Abstract. This document reports to the NINDS Council the results of the Alzheimer’s Disease-Related Dementias (ADRD) Summit 2016, held in Natcher Auditorium on the NIH campus. The March 29-30, 2016 event complements the National Institute on Aging’s (NIA) Alzheimer’s Disease (AD) 2012 and 2015 Research Summits, and follows the ADRD Conference 2013 held by NINDS in collaboration with NIA. These conferences 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 conferences, the ADRD Summit 2016 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 5 to 10 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 2016 recommendations in the next annual update of the National Plan, thus refining, revising, and adding to the previously included ADRD 2013 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 more than 47 million people worldwide. Alzheimer’s disease alone, as one dementia disorder, affects more than 5 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) that was signed into law in 2011 by President Obama, 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. The National Plan’s Goal 1 aims to prevent and effectively treat AD/ADRD (delay onset, slow progression) by 2025. 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 first ADRD Summit, the ADRD Conference 2013, established initial, detailed ADRD-specific research priorities in the National Plan, including those related to health disparities (HD). As follow-up to the ADRD Conference 2013, NINDS held the second ADRD Summit, the subject of this report to Council, on March 29-30, 2016.

AD, with its characteristic brain pathology of beta-amyloid (plaques) and tau (tangles), is the most common dementing disease, contributing to about two-thirds of dementia cases. Though plaques and tangles are the most common brain pathologies observed in individuals with dementia, other pathologies contribute substantially to the burden of cognitive decline and dementia in neurodegenerative diseases, including in more than half of individuals with clinically diagnosed AD. Several pathologies, e.g., tau, alpha-synuclein, TDP-43 and cerebrovascular-related injury, are known to occur in all (tau) 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.

Thus, the National Plan addresses several other 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 dementia (LBD), vascular contributions to cognitive impairment and
dementia (VCID) and 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 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 Conference in 2013 and the ADRD Summit in 2016, together with NIA’s AD Summits in 2012 and 2015, and the 2013 AD in Individuals with Down Syndrome meeting, 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 two-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 first set in 2013 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 in FY 2016 as outlined in the Session Highlights section below.

The goals of the ADRD Summit 2016 were to review and assess progress on the research recommendations developed by the ADRD Conference 2013, 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 are expected to become part of the National Plan and inform future AD/ADRD bypass budgets. The 2016 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, 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 2016, NINDS also included a session led by non-governmental organizations (NGOs) to broaden stakeholder input.

In general, planning and execution of the ADRD Summit 2016 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. A brief outline of major activities in advance preparation, the Summit itself, and follow-up, appears below.

**Advance Preparation for 2016 Summit.** Pre-summit efforts began in late summer 2015, when NINDS and NIA leadership and staff convened with the ADRD Summit 2016 Scientific Chair to develop an overall strategy. Areas of focus included defining topic areas corresponding to the six summit sessions, and selecting scientific chairs for each session. The session chair/s, together with NIH session leads, then formed committees by selecting a roster of experts for each topic area. Committees thus consisted of 8 to 18 scientific members (Table 1) tasked with assessing progress on the 2013 ADRD research
recommendations (Montine et al., 2014; ADRD 2013), 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 2015 and March 2016. NIH staff provided the committees with responses to a joint NINDS/NIA Request for Information (NOT-NS-15-045) that solicited public input on updating the ADRD research priorities, as well as with a portfolio analysis of grants relevant to ADRD that received NIH funding in FY 2014 and/or 2015 together with publicly available information on major ADRD projects funded by industry and NGOs. Cross-committee coordination occurred through a monthly teleconference of the Summit Organizing Committee consisting of: session committee scientific chairs (as listed in Table 1); the Summit Scientific Chair (Dr. David Holtzman); NIH and other federal officials (Table 2), including NINDS/NIH Summit lead Dr. Roderick Corriveau; and the Steering Committee (Dr. Tony Phelps from NIA; Dr. Ron Petersen, Chair of the NAPA Council; Dr. Tom Montine, past ADRD Scientific Chair; and NINDS Council members Dr. Karen Chen and Dr. Bruce Obviagele).

As in 2013, and at the request of the NAPA Council, the highest priorities have been designated #1 by the session committees (see full recommendations below). 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 in 2013, each committee estimated the number of years needed to complete or fully implement each recommendation; however, the 2016 recommendations also include more specific timeframes that represent the session committee’s suggested calendar year for beginning implementation of recommendations based on readiness of the scientific community.

As a result of this preparatory work, the ADRD Summit 2016 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 2016 was advertised broadly to the scientific community, government agencies, and NGOs, resulting in 490 registrants. Of these, 325 individuals joined in person and there were more than 300 additional views online. As with the 2013 ADRD Conference, the primary goal of the Summit was to solicit input and feedback from a wide range of ADRD stakeholders on the draft recommendations, timelines, and timeframes that had been prepared in advance. Following a general overview, each session’s chairs presented a summary of scientific progress that had occurred since 2013 and then proposed updated and refined research recommendations for public input. The NGO session, which was new in 2016, thus presented two new draft recommendations. Each of the six topic sessions included ample time for discussion and exchange with attendees. Those viewing remotely also had the opportunity to offer online input. The public portion of the Summit concluded March 30 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 2016 Draft 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.

**Organizing Participants and Sponsorship.** Full membership of the ADRD Summit 2016 session committees appears in Tables 1 and 2. NIA participation complemented NINDS’ efforts through the efforts of Dr. Richard Hodes, Dr. Tony Phelps, and Dr. Nina Silverberg. Additional Summit sponsors included the NIH Office of Disease Prevention, the Foundation for the National Institutes of Health, the Alzheimer’s Association, Accelerate Cure/Treatments for Alzheimer’s Disease (ACT-AD), the American Heart Association/American Stroke Association, the Association for Frontotemporal Degeneration (AFTD), Axovant Sciences, the BrightFocus Foundation, and the LEAD Coalition (Leaders Engaged on Alzheimer’s Disease Coalition).

**Session Highlights.** The six 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. Summit highlights, including reference to challenges, progress, and priorities going forward, are described below. Note that the format of the 37 draft 2016 prioritized research recommendations (page 10) is not uniform across all six topic areas: this was a deliberate decision intending to enable flexibility of optimal prioritization within each topic area. Timelines, however, are uniform across topic areas (1-3 yr, 3-7 yr, 7-10 yr, or >10 yr) and reflect time to completion or to achieve fully operational status for the recommendation after work is initiated. As previously stated, in 2016, the organizing committee chose to indicate the suggested start years for implementation for all recommendations.

