clinical practice may be determined to convey the diagnosis that would not only provide access to appropriate care and services but also minimize stigma and distress without losing scientific accuracy. Personal experiences shared by a former ADRD caregiver and by an individual living with Alzheimer's disease during the session allowed the Summit participants to hear these important voices often unheard at scientific conferences, and it became clear that the process for determining the recommended nomenclature and the nomenclature itself should be inclusive of all cultures, ages, and different perspectives.

The two prioritized recommendations from ADRD 2019 lay out the next steps for establishing the structure/process through which to gather input from different stakeholders: 1) form, in a staggered manner, three nomenclature workgroups that cross-talk (Research, Clinical Practice, and Public Stakeholders Workgroups), and 2) hold a symposium to integrate and refine recommendations from these three workgroups into standardized, acceptable and accurate nomenclature that works across the spectrum of stakeholders. These were generally well-received with some suggestions to help anticipate the potential societal, behavioral, and cultural changes that may come from the implementation of new terminology, and to have a plan to measure the impact.

Topic 4: Lewy Body Dementias (LBD) (Chairs: Bradley Boeve, MD; Carol Lippa, MD)

As "one of the most common disorders most people have never heard of," LBD includes Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). Since 2016, there has been some progress in improving our knowledge of the genetic profile of LBD and establishing clinical trials and longitudinal cohorts, which was one of the top recommendations in 2016. In the private sector, currently multiple pharmaceutical companies are involved in LBD trials, and the Lewy Body Dementia Association (LBDA) also established in 2017 a clinical trial-ready LBD research network called the Research Centers of Excellence (RCOE). A few small companies in the audience at ADRD 2019 shared their perspective and commented that the ability to connect with resources is critical to starting a clinical trial, and another researcher emphasized a need for clinical trials that also include participants with prodromal LBD.

In 2019, there weren't any major changes to the previous LBD recommendations that came out of ADRD 2016. Many of the priorities remain the same, but the recommendations in 2019 have been reformatted into two big focus areas: clinical science and basic science. Many of the recommendations focus on better characterization of LBD and biomarker development through more longitudinal clinical, neuropsychology, imaging, and pathological studies. Most experts seemed to agree in 2016 and again in 2019 that there is no reliable, in vivo diagnostic biomarker for differential diagnosis of LBD or tracking of disease progression. To facilitate efforts towards advancing discovery, development, and validation of biomarkers (both imaging- and fluid-based), NIH has created a LBD biomarker development program in 2016 that is supporting 7 active projects and also leverages other existing data and biospecimens from other NIH-supported programs. Additionally, in alignment with one of the MED recommendations, one of the LBD basic science recommendations was to further investigate how Lewy bodies interact with other pathologies, which is another area that NIH is hoping to stimulate through the LBD Center without Walls program that NIH is planning to create this year.

Topic 5: Vascular contributions to Cognitive Impairment and Dementia (VCID) (Chairs: Donna Wilcock, PhD; Jeff Williamson, MD, MHS)

Since ADRD 2016, the VCID field has seen progress both on the basic and clinical side. Implementing the recommendations that came out of the Summit in 2016, NIH has been stimulating further research to better understand diffuse white matter disease mechanisms in VCID, and established a national VCID Biomarkers Consortium (MarkVCID) that consists of 6 biomarker development sites and a coordinating center with a goal to develop and validate clinical trial-ready VCID biomarkers. Recently, NIH also released a funding opportunity to study post-stroke populations in the US to determine which specific subsets of stroke events and other clinical factors in combination with stroke cause or not cause cognitive impairment/dementia. Early in 2019, the SPRINT-MIND study showed findings that indicated that aggressive control of blood pressure leads to reduction of mild cognitive impairment risk, while there was not a significant decrease in dementia risk. However, the results warrant further opportunities to build upon these findings. To that end, extended follow-up of the study supported by the Alzheimer's Association is on-going.

Top priorities in VCID research remain the same with more refined recommendations in 2019: development of next-generation experimental models and translational imaging methods for VCID and development and validation of VCID biomarkers. There was much discussion about a need to work collaboratively and creatively in the research community to study cardiovascular risk factors or resilience factors and their link to cognitive impairment/dementia across the life span, potentially through adding and improving measurements within existing cohort studies, including birth cohorts as well as cohorts with older participants. More careful consideration of age and sex of the animals used in basic and clinical research would be needed to better study these life course factors in animal studies as well. There also was a suggestion to develop better methods to further investigate perivascular drainage and the glymphatic system (**Figure 2**) and to improve experimental models to clarify the role of chronic low-level inflammatory factors and determine what the minimum level of inflammation is that triggers the ischemic cascade. In addition to two focus areas on basic mechanisms/experimental models and human-based studies, the VCID Session Committee added a new focus area on translational studies with two recommendations new in 2019 to leverage data and resources from human clinical studies/trials to test mechanisms of human VCID and to use basic VCID research findings in clinical trial design.

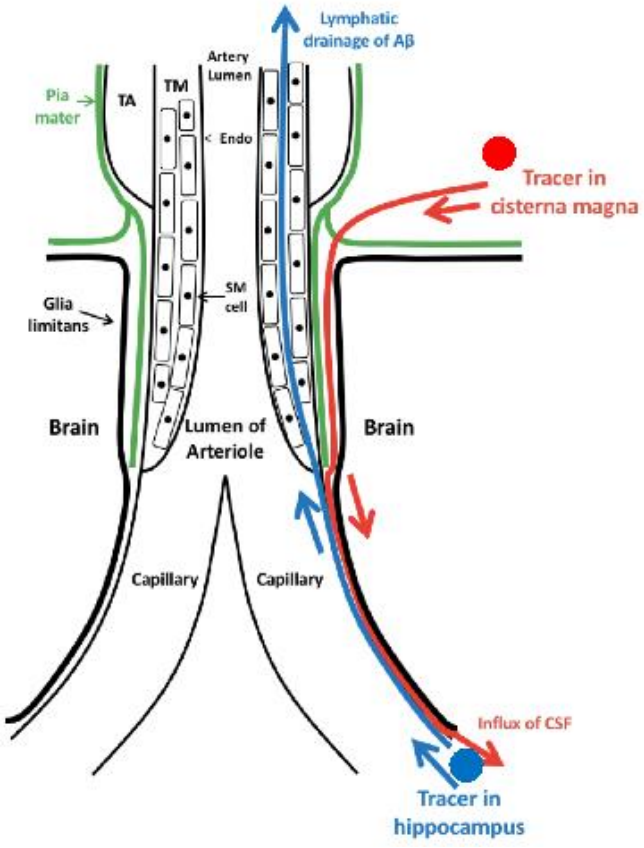

Figure 2. Model proposed at the Summit for paravascular/convective influx/glymphatic flow of CSF (from lateral ventricles, for example, into the parenchyma, and back out) and intramural periarterial(IPAD)/perivascular lymphatic flow (upward arrows from the parenchyma to lymphatic system)(Figure by Dr. Roxana Carare).

Topic 6: Frontotemporal Lobar Degeneration (FTLD) (Chairs: Adam Boxer, MD, PhD Leonard Petrucelli, PhD)

The FTLD Session in 2016 allowed us to appreciate the impressive pace of progress in the field and the revolution that has taken place since the discovery of repeat expansions in the *C9orf72* gene as a frequent cause of ALS and FTD in 2012. In 2019, the FTLD Session committee reprioritized the previous recommendations based on the recent progress and added a new recommendation to develop a cloud-based data infrastructure that would support management and analysis of data from FTD studies. The infrastructure should also provide the tools and computing power to support collaborative research through data integration and analysis across complex data modalities.

A top priority for basic science in FTLD remains the same in 2019: to clarify and explore cellular mechanisms related to tau pathogenesis, *C9orf72* expansion, and *GRN* mutations and other pathways. In alignment with this recommendation, NIH created the Tau Center without Walls (Tau CWOW) in 2016 that aims to identify genes and pathways that modulate tau toxicity in FTD and link tau proteostasis with neuronal activity in FTD. Overall, researchers are making great strides in elucidating FTD mechanisms at molecular and cellular levels by using cutting edge technologies such as Cryo-EM for integrative structural biology studies and iPSC technology to develop new FTLD models. Advanced single cell analyses combined with OMICS technology will help answer questions such as "how does each cell change its expression patterns in the context of health and disease, including different dementias?" As for clinical science, a recommendation to accelerate biomarker development became a top priority in 2019. Many in the FTD field seemed to agree that with the imminence of disease-modifying therapies, urgently needed are biomarkers for FTLD clinical trials that are under way. Many of these clinical trials test gene therapies, which is an area with much potential as therapies using antisense oligonucleotides have recently been successful in other rare diseases. Therefore, the FTLD Session Committee also recommends expanding efforts to genotype patients with FTD and identify new risk factor genes. The NIH-supported FTD Sequencing Consortium was established with this recommendation in mind, and on-going natural history studies such as ARTFL/LEFFTDS can help discover new genes and risk factors as well as diagnostic and predictive biomarkers.

During the open mic time, patient outreach, communication, and education was identified as a gap. There were suggestions to include more minority populations in FTLD clinical studies, for instance through FTD disorders registry, and to use the registry as a platform to encourage more collaboration where researchers could partner with the registry or with other researchers. A few caregivers in the audience shared their perspectives as well, mentioning the difficulties that patients, caregivers, and families face in study participation, especially due to unique challenges that come with FTD (e.g., rapid progression, rare disease, heterogeneity of symptoms across the spectrum). Since many studies often recruit asymptomatic individuals at risk, we must improve strategies to accommodate the needs of these potential participants, including family members who may want to participate but may not want to find out their genetic status.

Topic 7: Emerging Scientific Topics

As a new session to discuss emerging topics in AD/ADRD, the Emerging Topics Session featured two research areas that are frequently associated with AD/ADRD: TDP-43 and traumatic brain injuries.

Topic 7a: TDP-43 in Common Dementias (Chair: Julie Schneider, DM, 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 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. The rate of cognitive decline in people with hippocampal sclerosis is much faster with the presence of TDP-43 aggregates, suggesting that TDP-43 is deleterious. During this Session, a new term for a disease was introduced by the TDP-43 Session co-chairs: Limbic predominant Age-related TDP-43 Encephalopathy (LATE). While "LATE" can be a mimic of clinical Alzheimer's disease, there is emerging evidence that LATE can occur together with or as a separate entity from clinical Alzheimer's, and that it is linked to hippocampal sclerosis. There was significant enthusiasm from researchers in the audience about studying the role of TDP-43 in common dementias.

The top priority for studying TDP-43 pathology in common dementias was to develop biomarkers/risk profiles to establish *in vivo* diagnostic criteria for TDP-43 pathology in persons with or without cognitive symptoms. Challenges for developing an *in vivo* diagnostic biomarker for TDP-43 will be similar to the ones that the dementia research community has experienced for alpha-synuclein and therefore may require the use of other modalities such as structural MRI. Other recommendations focused on studies of disease mechanisms and pathology, and development of new animal models that accurately capture the various aspects of TDP-43 pathology seen in humans.

We now know that many different pathologies, including not only amyloid and tau but also cerebrovascular disease, Lewy bodies, hippocampal sclerosis, and TDP-43 contribute to dementia syndromes. Within the newly recognized significance of TDP-43 pathology lies opportunities to establish standard autopsy diagnosis, optimize neuropathologic methods, enable a new common language, increase public awareness, and catalyze further research.

Topic 7b: Traumatic Brain Injuries (TBI) and AD/ADRD Risk (Chair: Kristen Dams-O'Connor, PhD)

TBI symptoms often overlap with many dementias, and studies that suggest a link between TBI and dementia show associations with all AD/ADRD, not just AD. However, there are limitations with available data. In addition, as is the case for dementia prevalence, the prevalence of TBI based on electronic health records may be under-reported and is difficult to estimate. While additional research is needed, population-based sample research reports are consistent with as many as 10 million people in the U.S. living with some type of TBI-related disability. Some challenges in studying the link between TBI and dementia also include: misclassification that occurs depending how the question is asked in a survey; whether stable TBI-related impairment is confused for neurodegenerative decline; and selection bias due to the high rate of TBI in prisons, homeless shelters and other populations not recruited in the clinic. In addition, many cohort studies have only studied 1-year post injury, so more follow-up of chronic outcomes is needed.

The top two priorities in TBI and AD/ADRD risk were to 1) encourage cross-talk and interdisciplinary collaboration between TBI and dementia researchers, and 2) establish infrastructure to study TBI as a risk factor for AD/ADRD. There are on-going efforts supported by NIH to leverage existing networks to investigate TBI and AD/ADRD risk. One of the main research questions that could be addressed through the infrastructure is how TBI might initiate or exacerbate neurodegeneration that leads to AD/ADRD. Pathological studies clearly show that brains from individuals with TBI often show multiple histological

phenotypes, such as presence of amyloid plaques, microglial activation and other neuroinflammatory markers, along with diffuse axonal injury which is a hallmark of TBI. Identifying mechanisms that explain TBI's contributions to AD/ADRD may help prevent or delay the onset of dementia. During open discussion, participants talked about the role of subclinical concussions, and repetitive head trauma, and neuroinflammation in AD/ADRD. This revealed a knowledge gap in how the "dose" of exposure to brain injury plays a role, and more longitudinal and pathological studies are needed to fill this gap. There also were comments about a need to develop causal inference models as studies need to incorporate many other risk factors, including long-term effects of Post-Traumatic Stress Disorder (PTSD) that often is co-morbid with TBI.

Recommendations Guide

All recommendations in this report represent important research goals. Each topic committee was allowed up to 4 **focus areas** and was required to assign rank **priorities** from #1 to #4. However, for a research recommendation to be included in this report, it must be among the top priorities in its respective field. In addition, **timelines** that follow each recommendation in parentheses indicate the committee's recommended time to completion or to full operational status for the recommendation after work has been initiated, but they do not in any way reflect prioritization and rather serve to guide planning and implementation logistics. Finally, ordering of sessions in no way reflects prioritization – all sessions (MED, HD, Nomenclature, LBD, VCID, FTLD, and emerging topics) are of equally high priority.

The recommendations in this Report 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. As Scientific Chair of the ADRD Summit 2019, I respectfully submit this report to the NINDS Council on behalf of all committee co-chairs and members.

Sincerely,

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ADRD Summit 2019
Prioritized Recommendations

Topic 1:

Multiple Etiology Dementias - Diagnosing Dementia in the 21st Century

- **Focus Area 1: Improving Detection and Diagnostic Skills in the Community**

Recommendation 1 – Priority 1. Detect whether cognitive impairment is objectively present when a patient, care partner or clinician reports cognitive, behavioral or functional changes (3-7 y).

- For all MED recommendations, cognitive impairment refers to memory loss and other forms of cognitive decline including dementia. Cognitive impairment may also be accompanied by behavioral symptoms that occur as a precursor to and with cognitive decline.
- Conduct practical trials to improve the diagnosis of cognitive impairment including dementia that lead to useful outcomes for patients and families. Approaches should focus on the detection and characterization of cognitive impairment syndromes but not, for the purposes of this specific recommendation, differential (etiological) diagnosis. Approaches should be reimbursable, 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 evaluate or ensure that cognitive assessments are linked to guidance for the provider for appropriate follow-up, including specialty referrals and caregiver support.
- Evaluate the impact of interventions to improve diagnosis in different settings where better detection is likely to have benefits for patients, where there is a high frequency of undetected cognitive disorders, and where there is capacity for the practice change. Potential settings include primary care, geriatrics, pre-surgery, and clinics that serve persons with other medical conditions who are at high risk for cognitive decline (e.g., Parkinson's disease, certain metabolic disorders such as diabetes, HIV, cerebrovascular and cardiovascular disease).
- Develop and evaluate interventions that incentivize dementia diagnosis and best practices in everyday clinical settings, for example, by enhancing and integrating electronic health record (EHR) support related to clinical and administrative workflows that address evaluation, disclosure, psychoeducation, care planning community resources, documentation and billing; increasing the value that primary care providers

place on timely dementia detection and management; and improving basic diagnostic and management skills regarding later-life cognitive disorders.

- Design and assess detection of cognitive impairment based on an evaluation that begins with a self-administered assessment prior to the health care provider appointment. Determine the validity, feasibility, risks and benefits of self-administered cognitive, behavioral and functional assessments, which may include technology-related (e.g., online) assessments, as part of clinical workflows to increase the detection of cognitive impairment, including dementia. Assessments may be designed for administration at-home, in-clinic, in hospital, or in community settings (e.g. during public health screenings – blood pressure, flu vaccine clinics), but should require minimal or no staff time to complete.

Recommendation #2 – Priority 3. Improve differential diagnosis of symptomatic cognitive impairment (5-10 y).

- Improve clinical diagnostic instruments and educational approaches that increase provider confidence around the recognition and management of common and less complicated presentations of cognitive impairment in everyday clinical and community settings, and for knowing when a referral is needed (e.g., in less common, younger onset, rapidly progressing, or more complicated signs and symptoms).
- Improve diagnostic skills in healthcare professionals with measurable outcomes, e.g., recognizing and treating an LBD-associated sleep disorder, avoiding contraindicated medications in LBD, recognizing and treating reversible conditions that may cause cognitive impairment such as normal-pressure hydrocephalus or vitamin B12 deficiency, reducing risk of future cerebrovascular events or progression of white matter injury, referring to behavioral interventions and support services with demonstrated efficacy to improve quality of life in people with cognitive disorders.
- Conduct research to identify gaps in the timely and accurate differential diagnosis of AD/ADRD in health disparities populations, to understand the reasons for and impacts of these gaps, and to develop strategies to reduce inequities.
- Develop community-based clinical evaluation programs for antemortem clinical diagnosis coupled with biomarkers and perform similar clinical and biomarker diagnostic activities in referral centers to evaluate the role of referral bias and enable a more generalizable approach. A long-term goal is to link clinical activities to subsequent state-of-the-art neuropathological examinations to validate diagnoses.
- Develop new biomarkers (e.g. imaging and fluid) for people with symptomatic disease - both AD and non-AD dementias and AD/ADRD mimics, including prion disorders - that are integrated into clinical diagnosis.
- Determine the economic impact of earlier diagnosis and care on healthcare systems and patients.

- **Focus Area 2: Advancing Basic and Clinical Research in MED**

Recommendation #3 – Priority 1. Advance basic and clinical research on common mechanisms of multi-etiology cognitive impairment and dementia (3-7 y).

- *Advance Basic Science of Multi-etiology Biology.* Define interactions at the molecular and cellular level of the common pathobiologies of later life cognition including β-amyloidosis, 3R/4R tauopathy, 4R tauopathy, TDP43, arteriolosclerosis and other cerebrovascular disease processes, and α-synucleinopathy.
- *Translational Science.* Develop improved fluid and imaging biomarkers of the common pathobiologies of later life cognition - β-amyloidosis, 3R/4R tauopathy 4R tauopathy, TDP-43, arteriolosclerosis and other cerebrovascular disease processes, and α-synucleinopathy - especially those that can be used in tandem with one another in order to obtain a full antemortem etiological profile of persons with cognitive impairment in the context of genetic and behavioral factor risk.
- *Clinical Science.* Promote observations studies in diverse populations that use all available methods to characterize the status of the common pathobiologies of later life cognitive impairment, in both cognitively unimpaired and cognitively impaired individuals, in order to define novel risk factors for each as well as to establish prevalence estimates of each pathobiology as well as their combinations.
- Develop improved nomenclature that adequately represents multi-etiology processes and develop terminology to represent these processes across multiple stakeholders, including research and clinical practice.

- **Focus Area 3: Increasing the Dementia Capable Workforce**

Recommendation #4 – Priority 2. Increase education and training of health professionals and researchers focused on cognitive impairment and dementia (5-10 y).

- Increase training including certification programs in cognitive impairment and dementia for the current and emerging generation of all healthcare professionals who work with older adults, such that it leads to an increased dementia-capable workforce and increased access to care for patients and families.
- Increase training for the current and emerging generation of researchers in areas that will impact cognitive impairment and dementia including neuropathology, translational research, drug discovery, clinical trials, and grant review.
- Training of scientist and health professionals should include disparities training relevant to cognitive impairment and dementia, and trained individuals should be representative of the diverse population of the U.S.
- Training of scientists should include training in grant review relevant to cognitive impairment and dementia, and trained individuals should be representative of the diverse population of the U.S.

- **Focus Area 4: Intervention Studies to Mitigate Reversible Causes of Dementia**

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

- Conduct clinical trials in hospital and community-based settings where risk factors for cognitive decline can be appropriately targeted for intervention. Interventions may include, but are not limited to, exercise, cardiovascular risk reduction, obstructive sleep apnea, use of anti-cholinergic medications, treatment of hearing loss, prevention of delirium, and treatment of mood disorders.
- Studies should include participants at high risk for cognitive decline, 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.

- **Focus Area 5: Research to Implement Effective Dementia Care**

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

- 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 and leverage facilitators.
- Conduct implementation studies 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 families, clinicians, health system administrators, and payers. Studies must explicitly address the unique needs of health disparities populations and gender differences.

Topic 2:

Health Disparities in AD/ADRD

- **Focus Area 1: Assessment**

Recommendation 1 – Priority 1. Generate and/or improve cognitive assessment tools for populations facing AD/ADRD health disparities (1-3 y).

- Develop or modify cognitive assessment tools for populations facing disparities that will be sensitive to the earliest cognitive changes in AD/ADRD disorders but also specific (avoiding false positives) and eliminating or at least reducing cultural (e.g., language) and educational bias.

- Develop tests or modify an existing battery of tests sensitive to the earliest changes in multiple cognitive domains affected by AD/ADRD and valid in populations facing health disparities including those who do not speak English.
- Conduct analyses of existing and new measures to assure psychometric strength across cultural groups.
- Establish reporting guidelines for expanded demographics, such as language proficiency and reading level, when characterizing samples on which these cognitive tests are developed.
- These cognitive tests should be repeatable and sensitive to change over time to improve usability in longitudinal studies and intervention trials.
- Develop and validate brief and highly accurate screening tests for detecting subtle cognitive impairment for use in primary care or other community settings, in the multiple languages spoken by older adults.
- Engage local communities in the co-development of culturally-/community-informed measures to establish appropriate language and reduce cultural bias.
- To the extent possible, these tools will be harmonized to permit collaborating, pooling, and comparing data across languages, cohorts, and community and clinical settings.
- Make these linguistically and culturally valid cognitive assessment tools readily accessible and available to clinicians and researchers.

Recommendation 2 – Priority 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 (1-3 y).

- Engage and recruit individuals from diverse communities into aging research studies, regardless of cultural and linguistic factors (e.g., language proficiency).
- Conduct treatment variability analyses across demographic variables.
- Develop criteria by which proposed interventions can be measured to determine whether they are culturally sensitive to ensure their application to diverse populations.
- Generate a repository of assessment tools (i.e., symptom questionnaires, neuropsychological instruments and normative references, and informant-based surveys) validated for use among diverse populations.
- Genomic ancestry and self-identified race/ethnicity are variables that can and should be captured separately and independently. Genomic ancestry provides information about population stratification and admixture, but associations between ancestry and health outcomes may be mediated by social factors. Thus, the decision to use genomic ancestry or self-identified race/ethnicity or both must be guided by the research question, and social determinants of health, such as discrimination, intergenerational socioeconomic status, and other contextual factors, should always be included.

➢ Focus Area 2: Resolve AD/ADRD Health Disparities by Discovering Culturally Appropriate Pathways to Effective Prevention and Treatments

Recommendation 3 – Priority 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 (3-7 y).

- Measure changes in risk factors (both established and novel) over the life course and across generations to link assessments of adult cognitive status and AD/ADRD outcomes among populations facing disparities.
- Establish new AD/ADRD cohort studies or augment ongoing cohort studies that include several of the following to test the interaction of social, environmental, and biological mechanisms:
    - Sociocultural factors (e.g., ethnicity/race, discrimination) - required
    - Deep vascular phenotyping - required
    - *APOE* plus other –omics, including GWAS or whole sequencing, epigenetics, transcriptomics, metabolomics, and proteomics
    - AD/ADRD biomarkers, including but not limited to beta-amyloid, tau and neurodegeneration and VCID
    - Environmental factors (e.g., neighborhood level, air/water pollutants) and their omics biomarkers
    - Measures of early life exposures (e.g., perinatal health), including epigenetics
    - Evaluation of psychosocial factors (e.g., stress, depression) and their -omics biomarkers
    - Collection of biologic endpoints including but not limited to PET, CSF, and autopsy when possible; focusing on interactions of pathologies with social, environmental, and biologic factors

Recommendation 4 – Priority 2. Implement culturally tailored multimodal intervention trials and drug therapy trials to reduce AD/ADRD burden in populations facing disparities (3-7 y).

- Generate at least two new culturally tailored multimodal intervention trials to include vascular risk factor control, and lifestyle modification, and/or drug therapy trials to reduce AD/ADRD burden in populations facing health disparities.
- Initiate drug therapy trials in targeted populations facing AD/ADRD health disparities.
- Trials should include consideration of precision medicine approaches (that may be informed by –omics) for more precise therapeutic selection.

➢ Focus Area 3: Monitoring Changes in AD/ADRD Disparities

Recommendation 5 – Priority 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 (ongoing activity).

- Documenting and monitoring trends in health disparities in AD/ADRD prevalence and incidence is an essential step towards achieving health equity in AD/ADRD and is critical for prioritizing public health needs, prevention efforts, and treatment strategies. While some health disparities in AD/ADRD prevalence and incidence have been well-documented, the current picture is incomplete or non-existent for many under-represented minority groups and dementia syndromes.
- Recent studies suggest that dementia incidence rates may be declining, but most of this evidence is based on non-Latino whites, and it is largely unknown whether these trends extend to under-represented minority populations. Monitoring changes in AD/ADRD

health disparities will provide evidence on the extent to which there has been progress towards reducing AD/ADRD health disparities and provide insight into mechanisms.