As was the case with the 2013 ADRD Conference 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 and timeframes (starting years) 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, NGO, LBD, FTLD, VCID) are of equally high priority.

**Session 1. Multiple Etiology Dementias (MED) – Diagnosing Dementia in the 21st Century (Chairs: David Bennet, MD, David Knopman, MD)**

The MED session committee re-emphasized the main 2013 MED priority of improving recognition and diagnosis of cognitive decline, aiming for a balance of aspirational versus operational goals. It is increasingly clear that symptomatic cognitive impairment and dementia can result from a wide range of conditions. In individuals over 65 who develop mild cognitive impairment and dementia, the pathological changes that underlie observed symptoms and signs are often due to more than one disease process. For example, AD pathology (plaques and tangles) is usually accompanied by additional pathological processes that may also contribute to cognitive decline and dementia. Contributing further to diagnostic complexity is a lack of clarity regarding the degree of underlying brain pathologies present in a given individual during life. This provokes uncertainty about how much each disease process contributes to observed cognitive impairment and dementia. The revised 2016 MED recommendations advocate for a more detailed and streamlined plan of action that carefully addresses the most imminent challenges associated with recognizing and diagnosing cognitive decline. The first goal, and Recommendation #1, is to be able to reliably detect cognitive impairment when an individual or a relative voices a concern to health care providers. Finally, both the MED and the NGO sessions
recognized and discussed challenges associated with the variable use of cognitive impairment and dementia terminology by scientists, physicians, patients, and the public at large. As such, the two committees developed complementary recommendations on nomenclature, and the Summit agenda included a Special Joint Session on nomenclature (see below).

Session 2. Non-Governmental Organizations (NGOs) (Chairs: Susan Dickinson, Howard Fillit, MD)

A change from the 2013 ADRD Conference was the addition of a dedicated session for NGOs that represented various AD/ADRD communities, including nonprofit disease associations, patient advocacy organizations, and private foundations. The NGO committee highlighted how NGOs strive to catalyze ADRD research by fostering unique partnerships across diseases, national borders, and stakeholders, and by providing swift and flexible research funding that complements funding from NIH, other federal agencies, and industry. For its Recommendation #1, this committee emphasized that NGOs seek to establish a more effective dialogue with NIH about activities and progress toward achieving ADRD research goals – especially in the years between the NIH-hosted ADRD summits. Like the MED committee, the NGO committee recognized and addressed, in its Recommendation #2, challenges associated with nomenclature used for cognitive impairment and dementia. Both of these committees offered draft recommendations on dementia nomenclature, and these were presented and discussed during a Special Joint Session on nomenclature.

Special Joint Session: Nomenclature Discussion – Led by the NGO (Angela Taylor) and the MED Committees (David Knopman, MD)

Stakeholders refer to cognitive decline and dementia in diverse ways. There was broad agreement in pre-discussions and at the 2016 Summit itself that the variable use of terminology is a barrier to reducing disease burden. The lack of a standardized lexicon impairs much needed communication with patients, caregivers, and decision makers at all levels. Consequences are many and include missed therapeutic opportunities for reversible conditions or treatable symptoms that go unrecognized; confused communication and policy such as when one term is used (e.g., AD) but a broader applicability is intended (e.g., all forms of dementia); and frustration when families receive different diagnoses from different clinicians. A connected challenge is that while clinical diagnosis with a named dementia syndrome is accurate for some patients, for others it provides an incomplete and/or inaccurate clinical picture; moreover, there is a tendency to confound syndromic diagnosis with disease cause and etiology, which frequently remains unknown for all but rare genetic cases of dementia. Because of the high potential for impact, including in health disparities and stigma, the NGO and MED session committees both recommended beginning a national dialogue to establish standards for cognitive impairment and dementia nomenclature. There is consensus that although the most effective language and terms for different stakeholders may not be identical, the language framework must be standardized and interoperable.

Session 3. AD/ADRD Health Disparities (HD) (Chair: Jennifer Manly, PhD)

Despite the higher reported prevalence of cognitive impairment in African Americans and Hispanics compared to age-matched whites, for example in the 2006 Health and Retirement study and the 2016 Kaiser Permanente Northern California study, knowledge of relevant epidemiology and mechanistic pathways for ADRD in disparities populations remains more rudimentary than it is for whites. One reason is because individuals in health disparities populations are less likely to receive a diagnosis, and if they do it is typically at a later stage in disease progression. Despite challenges, some research progress
has been made since the 2013 ADRD Conference, particularly by: leveraging existing studies of diverse cohorts to include neuropsychological assessment and adding AD and ADRD biomarkers; using existing local expertise and resources to evaluate AD/ADRD in diverse communities; developing or adapting assessment tools for use in disparities populations; and investigating potential disparities mechanisms. NIH also launched two targeted funding initiatives that address AD/ADRD health disparities: Health Disparities and Alzheimer’s disease, and Emerging Directions for Addressing Health Disparities in Alzheimer’s disease. To help clarify goals, flow and purpose of the ADRD Health Disparities recommendations, the Health Disparities committee split the two focus areas defined in 2013 into four focus areas with seven fully revised recommendations prioritized from #1 to #7. The two original focus areas remain, i.e., Recruitment (now referred to as Community Partnerships, Recruitment, and Retention) as well as Treatment and Prevention Strategies. New focus areas include Monitoring Changes in ADRD Disparities, and Assessment. This reorganization of focus areas reflects new emphasis and prioritization, in particular on research mechanisms of disparities and life-course pathways of disease, tracking cognitive and other relevant changes over time, and the value of equal community partnerships.