- Health disparities in AD/ADRD should be documented and monitored across a range of social determinants of health, including race/ethnicity, nativity, primary language, income and wealth, educational background, gender identity and sexual orientation, and geographic location.
- Epidemiology and clinical course of many AD/ADRD subtypes (e.g., Lewy Body, Frontotemporal dementia, early-onset AD) are largely unknown in under-represented populations, in part due to economic barriers and discrimination that reduce access to healthcare, increase misinterpretation of early signs of dementia, and increase stigma within communities facing disparities. As a result, innovative approaches to diagnosing, documenting, and monitoring AD/ADRD subtypes are needed to understand the magnitude of health disparities.
- Valid estimates of AD/ADRD health disparities should be obtained from samples that are representative of the U.S. population. Estimates of AD/ADRD health disparities from non-representative samples could inaccurately represent disparities in the population of interest (i.e. the U.S. population as a whole or the population in specific geographic locations).
- Efforts should be made to determine whether health disparities exist for the younger onset dementias (<65 years of age) and non-Alzheimer's dementias. There is a need to engage specific groups to recruit and retain younger study participants.

Recommendation 6 – Priority 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 (ongoing activity).

- AD/ADRD awareness and knowledge, and perceptions of disease burden are unclear in representative populations facing disparities. New research to fill these critical gaps will inform public health educational programs and increase clinical trials participation.
- Evaluating disparities in access to care and costs of care for persons living with AD/ADRD and their families is essential for achieving health equity in AD/ADRD. Economic hardship is common in many families caring for someone with dementia, but the changes associated with AD/ADRD (e.g., loss of labor productivity, loss or sale of home) may disproportionately impact under-represented populations.

➢ Focus Area 4: A Diverse and Inclusive AD/ADRD Workforce

Recommendation 7 – Priority 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 (3-5 y).

- Develop an iterative training framework for AD/ADRD health disparities research at various training and career stages.
- Increase research opportunities and support of diverse scholars beginning in college and through their advanced research training.
- Expand the availability of funding opportunities to support diverse scholars in AD/ADRD health disparities training.

- Target training mechanisms to enable success of diverse junior faculty in obtaining first research grant funding.
- Leverage existing diverse AD/ADRD health disparities research groups and organizations to further attract, train, and retool a diverse, competent workforce.
- Implement a robust mentorship and sponsorship system for AD/ADRD trainees with meticulous tracking over time that could change the level of competence in conducting inclusive research and diversity of our scientific workforce.
- Retooling and expanding the knowledge base on conducting inclusive science of mid-career and senior scientists attracted to the field of AD/ADRD is essential if progress is to occur in successfully recruiting and retaining a diverse and competent research workforce.
- Leverage and enhance existing systems for monitoring progress in diversification of the AD/ADRD scientific workforce. Existing systems for monitoring workforce diversification are useful, however, enhancing an internal system to monitor the research workforce may be more responsive.
- Grant review is part of the scientific process and the participation in grant review of scientists with expertise in health disparities research and individuals who are members of underrepresented populations is essential to achieve the goals of increasing inclusion of populations facing disparities in research and increasing research focused on health disparities.

Recommendation 8 – Priority 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 (3-5 y).

- Due to well-established social determinants of health, as well as differing attitudes and expectations of aging, there is a need for culturally sensitive outreach and engagement with under-represented populations to enhance communication and understand different perspectives.
- Instead of relying solely on specialty clinic enrollment, use recruitment strategies that are community-based, representative (when possible based on the research question), and have limited exclusion criteria in order to reduce sampling biases and ensure population diversity regarding co-morbidities.
- Include individuals representing demographic diversity with respect to race/ethnicity, rurality, socioeconomic status, and life experiences in order to make cohorts as representative as possible.
- Disseminate best practices for community engagement and outreach for different populations facing health disparities as well as for different disease outcomes (e.g., AD, LBD, VCID, FTD, MED).
- Given the historical under-inclusion of certain populations in clinical research studies and the effort it takes to be as inclusive as possible, responsible efforts should be made to build relationships and follow-up with interested individuals for the entirety of the recruitment process.
- Inclusion is a critical part of what is needed; ensure that proven inclusion strategies are actively utilized to address critical AD/ADRD health disparities gaps and questions in clinical research and clinical trials.

Topic 3:

Dementia Nomenclature

- **Focus Area 1: Dementia Nomenclature Working Groups**

Recommendation 1 – Priority 1. Form research, clinical practice and public stakeholder dementia nomenclature working groups (1-2 y).

- **Part A - Form a Research Working Group** to develop, refine, and clarify medical nomenclature of diseases within the AD/ADRD spectrum for use in scientific research.
  - Nomenclature should be accurate for designating different categories of disease classification including: 1) the biological foundations of disease etiology such as pathologic changes (e.g., Alzheimer's amyloid plaques and tau-based neurofibrillary tangles; frontotemporal lobar degeneration [Picks, TDP-43 proteinopathy, other]; Lewy body disease, cerebrovascular disease and other indicators of cellular damage or and parenchymal-driven proteinopathy-based neurodegeneration, etc.), vulnerable brain regions (frontal, temporal parietal) and consider how to integrate this nomenclature with 2) the spectrum of clinical syndromes and symptoms including progressive amnestic mild cognitive impairment and dementia, visuospatial syndrome, primary progressive aphasia, behavioral variant frontotemporal dementia, dementia with Lewy bodies, etc.
  - The Research Working Group should include researchers and representation from the two other dementia nomenclature working groups to a) review current terminology for disease etiologies, syndromes, disease staging, considering a full range of age of onset (including those under 60), and b) identify opportunities to standardize approaches to terminology.
  - Solicit input from experts and consultants from groups experienced with terminology in other disease areas, historical perspectives of labeling disease including biologic diseases (e.g. cancer nomenclature) and psychiatric diseases (DSM nomenclature).
  - Solicit input from cross-cutting stakeholders including affected individuals, advocacy organizations, clinical medicine, public health, industry and regulatory agencies.

- **Part B – Form a Clinical Practice Working Group** to consider the Research Working Group recommendations for terminology for common clinical practice needs and for translation to the multiple stakeholders within the medical practice community.
  - Nomenclature should facilitate delivering a diagnosis that is scientifically accurate in a way that minimizes the distress of the patient, reflect the underlying disease process or processes, and convey the diagnosis, stage and prognosis of the disease to affected individuals and concerned parties (families, caregivers, payers). Nomenclature must also be able to translate research nomenclature into terms that patients and caregivers understand and that indicate specific recommendations for treatment and management. This is important for the determination of program eligibility and insurance coverage for services.
  - The Clinical Practice Working Group should include clinicians (primary care and specialists) and representation from the other dementia nomenclature working groups to review current terminology used to translate science/research to their patients and caregivers and identify potential areas of improvement for terminology for the benefit of advancing care and practice.

- Solicit input from cross-cutting stakeholders, such as payors, health systems and electronic health record vendors, on the impact of changing terminology (e.g. coding, reimbursement and quality measurement).
- Consider the implications of changing terminology on public health and the education of healthcare professionals, including physicians, nurses, speech, occupational and physical therapists, social workers, other care providers, and the public.

- **Part C** – **Form a Public Stakeholder Working Group** to assess the potential to develop nomenclature that is not stigmatizing, while being transparent, scientifically accurate, clinically useful and easy to understand.
- Nomenclature should be as much as possible diagnostically and scientifically accurate in a way that minimizes patient emotional impact, reflects the underlying disease process or processes, and convey the diagnosis, stage and prognosis of the disease to affected individuals and concerned parties (families, caregivers, payers). Nomenclature must also be able to translate research nomenclature into terms that patients and caregivers understand and that indicate specific recommendations for treatment and management. This is important for the public navigation of insurance coverage for services.
- Current terms (i.e. dementia, demented, Alzheimer's) can have pejorative/negative connotations and vary across American populations, though it is unknown whether the term "dementia" is an insurmountable obstacle or a failure to educate the public about the health implications of dementia and the opportunities for care. Communication with the public about dementia needs to be transparent and accompanied by education about the complexities of dementia and its various causes, treatment, services, and supports.
- The Public Stakeholders Working Group should include experts in stigma, health disparities and ethics, people living with dementia and their caregivers, advocacy groups, and representation from the other dementia nomenclature working groups, as well as cross-cutting stakeholders to gather expertise from experts in terminology and public communications.
- Convene diverse groups (by gender, race, ethnicity, age, geographic location, and socioeconomic status) to include representation from health disparity communities and to develop an understanding of how public stakeholders (those living with, at risk for, or assisting someone with dementia, as well as people who see themselves as at risk) view the usefulness of and sensitivities to today's terminologies.
- Define the role current terminology plays in contributing to stigma and preventing or delaying the pursuit of clinical care; based on the findings, develop strategies to educate the public about dementia that reduce stigma and promote early symptom reporting, which may include identifying potential changes in existing terminology.

➢ **Focus Area 2: Integration and Interoperability of Dementia Nomenclature**

Recommendation 2 – Priority 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 (2-4 y).

- Diverse stakeholder groups have both unique and overlapping needs for nomenclature, and as such must come together to determine if terminology can be made more systematic and interoperable to advance science, clinical care and public awareness, and reduce stigma.
- Organize a symposium of all working groups and stakeholder types to discuss outputs from the three nomenclature working groups and the strategy to identify areas of consensus, potential barriers, and any recommendations to update dementia nomenclature. The goal is to improve communication within and across all stakeholder groups and provide guidelines for disclosing a diagnosis.
- Issue a "white paper" report on the process, development, and proposed preliminary foundation for nomenclature structure for AD/ADRD diseases, any anticipated outcomes of recommendations to evaluate impact, and strategies for reducing stigma for patients and caregivers and public education.

Topic 4:

Lewy Body Dementias

- **Focus Area 1: Clinical Science**

Recommendation 1 – Priority 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 (1-7 y).

- Initiate clinical trials for the prevention and treatment of motor and non-motor manifestations of a) Lewy body dementia (LBD), which includes both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), b) the pre-dementia disorders including mild cognitive impairment (MCI) of Parkinson's disease (PD) and DLB, as well as late-onset psychosis (hallucinations and delusions), and c) the prodromal disorders including REM sleep behavior disorder (RBD), hyposmia, autonomic dysfunction, etc., and d) those at genetic risk (e.g., *LRRK2*, *SNCA* or *GBA*) in diverse populations using existing and newly-developed therapies that address clinically-significant symptoms that have the greatest impact on patient function and caregiver burden.
- To meet this recommendation it will be necessary to engage existing clinical networks and non-governmental organizations to establish new and expand existing networks of relevant clinical investigators, including movement disorder specialists, behavioral and cognitive neurologists, autonomic neurology specialists, psychiatrists, and sleep disorder specialists, to use well-characterized cohorts of established or at-risk LBD for treatment trials with novel therapeutic compounds as well as current FDA-approved drugs. These clinical 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. 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 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.

- Clinical tools to track cognitive changes via neuropsychological measures or batteries as well as track 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. These tools include, but are not limited to, "digital approaches" such as wearable devices, and computerized or app-based cognitive testing.
- Such new or existing methods for detecting and tracking LBD features should undergo multi-center validation, and normative data using the methods should also be generated.
- These efforts build upon the knowledge base that is 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, and reducing inflammation.
- It is critical that pharmaceutical companies be made aware of efforts to characterize patients and measure disease progression. If the perceived risk around entering into this are can be reduced, there is a much better chance that target-based discovery efforts in pharma will emerge. One idea would be to create a working group of neurology researchers from relevant pharma companies.

Recommendation 2 – Priority 2. Longitudinal antemortem LBD characterization (3-5 y).

- Create longitudinal clinical, biological, and imaging resources for LBD from the earliest stages through to autopsy a) to improve accuracy of detection and diagnostic criteria of LBDs, and at the pre-dementia or prodromal stage of LBD, b) to validate (i.e., Phase 3 studies) biomarkers that predict conversion to dementia, and c) to serve as recruitment source for trials listed in LBD Recommendation #1.
- To address the problems of delayed and under-diagnosis, existing or new longitudinal cohorts focused on cognition need to enroll adequate numbers of LBD, pre-dementia LBD, and prodromal or at-risk LBD patients. Multi-center prospective cohorts designed both in the U.S. and abroad. There is potential to merge datasets to achieve larger numbers, with increased power to detect clinical and biological markers of diagnosis and prognosis. These resources can also benefit trial recruitment, which is challenging and requires concerted efforts.
- Relevant studies would seek to develop methods to predict time to conversion to LBD or to develop measurable cognitive and motor deficits that may appear before conversion and continue afterwards. Such measures will be critical in order to execute economical disease-modifying trials.

- Although some predictive demographic and clinical factors are known for PDD development, few prospective biomarker studies exist. Recent studies have demonstrated the potential of biomarkers to predict shorter time to dementia conversion, in particular markers of co-morbid AD pathology, but more, broader biomarker work is needed. It is important that cross-site standardization (e.g., clinical, imaging) occur to the greatest extent possible across all LBD resources.

Recommendation 3 – Priority 3. Neuroimaging characterization of LBD (3-7 y).

- Develop imaging approaches to: a) enhance the differential diagnostic accuracy of LBD (and its neuropathologic subtypes) compared to other dementing illnesses and parkinsonisms (i.e., LBD vs. AD / FTLDs / PSP); b) detect latent and prodromal LBD; and c) monitor disease progression in natural history and treatment studies by integrating established and new imaging tools. Validate these tools against postmortem neuropathology.
- Evaluate the role of currently available imaging tools in the diagnosis and classification of LBD with emphasis on imaging modalities demonstrating high reproducibility across populations, imaging sites, and imaging platforms. Evaluate feasibility of imaging biomarkers developed in the research setting for use in clinical trials where imaging resources may be limited or heterogenous across sites.
- Investigate potential α-synuclein tracers for sensitivity/specificity to PD versus MSA deposits and α-synuclein versus beta-amyloid, TDP-43, tau and other protein deposits. Compare performance of α-synuclein tracers with alternative approaches such as nigrostriatal dopamine projection or myocardial sympathetic innervation imaging across neurodegenerative dementias and parkinsonian disorders.
- Incorporate multimodal analyses, including systems-level biomarkers or biofluid markers to enhance accuracy of diagnosis and reliability of prediction of disease progression.
- Develop parallel strategies to evaluate emerging technologies or analytical approaches for feasibility and value added for natural history studies and multicenter therapeutic trials. This approach will facilitate the development of synergistic multi-modal biomarker strategies (e.g., molecular imaging with radiotracers for α-synuclein, β-amyloid and tau binding agents or MR-based structural or functional imaging) in combination with systems-level functional biomarkers of disease severity to enhance the accuracy of diagnosis and the reliability of progression measurements during all stages of disease.

Recommendation 4 – Priority 4. Neuropathologic characterization of LBD and use of LBD pathology cohorts (2-7 y).

- While there have been efforts by investigators and groups of investigators to develop recommended methods to evaluate the neuropathology of LBD, no generally accepted standard exists. Efforts should be made to leverage clinically well-characterized, longitudinal cohorts of LBD and at-risk subjects to increase autopsies, enhance tissue diagnostic consensus standards, and increase tissue sharing.
- A research priority should be to develop best practices in neuropathologic evaluation of LBD as well as standardization of neuropathologic methods for evaluation (e.g., minimal sampling schemes and staining methods) and data collection (e.g., quantitative and semiquantitative data). A starting point might be NIA-AA guidelines for Alzheimer

disease neuropathologic change, which includes a LBD module, but it lacks in details and particulars.

- Investigations should also include peripheral tissue samples, which include skin, salivary gland, gastrointestinal system structures, and tissues outside the central nervous system. Best practices for standardizing methods of evaluation and data collection for these peripheral tissue samples should also be developed.
- Another priority should be to investigate means to increase autopsies on subjects with and at risk for LBD enrolled in prospective longitudinal studies that utilize standardized evaluations and collection of antemortem biomarkers (i.e., biofluid, neuroimaging, others). In addition to symptomatic LBD, autopsies should be sought of patients with mild cognitive impairment and other presymptomatic or related features of LBD, such as REM sleep behavior disorder (RBD), psychosis (visual hallucinations and delusions) and Parkinsonism. Research is needed on best practices for patient outreach and patient education to emphasize the importance of brain donation, as well as means to provide logistical support and resources necessary to facilitate brain donations.
- In order to make the greatest research use of autopsy specimens from patients with and at risk for LBD, a research priority should be to develop a clearinghouse that links scientists to tissue resources. This resource would ideally be an on-line and searchable database that links patient samples with particular clinical and neuropathologic characteristics and an inventory of where samples of this type can be found. Ideally, this clearinghouse would be linked to "-omics" or antemortem biomarker data (including neuroimaging data) that might be linked to the pathological specimens. This research priority will necessitate navigating the issue of blinding of protected health information (PHI). Samples accessible to the general research community will have global unique identifier (GUID), which permits sharing of data specific to a study participant without exposing PHI, as well as providing a tool to match participants across research data repositories.

- **Focus Area 2: Basic Science**

Recommendation 5 – Priority 1. Biomarker development (3-7 y).

- Use new or existing cross-sectional and longitudinal case-control studies of individuals with LBD, longitudinal cohort studies tracking cognitive and/or motor decline, autopsy cohorts with sufficient antemortem clinical and biomarker data, or studies capturing incident cases of LBD, to develop biomarkers for LBD-related pathologic changes, diagnosis, differential diagnosis, disease progression, and the relative burden of Alzheimer's and other pathologies. As new markers of molecular disease mechanisms are discovered, they should be incorporated into biomarker studies for diagnosis of prodromal disease and for monitoring molecular processes and their response to therapies.
- This recommendation proposes to capitalize on existing longitudinal case-control cohorts to encourage standardization of protocols and common data elements. Analyses of biomarkers in relation to genetic and environmental risk factors, clinical indices, imaging and neuropathology are important components of validation and interpretation of biomarkers.

- Biomarkers should be measured in a diversity of tissues (including, but not limited to, brain, skin, colon, salivary gland biopsies, PBMCs, others) and biofluids (e.g., whole blood, plasma, CSF, urine, microbiome samples, and others).
- Assay and method standardization should be encouraged through sharing and replication of methods and through availability of biosamples.
- Consideration should be given to developing comparable biomarkers in model systems (e.g., transgenic animals; iPSc-derived models, etc.) and in humans.
- This recommendation in conjunction with several others is critical to providing insights on the biological substrates which contribute to the temporal evolution of the major LBD clinical phenotypes (i.e., PD then progression to MCI and dementia, compared to MCI with progression to DLB) as well as the variable clinical manifestations within and across individuals (i.e., why some have psychosis early in the course whereas others never experience psychosis).

Recommendation 6 – Priority 2. Genetic, epigenetic, and environmental characterization (3-7 y).

- Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that impact the risk for and clinical features of LBD.
- This goal will require single nucleotide polymorphism (SNP) genome-wide association studies, as well as whole exome sequencing, whole genome sequencing, and expression studies of large cohorts of LBD on whom systematic, standardized environmental exposure information is also collected, as well as studies of families with multiple affected members. This recommendation also includes identification of genetic and epigenetic factors influencing the risk of developing DLB and of dementia in patients with pre-existing PD. Genetic studies should enable stratification of patients by phenotype, diagnosis, prognosis, and response to treatment.
- Studies should include diverse populations and incorporate measures of environmental factors that may vary across these populations and reflect healthy disparities. Examination of gene-environment interactions is essential.
- Although some success has been achieved with the execution of large-scale association, genome-wide association and whole exome sequencing studies, limitations exist around pursuing these aims further with existing data, most of which relate to genetic, clinical, biological, pathological, environmental, and other large-scale data. This recommendation also includes a need to support modern data-driven approaches, such as machine learning on complex genomic data, to facilitate identification and understanding of abnormal pathways.
- There is a need for a central knowledge platform to allow easy data sharing (e.g., via cloud), 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 7 – Priority 3. Understanding the molecular, cellular and pathophysiology of α-synuclein in the context of non-motor brain areas (2-4 y).

- While the fundamental biology of α-synuclein has been extensively studied in many experimental paradigms, particularly in the context of motor systems, the normal

function and misfolding of this protein, as well as function of this protein, in areas vulnerable to the broader set of LBDs remains underexplored. The effect of small molecules therapies meant to target motor systems on non-motor systems (e.g., cognition) is unknown. This recommendation is therefore aimed at improving our knowledge of the normal function of α-synuclein and role of α-synuclein in non-motor systems. These experiments will aim to inform current clinical development by identifying potential safety concerns.

- Understanding the fundamental biology of α-synuclein in the context of the broadest numbers of neurons that are vulnerable to LBD will be important. Questions to be asked, mainly using animal models, will relate to cellular, regional physiology, and pathophysiology of neurons when α-synuclein expression is modified. Identifying sequelae of the removal of α-synuclein from the mature brain across multiple regions, in terms of neuronal health and function, will be an important component of this investigation.
- Additional models, which should include human-derived materials such as induced pluripotent stem cells, should integrate genetic discoveries from human population studies that have identified pathways relevant to disease risk and progression with the directed goal of identifying biological pathways and networks that ultimately regulate expression of the *SNCA* gene and other risk factors for disease. Both Mendelian alleles and non-mendelian pathways, such as genetic risk scores, should be considered in a continuum of genetic risks for LBDs.
- Understanding the regulation of α-synuclein protein levels and its aggregation, as a product of both regulation of expression, misfolding, and clearance will be important. In addition, post-transcriptional regulation within cells, will be important to provide tractable hypotheses relevant to genetic risk of LBDs. This recommendation should also be considered in the context of the aging brain, which will be discussed further below. This consideration should improve our thinking about which human subjects might benefit from modification of α-synuclein, or other targets, in LBDs and may inform clinical action around measurement of target engagement.
- It is clear that aging contributes substantially, and critically, to LBD risk. The role of aging should be interrogated further using model systems that allow for modeling this risk factor and also in the analysis of available resources such as high volume ‘omics’ datasets, including novel methods such as mRNA expression, proteomics, metabolomics, etc.
- Identification of biological mechanisms that explain both sex differences and resilience in LBD, as identified in human pathological studies, will be of high value. Inclusion of both male and female samples at appropriate number to support well-powered analyses of both sexes is required.

Recommendation 8 – Priority 4. Identify mechanisms by which Lewy body diseases may spread between and affect different brain regions and how Lewy bodies interacts with other pathologies (5-7 y).

- A major recent conceptual framework for how we think about neurodegenerative diseases is the proposal that many diseases can spread between brain regions. Whether α-synuclein has the ability to spread in general or only across certain types of cells (resulting in selective vulnerability) is unknown. It is also unclear whether α-

synuclein interacts with other proteins (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 animal models and therapeutics. These studies would move forward new mechanistically tractable targets that could be engaged for clinical studies.

- This recommendation recognizes the need to 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. Such models will need to be able to identify the key pathways mediating the propagation of toxic protein assemblies between cells in appropriate, physiologically relevant, context.
- 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. These studies should be used to identify the anatomical , biochemical, and molecular underpinnings of brain regional differences in Lewy body pathology associated with variable behavioral outputs in animal models that are relevant to human clinical phenotypes. Where feasible, validation of findings from this type of research should use biospecimens and data from humans, including PDD and DLB.
- Identifying mechanisms by which α-synuclein and β-amyloid pathologies interact in the intact brain is a critical step towards a fuller picture of the complex pathology of LBDs. Development of models in which both pathologies are present either within the same cells or in proximate cell populations should be supported.
- The contribution of immune-mediated mechanisms and inflammation in LBD pathogenesis should also be investigated.

Topic 5:

Vascular Contributions to Cognitive Impairment and Dementia (VCID)

- **Focus Area 1: Basic Mechanisms and Experimental Models**

Recommendation 1 – Priority 1. Develop next-generation experimental models and translational imaging methods for VCID (3-5 y).

- Establish new animal models that: (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 small vessel disease.
- White matter degeneration is a pathologic process that currently lacks suitable animal models for mechanistic studies.

- Studies are encouraged that leverage existing models of systemic cardiovascular disease such as heart failure, atrial fibrillation, or renal disease, to examine the brain for pathological signatures of VCID.
- Models should incorporate lifestyle and genetic factors of VCID, including *HDAC9*, *collagen IV*, and *MFSD2a*. Lifestyle factors include chronic conditions such as diabetes, hypertension, and hyperhomocysteinemia.
- Incorporation of VCID pathologies with AD pathologies in animal models would be particularly informative for interactions of AD and VCID pathological processes.
- Use of in vitro and/or iPSC models to study specific molecular mechanisms that are not feasible in animal models.
- Age and sex should be included as variables in all model studies.
- New tools will need to be developed to study the models with an eye to identifying key molecular mechanisms of VCID. Suggested tools for development include enhanced in vivo microscopy to allow imaging of deep structures such as subcortical white matter, higher resolution MRI and CT/PET modalities for live animal imaging, and ex vivo technologies that improve translation of cellular models to the in vivo system.

Recommendation 2 – Priority 3. Foster basic science research on neurovascular unit function and how it is impacted by the following: aging, cardiovascular disease, AD pathology and genetics (3-5 y).

- Understand the factors influencing “paravascular” clearance of CSF alongside brain vessels, and “perivascular” clearance of CSF within the vascular basement membrane. Delineate the relative contributions of these pathways to cerebrospinal fluid and interstitial fluid drainage under normal physiologic conditions and in VCID.
- Of critical importance is the study of peri- and paravascular clearance pathways and how these pathways contribute to proteostasis, immune cell trafficking, and lymphatics in the brain.
- Continued investigation of 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 (arterioles, capillaries and venules), and how VCID pathology affects each of these zones.
- Recent data indicates blood-brain barrier integrity is affected early in the pathological process of both VCID and AD. Understanding the mechanisms underlying the integrity loss of the neurovascular unit is important.
- In addition to controlling blood supply, cells of the neurovascular unit release molecules with significant contribution to the trophic environment in the brain. Establishing how this function is affected in VCID is recommended.
- Understanding how the normal function of the neurovascular unit is impacted by risk factors of VCID such as aging, cardiovascular and cerebrovascular disease, AD pathology and genetics, will be critical for understanding disease mechanisms.
- Investigate the neurovascular unit as a site of interaction between AD and VCID pathologies.