Session 4. Lewy Body Dementias (LBD) (Chairs: Dennis Dickson, MD, Karen Marder, MD)

LBD includes Parkinson’s disease dementia (PDD) and dementia with Lewy bodies (DLB). These disorders are characterized by aggregation of alpha-synuclein in specific brain regions with dopaminergic degeneration, along with or in the absence of a variety of other changes. As with other ADRD, LBD research and clinical care will benefit significantly from nomenclature standards. There have been several advances over the last three years in defining genetics, brain network changes, biomarkers, and cell biology of LBD, including the potential role of prion-like spreading of synuclein pathology. In 2016, NINDS issued the RFA entitled Biomarkers for the Lewy Body Dementias. The LBD committee retained Recommendation #1 from 2013, affirming the need to establish longitudinal cohorts; to better define genetics and network changes; to develop more specific biomarkers for synucleinopathy; and to more thoroughly understand pathogenic mechanisms underlying these disorders that should enable future treatments. Initiating clinical trials remains the top priority, and 2016 recommendation refinements include drawing specific attention to both non-motor and motor symptoms of LBD.

Session 5. Frontotemporal Lobar Degeneration (FTD) (Chairs: Michael Hutton, PhD, William Seeley, MD)

The average age for diagnosis of FTD is about 57, making it a condition with significantly younger onset and midlife impact compared to AD, which has an average age of diagnosis of about 70. Prevalence of FTD is rare but uncertain, in significant part due to a lack of diagnostic clarity addressed earlier in this document. Despite the challenges of relatively few specimens being available in brain banks and the existence of many FTD molecular subtypes and clinical phenotypes, there has been considerable progress since 2013. Three NIH research teams have been funded to engage in longitudinal studies of familial and sporadic FTD to understand disease progression both pre- and post-symptom onset; to identify new biomarkers for diagnosis, progression, and prognosis; and to establish a clinical research consortium to support FTD therapy development. Moreover, scientists have discovered that variation in the C9ORF72 gene can lead to FTD-motor neuron disease (MND). The disease mutations are “repeat expansions,” in which specific DNA sequences are repeated hundreds or thousands of times. Recent findings suggest several possible mechanisms leading to disease from these C9ORF72 expansions, and that the underlying mechanisms could be potential targets for therapies to treat some forms of FTD-MND. In 2016, NINDS issued an RFA entitled Centers without Walls for the Identification and Validation
of Molecular Mechanisms Contributing to Tau Pathogenesis and Associated Neurodegeneration in Frontotemporal Degeneration. The FTD session committee made no major changes to the 2013 basic science recommendations, with refinement highlights including increased emphasis on understanding tau pathology and tau strain spreading; determining whether TDP-43 and FUS are toxic spreading-disease proteins; and understanding the normal RNA biology roles of TDP-43 and FUS. FTD clinical science recommendations also remain largely unchanged, with recognition of the need for increased recruitment outreach, in particular to minority groups, and increased bioinformatics infrastructure to support large-scale data collection, analytics, and sharing in genetic and ‘omics studies.

Session 6. Vascular Contributions to Cognitive Impairment and Dementia (VCID) (Chairs: S. Thomas Carmichael, MD, PhD, Steven Greenberg, MD, PhD)

The 2013 ADRD Conference stimulated significant new interest and activity in VCID (Corriveau et al., 2016). For example, NIH established the M⁴OVE AD Consortium via a collaborative NIA/NINDS funding announcement titled Interdisciplinary Research to Understand the Vascular Contributions to Alzheimer’s Disease. The Alzheimer’s Association hosted a focused think tank on vascular contributions to AD/ADRD with NIH input, and issued relevant RFAs including on the role of vascular metabolic factors in AD/ADRD pathogenesis. In 2014, for the first time, and with support from NINDS leadership, NIH officially recognized VCID as a field by tracking spending on VCID research in the NIH RePORTER database, aligning the acronym with vascular cognitive impairment/dementia. The science of VCID integrates and creates a focus for synergy among diverse interdisciplinary aspects of biology that have been separated historically. Thus, VCID research interrogates the roles of multiple cell types that support the function of neural tissue. In 2016, NINDS issued RFAs designed to establish the Small Vessel VCID Biomarkers Consortium and its Coordinating Center, and to address the Mechanistic Basis of Diffuse White Matter Disease in VCID. Additional scientific progress in VCID features new animal models that portray different types of ischemia in white matter pathology as well as co-morbidity with relevant human conditions. The VCID committee noted significant progress in characterization of the neurovascular unit (NVU), which has led to an updated definition that incorporates new concepts such as segmental differences in structure/function, new cell types, and the contributions of lymphatic flow. Downward temporal trends in the prevalence of dementia (e.g., Framingham data, data from European studies) continue to raise the intriguing question of the overall role and impact of traditional cerebro- and cardiovascular risk factors in dementia. These research questions are being addressed. The VCID committee maintained the overall structure and main content of the 2013 recommendations, but highlighted several new areas such as translational imaging methods, aging as a variable, genetics, resilience to VCID, and the role of tau in VCID.

Cross-Cutting Areas. Cross-cutting areas diversify research foci presented in the six research recommendation areas. These include resources infrastructure (biospecimens, bioinformatics, clinical trials); training and workforce needs (research and clinical); type of research (basic, translational, clinical); and nomenclature, as described above. The MED session topics are emblematic of such overlap, and as such this session as of 2016 includes a completely new recommendation on training. Notable areas of cross-cutting scientific interest include protein aggregation/degradation/neurodegeneration; the innate immune system; axonal/synaptic injury/repair, circadian and sleep function/dysfunction; the NVU/blood brain barrier (BBB); genetics/genomics; and metabolism/diabetes.
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 2016, 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 2016
Draft Prioritized Recommendations

Session 1:
Multiple Etiology Dementias (MED)

Focus Area 1: Improved Diagnostic Skills in the Community

Recommendation #1. Detect cognitive impairment when a patient or relative voices a concern to health care providers (3-7 y; 2017).

- Develop new educational efforts for, and practical trials on, improved diagnosis when there is a memory or cognitive complaint that lead to face-valid useful outcomes for patients and family.
- Develop educational efforts for improved diagnosis when there is a memory or cognitive complaint that is specifically designed for use in underserved populations.
- Improve basic diagnostic skills for use by primary-care providers regarding later-life cognitive disorders, emphasizing timely diagnosis of overt cognitive impairment (but not specifically focusing on differential etiological diagnosis).
- Develop new approaches (e.g., using computers or ancillary personnel in the office or using technology for home-based assessments) for cognitive and functional assessments in primary-care settings (meaning that they are reimbursable, time efficient, and easy to interpret) that use existing or new neuropsychological and functional assessment tools.
- Develop a more compelling evidence base for the value of currently available interventions for people with dementia: Present Centers for Medicare and Medicaid Services with evidence-based examples of targetable/reimbursable physician actions that improve quality of life for people with dementia and their families.