- Investigate the contribution of risk factors for clinical AD, including diabetes, obesity, lipid metabolism, hypertension, diet, exercise, sleep, head injury, and aging, on the neurovascular unit function.

Recommendation 3 – Priority 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 (5-7 y).

- 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.
- Studies should be encouraged that will examine common cerebrovascular disease risk factors in AD animal models. These studies should cover both beta-amyloid, and tau-related disease processes, both separately and together, as well as relevant immune signaling including the potential role of chronic inflammation.
- Develop tools to characterize the effects of altered cerebrovascular function on specific vascular cell types, microvascular zones, and brain regions.
- Apply multiomics and sophisticated bioinformatics to elucidate disease mechanisms.

➢ Focus Area 2: Human-Based Studies

Recommendation 4 – Priority 1. Develop, validate and longitudinally track: (1) cognitive, physical, or other functional assessment components that indicate the presence of VCID; (2) VCID biomarkers, including when VCID is accompanied by pathological AD (3-5 y).

- Human-based studies should seek to develop and validate a standardized assessment battery that includes cognition, may include fluid-based and image-based brain biomarkers, but may also incorporate physical function and other or non-CNS organ-related (heart, kidney, etc.) measures for indicating the likelihood of VCID. This would be an important step towards improving clinical diagnosis and measurement of clinically meaningful trial outcomes.
- Human studies should also include assessment of the prognostic utility of candidate non-invasive, lower-cost, systemic markers (e.g., retinal imaging, ocular tonometry) for detecting the presence and progression of cerebral small vessel disease.
- Human investigations should be designed to identify or confirm blood, urine or CSF biomarkers of microvascular processes related to cognitive/neurologic impairment, including biomarkers of tissue injury (e.g., microinfarcts, ischemic white matter damage); connectivity; specific vessel pathologies (e.g., cerebral amyloid angiopathy, arteriosclerosis); altered perivascular spaces and interstitial fluid clearance; impaired neurovascular coupling or cerebrovascular reactivity; BBB dysfunction; inflammation; and altered perfusion (e.g., measures of blood flow and oxygen extraction).
- Development of more sensitive functional outcome measures for human studies that provide novel information relevant to VCID.
- Develop cross collaborations with investigators in Congestive Heart Failure and Chronic Kidney Disease clinics and clinical research units.

Recommendation 5 – Priority 2. Test for efficacy across the spectrum of VCID severity: (1) interventions proven to reduce cardio- and cerebrovascular risk; (2) established care models (3-5 y).

- Establish additional clinical trials testing interventions that have shown efficacy in reducing cardiovascular and cerebrovascular risk. Interventions known to impact general vascular risk factors, including management of hypertension, statins, control of diabetes/metabolic syndrome, diet, exercise, and other lifestyle interventions may be successful pathways for reducing VCID. Consider multimodal clinical trials and modality-specific clinical trials; adding brain imaging, cognition in cardiovascular intervention trials.
- Within current and future large randomized and epidemiological cohort studies, develop or confirm surrogate markers 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 are at high risk of developing dementia. Such studies should also relate the burden of cardiovascular disease to imaging markers such as the frequency or distribution of lacunar strokes, neurophysiological markers such as cerebrovascular reserve or functional imaging, or molecular biomarkers obtainable from the subjects such as genetic or proteomic measures.
- Increase the harmonization of protocols across trials wherever feasible in order to permit meta-analyses.
- Extend prevention or treatment trials or initiate studies that test in VCID best existing models for delivering the care of persons with AD/ADRD and supporting their caregivers.

Recommendation 6 – Priority 4. Determine interrelationships among cerebro- and cardiovascular disease, VCID risk factors, aging, resilience, genetics, amyloid, tau, and neurodegeneration including along the life-course (3-5 y).

- Explore cardiovascular and cerebrovascular disease mechanisms and treatments as a possible explanation that may underlie the emerging trend of lower incidence of age-related dementia that has been reported in North America and Europe.
- Conduct life-course epidemiology investigations including studies on: a) VCID, syndromic AD, and aging in the context of specific populations with high vascular risk factors or disease burdens (including in disproportionately affected populations such as African-American, Hispanic, and Native American populations); b) environmental factors associated with increased resilience to vascular disease and cognitive impairment (e.g., Mediterranean diet, education, cognitive engagement, physical fitness, social networks, sleep; c) factors that increase risk for VCID based on the presence of monogenic conditions (e.g., CADASIL) or GWAS-identified variants associated with cerebrovascular disease (e.g., *HDAC9*); and d) potential gene-environment interactions.
- Analyses that advance ability to determine the link between VCID and the genomic loci associated with syndromic and genetic AD (e.g., *PICALM*, *CLU*, *APOE*, *TREM2*, *APP*, *PSEN1*, *PSEN2*) that appear to interact with vascular biology or BBB dysfunction.
- Encourage analytic studies that address the complex pathways leading from vascular risk factors CVD and cerebrovascular disease to changes in cognition, brain structure, Aβ, tauopathy, and neurodegeneration. Such studies may include systems-based

approaches, multiomics, and bioinformatics, incorporating multi-modal imaging, biochemical, genetic and clinical markers to help determine whether risk conditions common to both syndromic AD and cerebrovascular and CV disease reflect convergent pathways versus additive effects of independent pathways.
- Encourage interaction between scientists working with models of disease and organ system failure (CHF, CKD, microbiome degradation) and scientists working with VCID and related forms of AD/ADRD.
- Introduce leading edge science into birth cohorts such as discovering, further validating, and utilizing VCID biomarkers. Candidate cohorts are those such as statewide health systems or national medical systems. These have enhanced utility in understanding life-course factors contributing to later life VCID.

➢ **Focus Area 3: Translational Studies**

Recommendation 7 – Priority 2. Use data and other resources from large-scale clinical research and trials to test hypothesized mechanisms of human VCID based on basic science findings (3-5 y).

- 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 function, BBB permeability, interstitial clearance, vascular stiffness, and other measures of vascular physiology.
- Translationally characterize the influence of vascular risk factors and vascular-mediated pathways on cognitive, physical, and other function.
- 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.
- Information from human studies should be used to guide development of improved models, including cellular, rodent, and non-human primate.
- Leverage and expand on recent studies showing that stricter blood pressure control is related to fewer cardiovascular events and may slow cognitive decline in some individuals. Also, further study and refine understanding of diurnal variation in blood pressure, vascular health (stiffness, etc.) and also explore basic mechanisms of blood pressure's effect on cerebrovascular health.
- Investigate lifestyle factors like hypertension, hypercholesterolemia, hyperhomocysteinemia, and / or diabetes in animal models to study mechanisms of disease for translation.

Recommendation 8 – Priority 3. Incorporate VCID findings from basic science into the design of clinical research and trials targeting VCID-relevant cognitive impairment and dementia (5-7 y).

- 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.
- Incorporate validated vascular biomarkers in 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, young old, old, and oldest old life stages.
- Develop human based techniques that will evaluate basic science mechanisms such as the glymphatics and intramural periarterial drainage (IPAD).

Topic 6:

Frontotemporal Lobar Degeneration

- **Focus Area 1: Science: Pathogenesis and Toxicity**

Recommendation 1 – Priority 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 (2-10 y).

- The mechanism of tau-driven neurotoxicity and its relationship to the formation and spreading of tau pathological inclusions in a prion-like manner needs to be determined in order to identify optimal therapeutic approaches. In particular, which pathophysiological events (posttranslational tau modifications, microtubule dysfunction, interneuronal spread, or other tau (dys)functions) represent the most human-relevant, deleterious, and targetable processes? How and why does the process of tau aggregation begin? A focused effort to fully understand the mechanism of interneuronal spreading of aggregated tau is a priority.
- Innovative cell-based, animal model, and human post-mortem studies are the recommended approaches to determine pathogenic events that promote tau toxicity and pathology spreading. Genetic models should be complemented with other methods that mimic aspects of sporadic disease (inoculation studies, iPSCs, etc.).
- Identification of the predominant mechanism(s) of *C9orf72* hexanucleotide repeat expansion pathogenesis in FTD/ALS will guide the development of therapeutic strategies. To what degree is *C9orf72*-associated neurodegeneration related to RNA toxicity, dipeptide repeat protein aggregation, TDP-43 proteinopathy, loss of *C9orf72* or TDP-43 protein function, or other factors? There is a similar need to understand the mechanism(s) of neurodegeneration associated with *GRN* haploinsufficiency in FTD: lysosomal dysfunction, TDP-43 proteinopathy, neuroinflammation, or other mechanisms. Are there converging pathways across different FTD-related genes that drive the pathogenesis?
- The recommended approach is to expand the scope and precision of human neuropathologic studies of *C9orf72* and *GRN* mutation carriers to address which pathologic features correlate best with neurodegeneration. For example, more comprehensive studies are needed to understand the relationship between RAN-translated dipeptide repeat protein accumulation, TDP-43 aggregation, RNA foci and neurodegeneration in *C9orf72* carriers. The field should compare human findings with those derived from animal and cell-based models. Mechanistic hypotheses should be tested in appropriate models to drive therapeutic development. An important goal is also to understand the normal function of progranulin, especially during the response to brain

injury. This effort should include determining the role of *GRN* and the modifying factor *TMEM106B*, in lysosomal function. The link between *GRN* haploinsufficiency and the initiation of TDP-43 pathology also needs to be identified via this approach. Finally, the field should continue to identify therapeutic approaches designed to replace/increase *GRN* function.

Recommendation 2 – Priority 2. Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity (3-10 y).

- There is a need to clarify fundamental mechanisms associated with the TDP-43 and FUS proteinopathies and to more fully understand the normal function of these proteins. Do TDP-43/FUS represent toxic, spreading disease proteins? Does loss of normal protein function play a significant role? Is intracellular progression unified across TDP-43 pathological subtypes and what is the sequence of events? What are the upstream events that precede TDP-43/FUS aggregation?
- Our recommended approach is to expand the scope and precision of human neuropathologic studies, focusing on early-stage disease, define the sequence of molecular changes associated with TDP-43/FUS pathogenesis from loss of nuclear localization to the formation of assemblies, and continue to study and define the normal cellular functions of TDP-43 and FUS. Expand research efforts to understand the role of TDP-43/FUS in RNA biology and the potential importance of this function in pathogenesis (e.g. formation of RNA granules or seeding of protein aggregates by RNA). Focused efforts should also be directed at determining whether TDP-43 pathology spreads through interneuronal transmission as proposed for tau and α-synuclein.

Recommendation 3 – Priority 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 (1-3 y).

- Advances in clinical, molecular and genetic platforms enable the generation of large datasets requiring data storage and analysis solutions that are efficient in terms of computing capabilities and costs. Our recommendation is to develop a cloud-based data infrastructure that enables the secure storage of complex datasets, while providing the tools and computing capabilities to support collaborative research through data integration and analysis across complex data modalities. Since FTD clinical trials are at a nascent stage of development, the research community has an opportunity to set a standard for clinical trial data sharing. Support of a data infrastructure that would enable sharing of clinical trial data from both academic and industry-sponsored trials will accelerate advances in clinical trial design and support improvements in clinical assessments for FTD. There is also a substantial unmet need for high quality and well-characterized human post-mortem brain and peripheral tissue for FTD-spectrum research, especially the identification and accessibility of tissue resources which have been collected and analyzed using common protocols across centers. Centralized databases and broad community access to high quality cell, brain and biofluid resources will enable investigators to accelerate FTD basic and clinical research.

Recommendation 4 – Priority 4. Develop better FTD in vivo and cell-based model systems (1-3 y).

- There is a need to improve the tools for disease mechanism and target identification, validation, and drug development. Do existing FTD models reproduce the formation of pathological lesions, associated neurodegeneration, and behavioral impairment?
- The recommended approach is to prioritize development of robust models to study TDP-43, FUS, *GRN* haploinsufficiency, and *C9orf72* hexanucleotide repeat expansion disease, using known and emerging behavioral and pathological features of human disease as the standard for comparison. In addition, continue to evaluate transgenic models of tauopathy and revisit genomic tau transgenes and knock-in models. Emphasize the use of FTD- and FTD-MND-relevant behavioral and motor assays and models with mild clinical phenotypes (e.g., *GRN* mutation heterozygous mice), and develop human iPSC models for genetic and sporadic disease to enable molecular dissection of pathogenesis.

- **Focus Area 2: Clinical science**

Recommendation 5 – Priority 1. Develop FTD biomarkers for diagnosis, prediction and disease monitoring (2-7 y).

- There is a need for better tools for detecting early stage/preclinical disease, establishing molecular diagnosis, assessing target engagement, predicting and monitoring disease progression, and measuring treatment effects, in both proof-of-concept and efficacy studies. These tools need to be cost effective with consideration for ease of use and ability to deploy in remote populations.
- Our recommended approach is to develop molecular biomarkers (blood/CSF/microbiome/PET) for molecular diagnosis of FTLD-tau, -TDP-43, and -FUS. Studies should include post-mortem validation (e.g. immunocytochemistry). Multi-modal -omic approaches, combining complementary data from different methods (protein/RNA/metabolites/lipids) that implicate known molecular pathways/mechanisms should be further emphasized. Alterations in immune system function are increasingly recognized to accompany FTD, but their role in disease pathogenesis is poorly understood. Focused efforts to measure immunological changes (cytokines/cell surface molecules/cell type distributions/responses to stimuli such as bacterial lipopolysaccharides) at different stages of disease in both familial FTD and sporadic syndromes should be pursued. These efforts will help stratify clinical trial cohorts, enable tailored FTD therapy, and provide potential target engagement biomarkers for molecular targets.
- Systems-level outcome biomarkers (digital-wearable/MRI/fMRI/EEG) for detection of early symptoms and monitoring progression at different stages of disease are needed. Wearable/digital approaches (such as sensors and smartphone apps) that continuously monitor behavior remotely and can generate large amounts of data that may increase the power to detect change/treatment effects should be developed. In addition, there is a need to identify the most meaningful clinical endpoints for later-stage clinical trials and pursue deeper behavioral and motor phenotyping to detect emergence of Parkinsonism and motor neuron disease (MND). Efforts should be made to provide bioinformatic

support for biomarker data collection and outreach, for example by enabling remote cognitive testing and data upload from digital-wearable devices, and large-scale sharing of brain imaging or physiological data. Bioinformatic efforts should support integration of these novel systems data across clinical, imaging, genetic and fluid biomarker data. These efforts should include outreach to underserved and minority populations to ensure that developed biomarkers generalize to all at-risk populations.

Recommendation 6 – Priority 2. Advance FTD clinical trial design and execute new prevention and treatment studies (1-5 y).

- There is need to facilitate and manage new and ongoing FTD prevention studies and clinical trials. While progress has been made in building natural history cohorts of familial and sporadic FTD syndromes, the rarity of FTD patients and asymptomatic mutation carriers is a major barrier to testing new therapies. Moreover, in some populations, the initiation of a clinical trial will prevent further collection of natural history data.
- Our recommended approach is to expand support for ascertaining both familial and sporadic FTD cohorts and collect clinical, genetic, and biomarker data using a centralized database/coordinating center. New statistical methods to build more powerful endpoints that account for clinical/imaging/biomarker heterogeneity within specific cohorts should be developed. These data should be used to generate and refine disease models, clinical endpoints, and trial design. Master protocols for FTLD-tau (PSP and *MAPT* mutation-related) and FTLD-TDP-43 (semantic variant primary progressive aphasia (svPPA), FTD-MND, *GRN* or *C9orf72* mutation carriers) should be developed to enable rapid implementation of emerging therapeutic approaches. Conduct community outreach efforts and build tools (such as online registries) to engage underserved, minority and remote populations for inclusion in natural history and clinical trials. Invest in newer data science approaches and build tools that enable online registries to find and engage underserved, minority and remote populations for inclusion in natural history studies and clinical trials.

Recommendation 7 - Priority 3. Expand efforts to genotype patients with FTD, identify new risk factor genes and epigenetic modifiers (1-5 y).

- The most common familial FTD genes have been identified, but genetic modifiers and risk factors for both familial and sporadic FTD are not well understood. Providing genotyping support to enable research on patients with a known genetic status remains a priority.
- Our recommended approach is to provide increased clinical resources to identify and collect FTD patient cohorts, including any remaining genetically unexplained FTD families, with a range of phenotypes. 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. Improve bioinformatics infrastructure for capturing phenotype and genotype information and enabling data sharing. Include families with combined FTD and MND/amyotrophic lateral sclerosis

(ALS) phenotypes in gene discovery studies. Conduct community outreach efforts to capture genetic causes of and risk factors for FTD in underserved and minority populations.

Recommendation 8 – Priority 4. Understand phenotypic heterogeneity and natural history including in health disparities populations (>10 y).

- There is need to understand how genetic background, brain development, and environment are linked to the patient's clinico-pathological syndrome and what factors influence onset age and pace of progression. Understanding these factors may enhance trial design by accounting for variations in anatomical and temporal progression across cohorts and will aid interpretation of trial outcomes. For sporadic FTD, innovative approaches are needed to clarify the pre-symptomatic and prodromal stages of disease in the face of low prevalence.
- Our recommended approach is to conduct natural history studies of preclinical autosomal dominant FTD (especially *MAPT*, *GRN*, and *C9orf72* mutation carriers) by following cohorts of individuals from health to disease. Such studies should employ clinical, biofluid, MRI and other novel assessment tools. In addition, we recommend pursuing parallel longitudinal studies of patients with sporadic FTD, starting from early symptomatic FTD and prioritizing clinical syndromes for which the clinico-pathological correlation is high (e.g., PSP and tau, semantic variant primary progressive aphasia and TDP-43 Type C, FTD with MND and TDP-43 Type B). We recommend seeking genetic, anatomical, and environmental disease modifiers that influence clinico-pathological heterogeneity across inherited and sporadic cohorts. Conduct community outreach efforts to capture underserved and minority populations for inclusion in natural history studies, enabling a more comprehensive picture of disease modifying factors.

Topic 7:

Emerging Scientific Topics

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

Recommendation 1 – Priority 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 Alzheimer's clinical syndrome (5-7 y).

- Develop biomarkers (e.g. imaging, biofluids, etc.) of TDP-43 pathology in pre-symptomatic and manifest common dementias – these may or may not be similar to those that are, or will be in the future, established in FTLD/TDP research.
- Investigate genetic drivers of TDP-43 pathology in common dementias including via GWAS, candidate gene approaches (*GRN*, *TMEM106B*, *ABCC9*, *KCNMB2*, and *APOE*) and other methods of genetic profiling.
- Identify risk factors for TDP-43 pathology in pre-symptomatic and common dementias including but not limited to autoimmune disease/inflammation/thyroid antibodies, vascular disease, and traumatic brain injury.

- Identify cognitive, behavioral, and longitudinal phenotypic profiles of TDP-43 pathology in common dementias.

Recommendation 2 – Priority 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 (3-5 y).

- Support fundamental research that investigates the molecular mechanisms of TDP-43 pathobiology in common dementias and relationships with aging and FTLD pathobiology.
- Support studies that investigate whether the pathways of TDP-43 pathobiology in common dementias are unique or consistent with those in other TDP-43-proteinopathies, including FTLD and ALS.
- Support investigations that focus on the role of endosome/lysosome biology in the context of TDP-43 pathology in common dementias.
- Study the role of the minor allele of TMEM106B and relationships with TDP-43 and resilience especially to cognitive impairment in older persons.
- Use transcriptomics and related molecular and cellular biology studies to investigate mechanisms inducing TDP-43 pathology in common dementias.

Recommendation 3 - Priority 3. Examine the pathologic phenotype(s) of TDP-43 pathology in asymptomatic persons and those with common dementias (5-7 y).

- Investigate the value of different methodologies and the potential for harmonization for the pathologic assessment of TDP-43 pathology including the type of stain (phospho vs. nonphosho antibodies), pathologic assessment (nuclear clearing vs. proteinopathy), TDP-43 inclusion morphology (with analogy to the TDP-43 sub-types of pathology in FTLD-TDP), value of different staging methodologies and burden assessments of TDP-43 pathology in common dementias.
- Study TDP-43 pathology in pre-symptomatic and common dementias compared to FTLD/ALS. Specifically, investigate cellular phenotypes, subtyping, distribution, and hippocampal pathology.
- Investigate hippocampal phenotypes and progression to hippocampal sclerosis associated with TDP-43 pathology in pre-symptomatic persons and those with manifest common dementias.
- Investigate the potential link between TDP-43 pathology and the other common vascular and degenerative pathologies (amyloid, tau, and alpha-synuclein) and their role and interaction in promoting common and multi-etiology dementias.

Recommendation 4 – Priority 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 (3-7 y).

- Develop and characterize animal models designed to simulate TDP-43-dependent clinical, pathologic and molecular phenotypes in common dementias. This may include:
    - Transgenic animal models that express wild-type or mutant TDP-43. Consider using regulatable promoters to drive transgene expression in the appropriate cell type(s) and during the appropriate time of life of the animal.

    - Knock-in, gene-edited or virally transduced animal models.
- Study transmission/neuron-to-neuron spread models that simulate anatomical progression of TDP-43 pathology in common dementias.

➢ Focus Area 2: TBI and AD/ADRD Risk

Recommendation 5 – Priority 1. Encourage crosstalk and interdisciplinary collaboration between TBI and dementia researchers (1-3 y).

- Convene a working group of stakeholders from the TBI & dementia communities to evaluate the extent to which current knowledge in AD/ADRD can be applied to the study of dementia after TBI.
- Leverage existing data resources, research cohorts, and newly developing clinical studies to promote collaboration and accelerate discovery by including TBI exposure in AD/ADRD studies and enriching the design of TBI studies to include multimodal clinical and biological endpoints relevant to neurodegenerative diseases and incident dementia diagnostics.
- Maximize measurement harmonization across TBI and dementia clinical cohort studies to facilitate comparisons and data sharing.
- Encourage collaboration with biostatisticians & epidemiologists to address causal inference and life course changes in the study of TBI-AD/ADRD.

Recommendation 6 – Priority 2. Establish infrastructure to study TBI as a risk factor for AD/ADRD (1-5 y).

- Establish diverse longitudinal prospective studies of individuals with TBI and unexposed controls with harmonized multimodal clinical evaluations and autopsy endpoints.
- Expand efforts to collect brain tissue from individuals with diverse TBI histories (e.g., a history of participation in contact sports or military service, single or repetitive TBI of all severities) in regard to age at injury, severity, mechanism, and chronicity.
- Harmonize methods of neuropathological evaluation across tissue banking centers and develop infrastructure for remote access to facilitate comparison across tissue banks.

Recommendation 7 – Priority 3. Promote basic and clinical research examining the development and progression of TBI AD/ADRD neuropathologies and associated clinical symptoms (2-10 y).

- Characterize TBI-induced neuropathologies and identify similarities and differences, with other neurodegenerative disorders.
- Identify mechanisms (e.g., axonal pathology, inflammation, immune response, neurovascular changes, blood-brain barrier breakdown) that initiate and maintain progressive neuropathological processes after TBI in human and animal models.
- Identify potential neuropathological substrates of dementia in TBI. Characterize the relative burden of individual pathologies in relation to injury severity and mechanism.

Recommendation 8 – Priority 4. Characterize the clinical phenotype of progressive dementia associated with TBI and develop non-invasive diagnostic approaches (2-10 y).

- Establish and validate a provisional clinical definition of TBI-associated dementia(s) that distinguishes chronic static TBI-related symptoms from a progressive neurodegenerative disease.
- Conduct clinical studies to characterize the clinical phenotype, phenotypic heterogeneity, clinical course, and effect modifiers (e.g., post-traumatic stress disorder, sleep disorders, etc.) of post-traumatic dementia in comparison to known dementia subtypes.
- Develop TBI-AD/ADRD biomarkers (e.g., imaging and blood) to non-invasively identify the development of TBI-AD/ADRD pathologies and track their progression over time in relation to dementia.
- Leverage existing and build new infrastructure for accelerating TBI-AD/ADRD biomarker discovery through data and specimen sharing.
- Investigate associations between clinical dementia phenotypes and non-invasive markers of TBI-AD/ADRD to begin to characterize relative contributions of distinct pathological substrates to clinical features and disease progression.
- Investigate the role of comorbid PTSD and TBI in the spectrum of AD/ADRD risk, phenotype, and progression

Table 1: ADRD Summit 2019 Non-Federal Committee Members

Topic Area	Panelist Name	Title and Affiliation
Multiple Etiology Dementias (MED)	David Knopman, MD (co-chair)	Professor, Department of Neurology, Mayo Clinic
	Kate Possin, PhD (co-chair)	Associate Professor, Neurology, University of California San Francisco
	Alireza Atri, MD, PhD	Director, Banner Sun Health Research Institute
	Patricia Boyle, PhD	Professor, Rush University Medical Center
	Jeffrey Burns, MD, MS	Professor, Department of Neurology, Neurocognitive Division Chief, KU Medical Center
	Cynthia Carlsson, MD	Associate Professor, Department of Medicine, Division of Geriatrics, University of Wisconsin-Madison
	Sharon K. Inouye, MD, MPH	Professor, Harvard Medical School
	Heather Snyder, PhD	Senior Director, Alzheimer's Association
Health Disparities (HD)	Lisa Barnes, PhD (co-chair)	Professor, Professor of Gerontology and Geriatric Medicine, Rush University Medical Center
	Hector González, PhD (co-chair)	Associate Professor, Neuroscience, University of California San Diego
	Myriam Fornage, PhD	Professor, University of Texas Health Science Center at Houston
	Rebecca Gottesman, MD PhD	Professor of Neurology, Johns Hopkins University School of Medicine
	J Taylor Harden, PhD, RN, FGSA, FAAN	Director Emeritus, National Hartford Center of Gerontological Nursing
	Jennifer Manly, PhD	Professor of Neuropsychology and Neurology, Columbia University
	Elizabeth Rose Mayeda, PhD, MPH	Assistant Professor of Epidemiology, University of California Los Angeles
	Luis D. Medina, PhD	Assistant Professor, University of Houston
	Bruce Ovbiagele, MD	Associate Dean, San Francisco VA Health Care System
Dementia Nomenclature	Ronald Petersen, MD, PhD (co-chair)	Professor of Neurology, Mayo Clinic College of Medicine
	Angela Taylor, BMus (co-chair)	Senior Director of Research and Advocacy for the Lewy Body Dementia Association
	Paul Appelbaum, MD	Professor, Department of Psychiatry, Columbia University