Recommendation #2. Improving differential diagnosis of symptomatic cognitive impairment (3-7 y; 2017).

- Improve clinical diagnostic instruments and approaches for major dementia/cognitive disorder systems, and conduct practical trials to assess the effectiveness (clinical utility) of new diagnostic instruments and procedures.
- Improve diagnostic skills in neurologists, geriatricians, neuropsychologists and geriatric psychiatrists with measurable outcomes, e.g., recognizing and treating an LBD-associated sleep disorder, treating normal-pressure hydrocephalus, or reducing risk of future cerebrovascular events or progression of white matter injury. These outcomes would also include behavioral interventions to improve quality of life in people with cognitive disorders.
- 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 remedy referral bias in interpretation of biomarker-assisted diagnoses. A long term goal is to link clinical activities to subsequent state-of-the-art neuropathological examinations to validate diagnoses.
- Develop tools, including educational and diagnostic ones, for recognizing cognitively impaired people with multi-etioloogy disorders in diverse medical settings.
• Develop new imaging and fluid biomarkers for people with symptomatic disease – both AD and non-AD dementias - that are integrated into clinical diagnosis.

**Recommendation #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 y; 2017).

- Increase training in cognitive impairment and dementia in the emerging generation of clinicians, clinical scientists, caregivers and other professionals across the integrated spectrum of cognitive impairment and dementia care and clinical research.
- Training should be iterative and at different career stages, including for but not limited to neuropathologists, psychiatrists, geriatricians, neuropsychologists, neurologists, behavioral neurologists, and epidemiologists.
- Translational research and drug discovery are also to be targeted for increased training in areas that have a chance to impact cognitive impairment and dementia.
- Training of scientist and health professionals is to include disparities training relevant to cognitive impairment and dementia, and trained individuals should be representative of the diverse population of the U.S.

**Recommendation #4.** Develop diagnostics/biomarkers in asymptomatic individuals (3-7 y; 2017).

- Develop improved imaging and fluid biomarkers for AD, cerebrovascular disease (including the health of the neurovascular unit [NVU]), and non-AD degenerative dementias to estimate an individual’s future risk for cognitive impairment.
- Conduct validation studies in asymptomatic populations, especially in minority groups and in middle age using population-based studies.
- Validate diagnostic and theragnostic (outcomes that track therapeutic responses) utility of biomarkers used in asymptomatic people.

➢ **Focus Area 2: Basic and Clinical Research in Interactions between Dementia Pathophysiology**

**Recommendation #5.** Promote basic and clinical research in multi-etiologic dementia (3-7 y; 2017).

- Define interactions at the molecular and cellular levels between vascular risk factors such as diabetes, hypertension and hyperlipidemia and Alzheimer-type mechanisms (amyloidosis and neurofibrillary tangle pathology).
- Define interactions at the molecular and cellular levels between arteriolar pathologies, microvascular pathologies and Alzheimer-type mechanisms.
- Define interactions at the molecular and cellular levels between Alzheimer-type mechanisms and: 1) α-synucleinopathy, 2) TDP43 proteinopathy, or 3) other proteinopathies relevant to neurodegenerative cognitive disorders.
- Describe quantitatively the clinical synergies between different etiologies.
- Develop approaches to grading clinical relevance of one etiology in the presence of more than one etiologic entity.
- Identify molecular pathways that accelerate cognitive dysfunction or that protect cognition that are agnostic to specific pathologies, i.e., that might act on mechanisms of cell death or synaptic dysfunction common to more than one neurodegenerative process.
• Identify pleiotropic effects of multiple pathologies in non-cognitive but related symptomologies such as those of gait impairment or physical frailty.

➢ Focus Area 3: Determining the Role for Screening for Cognitive Dysfunction

Recommendation #6. Determining the value of screening for clinically relevant cognitive impairment in the absence of a cognitive complaint (7-10 y; 2017).

• Conduct observational studies that measure the benefit or detriment of identification of cognitive impairment on the index case, family, health care system, and health care provider decision making.
• Develop practical trials of screening for cognitive impairment if measurable, meaningful outcomes can be identified.
• Develop culturally sensitive instruments for large scale screening with sufficient specificity to minimize impact of false positives on a participant, family member, or the health care system.
• Design screening trials for cognitive impairment in at-risk populations (i.e., older adults [over 70], people with multiple co-morbidities and/or functional deficits, etc.) that explicitly address recruitment challenges in such populations.
• Evaluate the capacity of the U.S. health care system to accommodate large numbers of people with cognitive disorders, should cognitive screening be demonstrated effective in identifying people with undiagnosed MCI and dementia.
• Determine the value of the practice of baseline cognitive assessment in middle adulthood that can serve as a baseline for future determination of meaningful change (akin to a “brain health check”). Determine whether such assessments could be performed best in-person or remotely through the use of new technologies.
• Determine the benefit of cognitive screening in underserved communities.

➢ Focus Area 4: Revisiting the Nosology of Cognitive Impairment in Late Life

Recommendation #7. Developing a consistent nomenclature in Dementia Research and Care (1-3 y; 2017).

• Recommend that nomenclature for all dementias be integrated into a common structure, such that different stakeholders can use unambiguous terms. One goal is to simplify the lay public’s ability to understand the diagnosis while preserving accuracy of terminology.
• Develop a universal lexicon for characterizing acquired cognitive impairment that spans the needs of therapeutic endeavors (regulatory requirements), clinical research, clinical practice and advocacy. The universal lexicon should carefully consider the “brand” value (i.e., familiarity) of currently used terms.

Session 2: Non-Governmental Organizations (NGOs)

➢ Focus Area 1: Catalyzing Research through Unique Programs and Partnerships

Recommendation #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).

• Post publicly on the NAPA site all recommendations, implementation plans and success criteria in support of ADRD Summit planning.
• Include NINDS representation at the quarterly NAPA Council meetings.
• Invite NINDS to present annually to NAPA Council on progress toward the ADRD recommendations.
• Hold an annual satellite meeting to the NAPA Council meeting during which NINDS, NIA and NGOs share activities, funding-related information, and progress relevant to the ADRD recommendations (consider a ~2 hour meeting, held 6 months opposite the proposed annual NINDS presentation to NAPA Council).