Dementia Nomenclature (continued)	Sharon Denny, MA	Program Director, Association for Frontotemporal Degeneration
	Peggye Dilworth-Anderson, PhD	Professor of Health Policy & Management, University of North Carolina-Chapel Hill
	Cara Fallon, PhD, MPH	Postdoctoral Fellow, Department of Medical Ethics and Health Policy, University of Pennsylvania
	Mark Herthel, BS	President and Co-Founder, Platinum Performance®
	Cynthia Huling Hummel, BS, MDiv, DMin	National Council on Alzheimer's Research, Care and Service
	Jason Karlawish, MD	Professor of Medicine, Medical Ethics and Health Policy and Neurology, University of Pennsylvania
	David Knopman, MD	Professor, Department of Neurology, Mayo Clinic
	James B. Leverenz, MD	Director of the Lou Ruvo Center for Brain Health; Endowed Chair of the Neurological Institute, Cleveland Clinic
	Shari Ling, MD	Deputy Chief Medical Officer, the Center for Clinical Standards and Quality (CCSQ), Centers for Medicare and Medicaid Services (CMS)
	Sarah Locke, JD	Senior Vice President for Policy; Policy, Research and International Affairs (PRI), American Association for Retired Persons (AARP)
	Lisa McGuire, PhD	Division of Population Health, National Center for Chronic Disease Centers, Disease Control and Prevention (CDC)
	Ivana Rubino, PhD	Global Medical Head of Alzheimer's Disease, Global Medical, Biogen
	Dominic Sisti, PhD	Director of the Scattergood Program for the Applied Ethics of Behavioral Health Care; Assistant Professor, Department of Medical Ethics & Health Policy, University of Pennsylvania
	Sandra Weintraub, PhD, ABCN/ABPP	Professor of Psychiatry and Behavioral Sciences, Neurology and Psychology, Northwestern University Feinberg School of Medicine
	Mary Widmeyer, MD	Neurologist, Mayo Clinic

Lewy Body Dementias (LBD)	Bradley Boeve, MD (co-chair)	Director, Division of Behavioral Neurology, Department of Neurology; Professor of Neurology, Mayo Clinic
	Carol Lippa, MD (co-chair)	Director, Cognitive Disorders & Comprehensive Alzheimer's Disease Center; Director, Division of Cognitive Disorders, Thomas Jefferson University
	Dag Aarsland, MD, PhD	Chair of Old Age Psychiatry, King's College London
	Mark Cookson, PhD	Senior Investigator, Laboratory of Neurogenetics , National Institute on Aging Intramural Research Programs
	Dennis Dickson, MD	Professor of Laboratory Medicine And Pathology, Mayo Clinic
	Kirk Frey, MD, PhD	Professor, Radiology and Neurology, University of Michigan
	Douglas Galasko, MB, BCh	Professor, Department of Neurosciences, University of California San Diego; Staff Physician, VA Medical Center
	Jennifer G. Goldman, MD, MS, FAAN, FANA	Professor of Physical Medicine and Rehabilitation and Neurology, Northwestern University Feinberg School of Medicine
	Peter Lansbury Jr, PhD	Chief Scientific Officer of Lysosomal Therapeutics, Inc
	Sonja Scholz, MD, PhD	Investigator, Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke Intramural Research Program
	Angela Taylor, BMus	Senior Director of Research and Advocacy for the Lewy Body Dementia Association
	Daniel Weintraub, MD	Professor of Psychiatry and Neurology, University of Pennsylvania School of Medicine; Psychiatrist, Philadelphia Veterans Affairs (VA) Medical Center
Vascular Contributions to Cognitive Impairment and Dementia (VCID)	Donna Wilcock, PhD (co-chair)	Endowed Professor, University of Kentucky in Lexington
	Jeff D. Williamson, MD, MHS (co-chair)	Professor of Internal Medicine and Epidemiology, Wake Forest University School of Medicine
	Roxana Carare, MD, PhD	Professor of Clinical Neuroanatomy, University of Southampton
	Susan Catalano, PhD	Chief Science Officer, Cognition Therapeutic, Inc.
	Rebecca Gottesman, MD PhD	Professor of Neurology, Johns Hopkins University School of Medicine
	Douglas B. Gould, PhD	Professor of Ophthalmology and Anatomy, University of California San Francisco School of Medicine

Vascular Contributions to Cognitive Impairment and Dementia (VCID) (continued)	Vladimir Hachinski, MD (pre-Summit calls)	Professor, Clinical Neurological Sciences, Western University
	Anne Leonard, MPH, RN, BSN	Sr. Science and Medicine Advisor, American Heart Association
	Henrieta Scholtzova, MD, PhD	Research Assistant Professor, Department of Neurology and the Center for Cognitive Neurology, New York University Langone Medical Center
	Andy Shih, PhD	Associate Professor, Seattle Children's Research Institute; Department of Pediatrics, University of Washington
	Eric Smith, MD, MPH, FRCPC, FAHA	Associate Professor of Neurology, Radiology and Community Health Sciences, University of Calgary
	Heather Snyder, PhD	Senior Director, Alzheimer's Association
	Kristine Yaffe, MD	Endowed Chair and Vice Chair and Professor of Psychiatry, Neurology, and Epidemiology, University of California San Francisco
Frontotemporal Lobar Degeneration (FTLD)	Adam Boxer, MD, PhD (co-chair)	Endowed Professor, Department of Neurology, University of California San Francisco
	Leonard Petrucelli, PhD (co-chair)	Chair, Department of Neuroscience, Mayo Clinic Florida
	Patrick Brannelly, MBA	Program Director of the Rainwater Foundation's Tau Consortium
	Anthony Fitzpatrick, PhD	Assistant Professor, Biochemistry and Molecular Biophysics, Columbia University
	Nick Fox, MD	Professor, Clinical Neurology, University College London
	Carole Ho, MD	Chief Medical Officer, Head of Development, Denali Therapeutics
	Manolis Kellis, PhD	Professor, Computer Science, Massachusetts Institute of Technology
	Rodney Pearlman, PhD	President, The Bluefield Project to Cure Frontotemporal Dementia
	Jonathan Rohrer, MD, PhD	Clinician Scientist and Consultant Neurologist, University College London
	Jeffrey Rothstein MD, PhD	Director for the Brain Science Institute; Professor, Neurology and Neuroscience, Johns Hopkins University School of Medicine
	Holly Soares, PhD	Translational Neuroscience, AbbVie

Frontotemporal Lobar Degeneration (FTLD) (continued)	Nadine Tatton, PhD	Scientific Director, Association for Frontotemporal Degeneration
	Michael Ward, MD, PhD	Investigator, Inherited Neurodegenerative Diseases Unit, National Institute of Neurological Disorders and Stroke Intramural Research Program
	Henrik Zetterberg, MD, PhD	Professor of Neurochemistry at the University of Gothenburg, Sweden; Professor, University College London, UK
Emerging Scientific Topics	Kristen Dams-O'Connor, PhD (co-chair)	Director, Brain Injury Research Center, Mount Sinai; Associate Professor, Departments of Rehabilitation Medicine and Neurology, Icahn School of Medicine at Mount Sinai in New York
	Julie Schneider, MD, MS (co-chair)	Professor of Pathology (Neuropathology) and Neurological Sciences; Associate Director at the Rush Alzheimer's Disease Center, Rush University Medical Center
	Aaron Gitler, PhD	Professor of Genetics at Stanford University
	Pete Nelson MD, PhD	Director of the Neuropathology Division of the Pathology Department, University of Kentucky Medical Center
	Mary Jo Pugh, PhD	Research Career Scientist/Professor , IDEAS COIN, VA Salt Lake City and University of Utah
	Douglas Smith, MD	Endowed Professor and Vice Chairman of Neurosurgery, Director of the Center for Brain Injury and Repair, University of Pennsylvania
	Henrik Zetterberg, MD, PhD	Professor of Neurochemistry at the University of Gothenburg, Sweden; Professor, University College London, UK

Table 2: ADRD Summit 2019 Federal Committee Members

Panelist name	Title and Affiliation	Role
Walter Koroshetz, MD	Director, NINDS	Steering Committee
Roderick Corriveau, PhD	Program Director, Division of Neuroscience, NINDS	NIH Summit Lead
Debra Babcock, MD, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead
Patrick Bellgowan, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead
Francesca Bosetti, PhD	Program Director, Division of Neuroscience, NINDS	Organizing Committee
Marishka Brown, PhD	Program Director, NHLBI	Organizing Committee
Jue Chen, PhD	Program Officer, NHLBI	NIH Session Lead
Cerise Elliott, PhD	Program Director, Dementias of Aging Branch, Division of Neuroscience, NIA	NIH Session Lead
Robert Finkelstein, PhD	Director, Division of Extramural Research, NINDS	Organizing Committee
Lawrence Fine, MD	Branch Chief, Clinical Applications and Prevention Branch, NHLBI	Organizing Committee
Zorina Galis, PhD	Branch Chief, Vascular Biology and Hypertension Branch	Organizing Committee
Yunling Gao, PhD	Program Officer, Vascular Biology and Hypertension Branch	Organizing Committee
Jordan Gladman, PhD	Health Program Specialist, Division of Neuroscience, NINDS	Organizing Committee
David Goff, Jr., MD, PhD	Director, Division of Cardiovascular Sciences, NHLBI	Organizing Committee
Amelie Gubitz, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead
Carl Hill, PhD, MPH	Director, NIA Office of Special Populations, Office of the Director, NIA	Organizing Committee
John K. Hsiao, MD	Program Director, Dementias of Aging Branch, Division of Neuroscience, NIA	NIH Session Lead
Sophia Jeon, PhD	Health Science Policy Analyst, Office of Science Policy and Planning, NINDS	NIH Session Lead

Melinda Kelley, PhD	Director, Office of Legislation, Policy, and International Activities, NIA	NIH Session Lead
Jim Koenig, PhD	Program Director, Division of Neuroscience, NINDS	Organizing Committee
Eliezer Masliah, PhD	Deputy Director, Division of Neuroscience, NIA	Steering Committee, NIH Session Lead
George Mensah, MD, FACC	Division Director, NHLBI	Organizing Committee
Claudia Moy, PhD	Program Director, Division of Clinical Research, NINDS	NIH Session Lead
Margaret Ochocinska, PhD	Program Director, Translational Blood Science and Resources Branch, Division of Blood Diseases and Resources, NHLBI	Organizing Committee
David Owens, PhD	Acting Deputy Director, Division of Extramural Research, NINDS	Organizing Committee
Suzana Petanceska, PhD	Program Director, Dementias of Aging Branch, Division of Neuroscience, NIA	Organizing Committee
Terri Postma, MD	Centers for Medicare and Medicaid	Organizing Committee
Jonathan Sabbagh, PhD	Health Program Specialist, Division of Neuroscience, NINDS	Organizing Committee
Paul Scott, PhD	Director, Office of Science Policy and Planning, NINDS	Organizing Committee
Beth-Anne Sieber, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead
Nina Silverberg, PhD	Program Director, Division of Neuroscience, NIA	NIH Session Lead
Margaret Sutherland, PhD	Program Director, Division of Neuroscience, NINDS	NIH Session Lead
Margo Warren	Deputy Director, Office of Communications and Public Liaison, NINDS	Organizing Committee
Clinton Wright, MS, MD	Division Director, Division of Clinical Research, NINDS	Organizing Committee

Appendix 1: List of Past and Current 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

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

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

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)

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

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)

PAR-18-175: Pilot Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01)

PAR-18-028: Phase III Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline

PAR-18-513: Alzheimer's Clinical Trials Consortium (ACTC) Clinical Trials (R01); Additional Guidance Online

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

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

PAR-18-029; PAR-18-181: Clarifying the Relationship between Delirium and Alzheimer's Disease and Related Dementias (R01; R21/R33)

PAR-18-519: Sensory and motor system changes as predictors of preclinical Alzheimer's disease (R01)

PAR-18-329: Technology to Detect, Monitor and Assess Daily Functions in Individuals with Cognitive Decline, Alzheimer's Disease and/or Alzheimer's Disease Related Dementias (AD/ADRD) (R43/R44)

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

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

PAR-17-072: Revision Awards to Institutional Training Programs to Advance Research on Alzheimer's Disease and Alzheimer's Disease Related Dementias (T32)

RFA-AG-17-063: Institutional Training Programs to Advance Translational Research on Alzheimer's Disease and AD Related Dementias (T32)

PAR-17-054: Leveraging Existing Cohort Studies to Clarify Risk and Protective Factors for Alzheimer's Disease and Related Dementias (R01)

PAR 15-359: Novel Approaches to Diagnosing Alzheimer's Disease & Predicting Progression (R01)