➢ Focus Area 2: Nomenclature Standards when Discussing Dementia

Recommendation #2. 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 (ongoing activity; 2017).

• General considerations include: 1) differing nomenclature needs by demographic group (i.e., individuals with dementia; caregivers; health disparities; gender; sex; age; geographic; socioeconomic; education); 2) strategies to reduce stigma; and 3) nomenclature should be useful for all stakeholder groups to help engage and partner with disparities populations, raise public awareness, drive symptom reporting, increase research participation, and heighten political support to reduce the impact of dementia on society.

• Clinical care considerations include: 1) best practices for educating individuals with dementia and caregivers about the difference between dementia, a particular clinical syndrome and possible underlying etiology (e.g., normal versus MCI versus dementia; minor versus major neurocognitive disorder) to facilitate better communication across care settings; and 3) cognitive status milestones for referral to community resources (e.g., mild: difficulty with instrumental activities of daily living [IADLs] only, moderate: difficulty with activities of daily living [ADLs], severe: dependent on caregivers for basic activities of living).

• Research/Regulatory considerations include: 1) scientific nomenclature evolves with discovery; 2) nomenclature standards to differentiate between underlying disease etiology versus clinical syndromes; 3) standards for defining prodromal, preclinical and clinical syndromes; 4) review regulatory pathway to identify and address barriers related to nomenclature; and 5) solutions to nomenclature barriers or challenges in global research (e.g., international diagnostic criteria).

• Present strategic recommendations for public comment, including specific criteria for determination of success (at a summit or comparable event) from which to obtain feedback from stakeholder groups.
• Submit a perspectives article of final recommendations on this issue to an appropriate journal.
• Deliver final recommendations to NIH, the NAPA Council and HHS for inclusion in the NAPA plan.

Session 3:
Health Disparities (HD)

➢ Focus Area 1: Treatment and Prevention Strategies

Recommendation #1. Assess epidemiology and mechanistic pathways of disparities in health burden of AD/ADRD (3-7 y; 2016).
• The prevalence and risk factors of many AD/ADRD disorders among disparate populations is unknown and must be established to prioritize public health need, disease prevention efforts, and interventions.
• 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 disparate populations.
• Test the intersection of social, environmental and biological mechanisms of AD/ADRD to determine if mechanisms differ across populations (e.g., cerebrovascular and cardiometabolic risks are unequally distributed among disparities populations, which may disproportionately increase AD/ADRD disease burden).
• Enhance research methods for AD/ADRD to enable translation of observational evidence into interventions by identifying causal mechanisms in the context of long-term, interactive, and highly confounded effects.
• Design of epidemiologic studies should be carried out in partnership with experts who carry out interventions, in order to facilitate translation.
• Genetic and biomarker studies should include diverse populations and incorporate measures of environmental and psychosocial factors that are differentially patterned across disparities populations, recognizing that “race” correlates with both genetic ancestry and countless social factors; many of these social variables are independent risk factors for some AD/ADRD outcomes so biomarker research must account for social conditions.
• Initiate and leverage ongoing longitudinal community-based cohort studies of incident dementia in diverse populations. Leveraged studies should incorporate a wide range of risk factors that could be enhanced with cutting-edge imaging fluid biomarkers (e.g., blood and cerebrospinal fluid), and if possible, autopsy.
• Use social, environmental, genetic, and biomarker evidence to identify potential policies, systems, and interventions that could reduce the burden of AD/ADRD among disparate populations.

**Recommendation #2.** Enrich the design of trials of vascular health interventions to improve their application to AD/ADRD among aging diverse populations (3-7 y; 2017).

• Emerging evidence indicates that vascular health is critical to delaying or even preventing onset of dementia, potentially not only vascular contributions to cognitive impairment and dementia (VCID), but also LBD and AD, and may be differential across diverse populations. Improving the cardiovascular health of diverse populations would likely reduce AD/ADRD disparities.
• Intervention trials for cardiovascular and stroke outcomes can provide valuable secondary evidence on prevention of dementia, if high-quality standardized cognitive outcomes are included.
• Adopt high-quality neurologic assessments (e.g., imaging, neuropsychological, and autopsy data) in the design of vascular health intervention trials.
• Appropriately design proposed interventions that are culturally appropriate (e.g., language) to ensure their application to diverse aging populations.
• Adopt standardized assessments to enable cross-study comparisons and facilitate meta-analyses.

**Focus Area 2: Monitoring Changes in AD/ADRD Disparities**

**Recommendation #3.** Develop a system to monitor the magnitude and trends in health disparities in incidence of AD/ADRD (3-7 y; 2017).
There is no current data infrastructure that would enable evaluation of progress towards reducing or eliminating health disparities in AD/ADRD.

Systems for monitoring progress will help maintain focus on disparities and efforts to eliminate disparities.

The best feasible system will integrate information from multiple complementary sources, and this will require that we identify a central clearing house.

Both active (e.g., cohort) and passive (e.g., electronic medical records systems) systems should be identified, and a data monitoring system must be put in place to provide stability to collect, clean, and merge the data.

Data standardization protocols must be developed and validated.

Small sub-studies can be used to validate the measurement quality from diverse sources and ensure measures are harmonized for common AD/ADRD disorders.

Infrastructure must tie to passive data sources (with very large population bases) to monitor disparities in rare AD/ADRD disorders.

**Focus Area 3: Assessment**

**Recommendation #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 y; 2016).

- Conduct quantitative and qualitative validity studies of existing and newly generated instruments among individuals from diverse populations.
- Pool existing (global and item-level) data from ongoing or previously conducted studies of aging that include diverse populations for harmonization, advanced psychometric analyses (e.g., Item Response Theory) and for generation of normative references.
- Conduct studies using community-based approaches adopting both qualitative and quantitative methods to ascertain how disparities populations understand the behavioral and cognitive changes specific to AD/ADRD disorders. Additionally, develop culturally appropriate methods for collecting informant-based assessments of daily functioning levels.
- Develop, adapt, and validate measures of social mechanisms of disparities that are relevant for research on AD/ADRD.
- Develop brief, simple, and sensitive tools for screening for cognitive impairment and dementia in primary care settings.
- Adopt culturally appropriate, standardized assessments that are harmonized between studies to facilitate meta-analytic studies. This will enable inferences across research studies and clinical trials that include diverse participants.
- Develop practical guidelines for use of existing assessment and up-to-date diagnostic guidelines for use among diverse people and in settings with disparities populations.