Multiple Etiology Dementias (MED)

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)

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)

Lewy Body Dementias (LBD)

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)

Frontotemporal Degeneration (FTD)

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 (FTD) (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 National Institute on Aging and the National Institute of Neurological Disorders and Stroke

Vascular Contributions to Cognitive Impairment and Dementia (VCID)

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

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

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-AG-17-055: Brain Lymphatic System in Aging and Alzheimer's Disease (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-NS-16-021: Mechanistic Basis of Diffuse White Matter Disease in Vascular Contributions to Cognitive Impairment and Dementia (VCID)(R01)

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

Health Disparities (HD)

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

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)

PAR-15-350: Emerging Directions for Addressing Health Disparities in Alzheimer's Disease (R03)

Appendix 2: ADRD Summit 2016 Milestones Progress and Implementation

Topic 1: Multiple Etiology Dementias (MED)		
Focus Area 1: Improved Diagnostic Skills in the Community		
Milestone	**Timeline (Timeframe)[1]**	**Progress**
1. Detect cognitive impairment when patient or relative voices a concern to health care providers.	3-7 years (2017)	RFA-NS-17-012 resulting in DetectCID
2. Improving differential diagnosis of symptomatic cognitive impairment.	3-7 years (2017)	PAS-17-028 Other Responsive Awards
3. Increase training of health professionals to meet the expanding demand for cognitive impairment and dementia diagnosis and care, as well as the critical challenges of and need for human-based research.	7-10 years (2017)	PAR-17-072 RFA-AG-17-063 NOT-NS-19-003 Responsive Awards - IADRP
4. Develop diagnostics/biomarkers in asymptomatic individuals.	3-7 years (2017)	Responsive Awards
Focus Area 2: Basic and Clinical Research in Interactions between Dementia Pathophysiologies		
Milestone	**Timeline (Timeframe)**	**Progress**
5. Promote basic and clinical research in multi-etiology dementia.	3-7 years (2017)	PAS-17-028 PAR-18-661 RFA-NS-19-026 RFA-NS-19-030 PAR-19-167 RFA-NS-19-027 Other Responsive Awards
Focus Area 3: Determining the Role for Screening for Cognitive Dysfunction		
Milestone	**Milestone**	**Milestone**
6. Determining the value of screening for clinically relevant cognitive impairment in the absence of a cognitive complaint.	7-10 years (2017)	

[1] Timelines and timeframes are approximate throughout Appendix 2. Timelines represent time to completion or full implementation from the start of work; timeframes are the suggested year for beginning implementation based on readiness of the scientific community. Actual pace of milestone plan reflects resources.

Topic 2: Non-Governmental Organizations (NGOs)

Focus Area 1: Catalyzing Research through Unique Programs and Partnerships

Milestone	Timeline (Timeframe)	Progress
1. Establish more effective communication between NIH and NGOs on activities and progress toward ADRD goals in the off-years between triennial ADRD Research Summits.	Ongoing activity (2016)	NINDS Update Presentations at NAPA Council: 2/2017, 10/2018 ADRD Roundtable Meeting at the NIH 6/2017, 6/2018

Special Joint NGO & MED Topic: Addressing Nomenclature for Discussing Cognitive Impairment and Dementia

NGO Focus Area 2: Nomenclature Standards when Discussing Dementia
MED Focus Area 4: Revisiting the Nosology of Cognitive Impairment in Late Life

Milestone	Timeline (Timeframe)	Progress
2. (NGO) Organize a working group of dementia stakeholders, including founding partnerships with health disparities communities, to review the current nomenclature used in public awareness, clinical care services and research and to propose strategies to help advance early differential diagnosis and the understanding of dementia and its underlying causes. 7. (MED) Developing a consistent nomenclature in Dementia Research and Care.	Ongoing activity (2017)	*Elevated to National Plan*: 2016 Update; Appendix 2, Rec 4 2017 Update; Appendix 2, Rec 4 RESEARCH SUMMIT ON DEMENTIA CARE: TERMINOLOGY ISSUES ADRD Summit 2019, Topic 3

Topic 3: Health Disparities (HD)

Focus Area 1: Treatment and Prevention Strategies

Milestone	Timeline (Timeframe)	Progress
1. Assess epidemiology and mechanistic pathways of disparities in health burden of AD/ADRD.	3-7 years (2016)	PAR-15-349 PAR-15-350 VCID and Stroke in a Bi-racial National Cohort RFA-NS-19-012 Other Responsive Awards
2. Enrich the design of trials of vascular health interventions to improve their application to AD/ADRD among aging diverse populations.	3-7 years (2017)	

Focus Area 2: Monitoring Changes in AD/ADRD Disparities

Milestone	Timeline (Timeframe)	Progress
3. Develop a system to monitor the magnitude and trends in health disparities in incidence of AD/ADRD.	3-7 years (2017)	Responsive Awards

Focus Area 3: Assessment

Milestone	Timeline (Timeframe)	Progress
4. Improve tools for assessment of disparities in risks, preclinical disease characteristics, and costs of AD/ADRD among health disparities populations by leveraging existing data and cohorts, designing targeted studies, and using advanced psychometric analyses for improving tools for assessment of disparities in risks, preclinical disease characteristics, and costs of AD/ADRD among health disparities populations.	1-3 years (2016)	RFA-NS-17-012 resulting in DetectCID Other Responsive Awards
5. Increase utilization of culturally- and linguistically- appropriate assessment tools within ongoing and newly generated studies of AD/ADRD and vascular health intervention trials.	1-3 years (2016)	

Focus Area 4: Community Partnerships, Recruitment, and Retention

Milestone	Timeline (Timeframe)	Progress
6. Generate an AD/ADRD Health Disparities Task Force that is specifically designed to provide guidance and expertise for community engagement, study design, recruitment and retention into sites to ensure recruitment of diverse populations into newly generated epidemiological studies and clinical trials.	1-3 years (2016)	
7. Develop novel community engagement and outreach methods and identify existing methods to facilitate engagement, understanding and partnership with health disparities populations.	1-3 years (2016)	NIH AD/ADRD Recruitment & Retention Strategy for Clinical Research Planning Efforts

Topic 4: Lewy Body Dementias (LBD)

Focus Area 1: Establish Longitudinal Diverse Cohorts with Common Measures, Culminating in Autopsy

Milestone	Timeline (Timeframe)	Progress
1. Initiate clinical trials for motor and non-motor manifestations of Lewy Body dementias (LBD), which is meant to include both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), in diverse populations using existing and newly developed therapies that address symptoms that have the greatest impact on patient function and caregiver burden.	1-3 years (2016)	RFA-NS-18-017
2. Create longitudinal clinical, biological, and imaging resources for LBD from the earliest stages to autopsy to improve accuracy of detection and diagnosis of DLB at the pre-dementia or prodromal stage and to detect PD patients with a high risk of cognitive decline leading to PDD.	7-10 years (2016)	RFA-NS-17-016 PAR-18-661 PAS-19-210 PAR-19-170 Other Responsive Awards

Focus Area 2: Discover Disease Mechanisms Through Brain Mapping and Genetics

Milestone	Timeline (Timeframe)	Progress
3. Using well defined cohorts of LBD who have come to autopsy, systemically characterize disease-specific changes in the brain, spinal cord, and peripheral autonomic nervous system with state-of-the-art methods, including genomics, expression arrays, metabolomics, and proteomics to identify underlying disease mechanisms that will guide future biomarker and therapeutic approaches. Data generated in this initiative should be incorporated into an open-access, centralized data management system that links clinical, biological, and autopsy data.	3-7 years (2018)	RFA-NS-17-016 RFA-NS-18-015 Other Responsive Awards
4. Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that impact the risk for and clinical features of LBD.	3-7 years (2016)	PAR-17-054 Other Responsive Awards

Focus Area 3: Develop and Validate Biological and Imaging Biomarkers

Milestone	Timeline (Timeframe)	Progress
5. Develop imaging approaches to 1) enhance the differential diagnostic accuracy of LBD compared to other dementing illnesses, 2) detect latent and prodromal LBD, and 3) monitor disease progression in natural history and treatment studies by integrating established and new imaging tools. Validate these tools against postmortem neuropathology.	3-7 years (2016)	RFA-NS-16-022 RFA-NS-17-016 PAS-19-210 PAR-19-170 Other Responsive Awards

6. Use new (see 4.1.2) or existing longitudinal case-control studies of individuals with LBD, longitudinal cohort studies tracking cognitive decline, or studies capturing incident cases of LBD, to develop biomarkers for LBD-related pathologic changes, diagnosis, differential diagnosis, disease progression, and the relative amount of Alzheimer's and other pathologies. As new markers of molecular disease mechanisms are discovered, incorporate them into biomarker studies for diagnosis of latent or prodromal disease and for monitoring molecular processes and their response to therapies.	3-7 years (2017)	RFA-NS-16-022 RFA-NS-17-016 PAS-19-210 PAR-19-170 Other Responsive Awards

Focus Area 4: Model Disease Processes to Develop Potential Symptomatic and Disease Modifying Therapies

Milestone	Timeline (Timeframe)	Progress
7. Recognizing the importance of alpha-synuclein and AD pathophysiologic processes in LBD, new animal, cellular, and *in vitro* models are needed that recapitulate key features, including clinical heterogeneity, of these disorders with the ultimate goal of identifying strategies that can be carried forward into clinical trials.	7-10 years (2017)	RFA-NS-18-024 PAR-19-167 RFA-NS-19-027 RFA-NS-19-013 RFA-NS-18-024 Other Responsive Awards
8. Develop disease-modifying interventions for LBD based on discovering biomarkers, molecular targets, and genetic and environmental modifiers that enhance, delay or prevent the onset of disease.	7-10 years (2018)	RFA-NS-19-015 RFA-NS-18-017

Topic 5: Frontotemporal Lobar Degeneration (FTD)

Focus Area 1: Basic Science: Pathogenesis and Toxicity

Milestone	Timeline (Timeframe)	Progress
1. Clarify the mechanism of tau pathogenesis and associated neurodegeneration.	3-7 years (2016/2017)	RFA-NS-16-023 resulting in Tau Center Without Walls RFA-NS-18-015 Other Responsive Awards
2. Determine the molecular basis for *C9ORF72* expansion- and *GRN* mutation-related neurodegeneration.	7-10 years (2016/2017)	RFA-NS-18-015 Other Responsive Awards
3. Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity.	7-10 years (2016/2017)	RFA-NS-18-015 Other Responsive Awards
4. Develop better FTLD *in vivo* and cell-based model systems.	1-3 years (2016/2017)	PAR-19-167 RFA-NS-19-027 Other Responsive Awards

Focus Area 2: Clinical science

Milestone	Timeline (Timeframe)	Progress
1. Expand efforts to genotype patients with FTD and identify new genes and their functional relationship to FTLD pathogenesis.	3-5 years (2017/2018)	RFA-NS-17-017 Other Responsive Awards
2. Develop FTD biomarkers for diagnosis and disease progression.	3-7 years (2017/2018)	PAR-18-661 Other Responsive Awards
3. Create an international FTD clinical trial network.	1-3 years (2017/2018)	
4. Understand phenotypic heterogeneity and natural history.	>10 years; in progress	ARTFL-LEFFTDS NOT-NS-18-082 Other Responsive Awards

Topic 6: Vascular Contributions to Cognitive Impairment and Dementia (VCID)

Focus Area 1: Basic Mechanisms and Experimental Models

Milestone	Timeline (Timeframe)	Progress
1. Develop next-generation experimental models and translational imaging methods for VCID. Establish new animal models that: (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 dementia via both white matter and grey matter or (iv) include genetic and acquired conditions that are associated with VCID.	3-7 years (2016)	PAR-19-167 RFA-NS-19-027 Other Responsive Awards - IADRP
2. Encourage basic science research that investigates the impact of aging, AD pathology, and genes on peri- and para-vascular clearance mechanisms, the NVU, and cerebrovascular function.	3-7 years (2018)	RFA-NS-16-021 RFA-AG-17-055 PAR-18-413 Other Responsive Awards
3. Encourage basic science research that investigates the impact of cerebrovascular risk factors/genes and atherosclerosis on AD-related neurodegeneration.	3-7 years (2018)	Responsive Awards

Focus Area 2: Human-Based Studies

Milestone	Timeline (Timeframe)	Progress
1. Develop and validate longitudinally tracked noninvasive markers of key vascular processes related to cognitive and neurologic impairment.	Develop: 1-3 years (2016) Validate: 3-7 years (2018)	RFA-AG-15-010 RFA-NS-16-019 & RFA-NS-16-020 resulting in MarkVCID Other Responsive Awards
2. Determine interrelationships (cross-sectional and longitudinal) among aging, cerebrovascular disease and risk factors, resilience factors, genetic variants, amyloid, tau, and neurodegeneration.	3-7 years (2018)	RFA-AG-15-010 PAR-17-054 VCID and Stroke in a Bi-racial National Cohort (REGARDS) RFA-NS-19-012 Other Responsive Awards
3. Identify lifestyle and vascular interventions to treat, prevent, or postpone VCID.	7-10 years (2022)	RFA-NS-19-015 Other Responsive Awards