**Recommendation #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 y; 2016).

- Develop criteria by which proposed interventions can be measured to determine whether they are culturally sensitive to ensure their application to diverse populations.
• Assess a broad range of social variables across the life course that could contribute to AD/ADRD disparities or interact with genetic and cardiovascular risks to exacerbate biological risks.
• 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.

**Focus Area 4: Community Partnerships, Recruitment, and Retention**

**Recommendation #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 y; 2016).

- The purpose of this Task Force is to provide expertise to investigators on how to recruit, retain and examine underserved populations for participation in epidemiological studies and clinical trials for FTD and other tauopathies, LBD, VCID, Mixed Etiologies Dementia (MED), and AD.
- Address many reasons for low rate of research participation, including inadequate connection with health systems, screening, and diagnosis; low knowledge; alternative health beliefs; and distrust of research.
- Instead of relying on specialty clinic enrollment, use recruitment strategies that are community-based, representative (e.g., probability sampling) and have limited exclusion criteria in order to reduce sampling biases and ensure population diversity and a range of 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.
- Enroll people without known dementia at baseline in order to provide data on the full spectrum of cognition and to examine the transition from no cognitive impairment to dementia. This research can provide opportunities to address knowledge gaps relating to incidence rate estimates and characterization of latency and prodromal phases of AD/ADRD syndromes in health disparities populations.
- Disseminate best practices for community partnership and outreach among specific disparities populations.

**Recommendation #7.** Develop novel community engagement and outreach methods and identify existing methods to facilitate engagement, understanding and partnership with health disparities populations (1-3 y; 2016).

- Due to cultural, educational system, language differences, and alternative beliefs about cognitive decline and normative expectations for behavior among older people, as well as differing attitudes about discussing potentially stigmatizing illnesses with non-family members, there is a strong need for outreach to disparities populations with a goal of enhancing communication and understanding of perspectives.
- Conduct studies using community-based approaches adopting both qualitative and quantitative methods to ascertain how disparities populations understand the behavioral and cognitive changes specific to AD/ADRD disorders along with appropriate methods for collecting informant-based assessments of daily functioning.
- Use Community Advisory Boards to involve local leadership, partner with local institutions for recognition and access, use educational programing to improve case detection, and provide practical resources (e.g., transportation) for intensive community outreach.
• Partner with community leaders (e.g., pastoral care and spiritual leaders) to address cultural and religious beliefs that are barriers to autopsy.
• Organize community events and develop recruitment materials and media featuring local spokespersons and testimonials from members of disparities populations to destigmatize and highlight the value of procedures such as lumbar puncture.

Session 4:
Lewy Body Dementias (LBD)

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

Recommendation #1. Initiate clinical trials for motor and non-motor manifestations of Lewy body dementia (LBD), which is meant to includes 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 y; 2016).

• LBD encompasses DLB and PDD. In LBD, there is cognitive decline and often fluctuating alertness and thinking, visual hallucinations, and Parkinsonism. When the cognitive decline develops after an established motor disorder, the disease is referred to as PDD. When the dementia develops prior to or at the same time as the motor disorder, the disease is referred to as DLB. While there have been many therapeutic trials focused on PD, patients with LBD have been excluded. Consequently, there is little information about the efficacy of approved drugs, (e.g., dopamine replacement), experimental agents and non-pharmacological therapies in LBD. The aim of this recommendation is to engage existing clinical networks and non-governmental organizations to establish new networks of clinicians, including movement disorder specialists, behavioral neurologists, psychiatrists, or sleep disorder specialists, to use well-characterized cohorts of LBD for treatment trials with current Food and Drug Administration-approved drugs. It is important that cross-site standardization (e.g., common clinical, imaging, and outcome measures) be carried out to the greatest extent possible.

Recommendation #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 y; 2016).

• DLB is currently under-diagnosed compared with AD and the diagnosis is often made too late to allow optimal symptomatic management and prevention when suitable agents become available. The aim of this recommendation is to capitalize on existing longitudinal cohorts studying late life dementia disorders by enriching the population with individuals with potential early manifestations of DLB, including dream enactment behavior (also known as rapid eye movement sleep behavior disorder), hyposmia, autonomic dysfunction, recurrent delirium, late onset psychosis and psychiatric disturbances, and mild cognitive impairment.
• Although the majority of PD patients, if followed long enough, will develop dementia, the time from the onset of motor symptoms to dementia varies markedly. Dementia in PD has a major impact on function, quality of life, and medical costs. Although some potentially predictive demographic and clinical factors are known for PDD, such as older age of onset of PD, mild cognitive impairment, or a postural instability/gait disorder clinical subtype of PD, very few
prospective biomarker studies exist. Such biomarkers may provide insight into the mechanisms leading to cognitive decline in PD and thus represent future therapeutic markers. It is important that cross-site standardization (e.g., common clinical, imaging, and outcome measures) be carried out to the greatest extent possible across all LBD resources.

- **Focus Area 2: Discover Disease Mechanisms Through Brain Mapping and Genetics**
  
  **Recommendation #3.** Using well defined cohorts of LBD who have come to autopsy, systematically 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 y; 2018).

  **Recommendation #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 y; 2016).
  
  - This goal will require signal 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. There is a need for a central data repository or reference center that would easily allow data sharing and creation of high-dimensional data sets.

- **Focus Area 3: Develop and Validate Biological and Imaging Biomarkers**

  **Recommendation #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 y; 2016).
  
  - 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, scanning sites, and imaging platforms. 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-amloid 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 #6.** Use new (see Recommendation 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 y; 2017).

- This recommendation proposes to capitalize on existing longitudinal case-control cohorts to encourage standardization of protocols and common data elements. Clinical data should be linked to biobanks of fluids, tissues, and other biomaterials collected on the cohort through an open access database to foster biomarker development. Biomarkers are needed not only to correlate with clinical, but also with pathological LBD changes, markers of neurodegeneration, and markers of disease risk. Biomarkers could be measured in a diversity of tissues (including, but not limited to, brain, skin, colon biopsies, others) and biofluids (e.g., blood, CSF, urine, microbiome samples, and others).

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

**Recommendation #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 y; 2017).

- This recommendation recognizes the need to develop models that fit not only what is known about the molecular pathology of LBD based upon current evidence, but also what can be learned from proposed systematic mapping, profiling of brain and biofluids, and epidemiological studies. New and existing models should enhance understanding of 1) selective vulnerability, 2) mechanisms of neuronal dysfunction, 3) factors that determine disease progression, transmission or propagation, and 4) how to design and test therapeutic interventions.
- Ideally, new animal, cellular and *in vitro* models will incorporate new research discoveries and may include the use of human materials, such as induced pluripotent stem (iPS) cells and isolated disease-related protein aggregates obtained from subjects enrolled in clinical, genetic, or biomarker studies.

**Recommendation #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 y; 2018).

- This recommendation builds 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 pharmaceutical 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.

Session 5: 
Frontotemporal Lobar Degeneration (FTD)

Focus Area 1: Basic Science: Pathogenesis and Toxicity

Recommendation #1. Clarify the mechanism of tau pathogenesis and associated neurodegeneration (3-7 y; 2016/2017).

- The mechanism of tau-driven neurotoxicity and its relationship to the formation and spreading of tau pathological inclusions 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 dysfunctions) 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 spreading of pathological tau. Genetic models should be complemented with other methods that mimic aspects of sporadic disease (inoculation studies, iPSCs, etc.).

Recommendation #2. Determine the molecular basis for C9ORF72 expansion- and GRN mutation-related neurodegeneration (7-10 y; 2016/2017).

- There is need to identify the predominant mechanism(s) of C9ORF72 hexanucleotide repeat expansion pathogenesis in FTD/ALS. To what degree is 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 FTLD: lysosomal dysfunction, TDP-43 proteinopathy, neuroinflammation, or other mechanisms.

- The recommended approach is to expand the scope and precision of human neuropathologic studies of C9ORF72 and GRN mutation carriers to address which pathological 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 aggregation also needs to be identified via this approach. Finally, the field should continue to identify therapeutic approaches designed to replace/increase GRN function.
**Recommendation #3.** Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity (7-10 y; 2016/2017).

- There is 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 structural differences in TDP-43 protein across pathological subtypes? What are the upstream events that precede TDP-43/FUS aggregation?
- Our recommended approaches are to expand the scope and precision of human neuropathologic studies, focusing on early-stage disease, to define the sequence of molecular changes associated with TDP-43/FUS pathogenesis from loss of nuclear localization to the formation of assemblies. Continue to define the normal cellular functions of TDP-43 and FUS. Expand work 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 #4.** Develop better FTLD in vivo and cell-based model systems (1-3 y; 2016/2017).

- There is a need to improve the tools for disease mechanism and target identification, validation, and drug development. Do existing FTLD models reproduce the formation of pathological lesions, associated neurodegeneration, and behavioral impairment?
- The recommended approach is to prioritize development of robust models to study TDP43, FUS, GRN haploinsufficiency, and C9ORF72 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-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 dissection of molecular pathogenesis.

➢ **Focus Area 2: Clinical science**

**Recommendation #1.** Expand efforts to genotype patients with FTD and identify new genes and their functional relationship to FTLD pathogenesis (3-5 y; 2017/2018).

- There is a need to accelerate discovery of new familial FTD genes and genetic risk factors and to provide genotyping support to enable research on patients with a known genetic status.
- 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. Pursue a focused effort to find additional genetic causes and risk factors for FTD through whole genome and targeted deep sequencing approaches, initially in small families and expanding into large cohorts of unrelated FTD patients to confirm pathogenicity. Support functional analysis of variants identified through whole genome sequencing. Improve bioinformatics infrastructure for capturing phenotype and genotype information and enabling data sharing. Include families with combined FTD and 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 #2.** Develop FTD biomarkers for diagnosis and disease progression (3-7 y; 2017/2018).

- There is a need for better tools for detecting early stage disease, establishing molecular diagnosis, assessing target engagement, monitoring disease progression, and measuring therapeutic efficacy.
- Our recommended approach is to develop molecular biomarkers (PET/CSF/blood measures) for molecular diagnosis of FTLD-tau, -TDP, and -FUS. Studies should emphasize early post-mortem validation (e.g., PET ligand autoradiography) and biomarker-to-pathology correlations (e.g., tau-PET to tau deposition at autopsy). These efforts will segment clinical trial cohorts, enable tailored FTLD therapy, and provide potential target engagement biomarkers for these molecular targets. These studies should be complemented by efforts to define the most sensitive systems-level outcome biomarkers (MRI/fMRI/PET/EEG/clinical/digital-wearable) for monitoring progression during early stage disease, seeking to inform early clinical proof-of-concept studies and ultimately minimize sample size requirements in Phase III clinical trials. In addition, there is a need to identify the most meaningful clinical endpoints for Phase III trials and pursue deeper motor phenotyping to detect emergence of motor neuron disease (MND). Efforts should be made to provide bioinformatic support for biomarker data collection and outreach, for example by enabling web-based cognitive testing or data upload from digital-wearable devices and large-scale sharing of brain imaging or physiological data. These efforts should include outreach to underserved and minority populations to ensure that developed biomarkers generalize to all at-risk populations.

**Recommendation #3.** Create an international FTD clinical trial network (1-3 y; 2017/2018).

- There is need to facilitate orchestration of impending FTD clinical trials.
- Our recommended approach is to establish an international network of FTD clinical experts to ascertain FTD cohorts and collect clinical, genetic, and biomarker data using a centralized database/coordinating center. These data should be used to refine disease models, clinical endpoints, and trial design. Specific trial platforms for FTLD-tau (PSP and MAPT mutation-related) and FTLD-TDP (GRN or C9orf72 mutation carriers) should be developed to enable rapid implementation of emerging therapeutic approaches. Conduct community outreach efforts to capture underserved and minority populations for inclusion in clinical trials.

**Recommendation #4.** Understand phenotypic heterogeneity and natural history (>10 y; in progress).

- There is need to understand how genetic background, brain development, and environment are linked to the patient's specific clinico-pathological entity 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 presymptomatic and prodromal stages of disease in the face of low prevalence.
- Our recommended approach is to conduct natural history studies of preclinical inherited FTD (especially MAPT, GRN, and C9orf72-related FTD) by following cohorts of individuals from health to disease. 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., progressive supranuclear palsy and tau, semantic variant primary progressive aphasia and TDP-43 Type C, FTD-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. Finally, we recommend using cohorts to support longitudinal biomarker discovery and identify optimal clinical trial endpoints, considering the Dominantly Inherited Alzheimer's disease Network (DIAN) as a model. 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.

Session 6:
Vascular Contributions to Cognitive Impairment and Dementia (VCID), Including Vascular Cognitive Impairment and Vascular Dementia

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

**Recommendation #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 y; 2016).

- Animal model and human studies (clinical, genetic, pathological, imaging, etc.) should be designed to inform each other from the cellular to the systems level.
- Because of the pathogenic diversity of VCID syndromes, multiple models, each recapitulating key features of a specific human disease process, are needed.
- In particular, establish animal models that reproduce small vessel disease and other key pathogenic processes thought to result in cognitive impairment, e.g., models of chronic blood-brain barrier (BBB) breakdown such as those caused by disrupted endothelial-pericyte or endothelial-astrocyte signaling and models of hypoperfusion or progressive white matter ischemic pathology. Investigate pathological mechanisms of BBB leak on NVU damage and neuronal network structure and activity.
- Incorporate environmental and monogenic models of vascular disease into modeling the interaction of VCID with progressive brain disease and with AD. Monogenic examples include HDAC9, Collagen 4 isotypes and MFSD2a. Environmental effects on animal models include dietary manipulations producing rapid VCID-relevant changes in mice (hyperhomocysteinemia) and rats (spontaneously hypertensive, stroke prone rat - SHR/SP - with diet modification and carotid ligation), dietary modifications in AD mice and the interaction of hypertension and amyloid pathogenesis in processing of APP.
- Encourage basic research (e.g., real-time multiphoton imaging) that investigates how localized vascular disease can coalesce into large-scale regions of damage that lead to dementia. Such rodent models should also easily be applied to AD research, so VCID and AD can be studied individually and in combination, e.g., models with deletion of genes from vascular cells such as endothelial cells, pericytes, and vascular smooth muscle cells.
- Develop new tools for cell- (endothelial, smooth muscle, pericyte, etc.) and region- (gray versus white matter, cortex versus striatum, etc.) specific genotyping and phenotyping of the cerebrovascular tree and NVU (glia, immune cells, etc.).
- Test the effect of pathogenic factors on cerebral blood vessels and how these impact brain function at the synaptic, neuronal, network, systems, and behavioral levels, and in gray or white matter.
• Explicitly incorporate aging into animal models, e.g., explore interaction between age and other risk factors introduced by animal model (hypertension, diabetes/metabolic syndrome, amyloid/tau expression), relationship between cellular senescence and VCID, markers of cellular aging (e.g., CpG methylation, telomere shortening). Use animal aging to determine temporal sequence/causality of various biological processes, vascular changes, and tissue injuries.
• Develop imaging approaches in animal models with relevance to human applications that may identify pathophysiological mechanisms or serve as imaging biomarkers of disease progression, e.g., diffusion tensor imaging, dynamic contrast enhanced MRI or resting state MRI.

**Recommendation #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 y; 2018).

• Encourage basic research that intentionally investigates interactions among risk factors for dementia and cerebrovascular function, so as to generate preclinical data with increased translational potential. The largest risk factors for AD remain age and apolipoprotein E genotype (APOE), yet they are not consistently modeled in many preclinical studies focused solely on Aß-mediated effects in young to middle-aged mice fed a far healthier diet than most North Americans consume.
• Investigate Aß-mediated effects on cerebrovascular function, including all cells involved in the NVU. Initiate new basic research that provides rigorous and novel insight into how factors involved in AD pathogenesis (amyloid, tau, apoE, other AD-associated gene products, etc.) affect cerebrovascular function or vascular-related brain injury.
• Investigate Aß-mediated effects on hemostasis, including blood clotting and fibrinolysis.
• Investigate the contributions of additional risk factors for AD, including diabetes/metabolic syndrome, obesity, lipid metabolism, hypertension, diet, exercise, sleep head injury, and aging, on cerebrovascular function.
• Develop models of small vessel disease and a platform of informative outcome measures to understand how small vessel disease contributes to both white and grey matter lesions, neurodegeneration, and cognitive function.
• Determine additive or synergistic effects among risk factors.
• Strategically mine genome-wide association studies (GWAS) and whole genome sequencing studies and clinical trials focused on vascular applications for additional pathways and targets that further increase the translatability of animal model studies.
• Small vessel disease animal models can be used to study the influence of AD genetic risk factors such as APOE.

**Recommendation #3.** Encourage basic science research that investigates the impact of cerebrovascular risk factors/genes and atherosclerosis on AD-related neurodegeneration (3-7 y; 2018).

• The high co-morbidity of cerebrovascular disease with AD 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 Aß- and tau-related disease processes, both separately and together.
• Develop tools for cell- (endothelial, smooth muscle, pericyte, etc.) and region- (gray versus white matter, cortex versus striatum, etc.) specific characterization of the effects of altered cerebrovascular and NVU (glia, immune cells, perivascular cells etc.) function. Specifically,
determine how the cellular constituents of the NVU interact with AD progression (such as influence of endothelial cell efflux transporters on amyloid clearance), how loss of pericytes and other NVU components increase amyloid accumulation; and how peri- and paravascular clearance mechanisms and the lymphatic system interact with vascular and AD pathologies.

- The development of animal models should move beyond stroke models and into more chronic models of cerebrovascular disease that are commonly co-morbid with AD such as comorbid hypoperfusion. Models of cerebrovascular disease should, when possible, distinguish between white matter and gray matter damage and determine how each type contributes to AD progression.
- Pursue studies to understand shared cellular and molecular mechanisms within the small vessel NVU leading to secondary neurodegeneration in amyloid-independent and tau-independent pathways, and within the amyloid and tau pathways (e.g., scavenger receptors, lipoprotein receptors, vascular cell-specific gene deletion and expression).
- Cognitive and behavioral tests should, when modeling VCID, include functional testing of brain regions impacted by cerebrovascular disease.

Focus Area 2: Human-Based Studies

Recommendation #1. Develop (1-3 y; 2016) and validate (3-7 y; 2018) longitudinally tracked noninvasive markers of key vascular processes related to cognitive and neurologic impairment.

- Identify biomarkers of key microvascular processes related to subclinical brain injury and 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).
- Identify a molecular neuroimaging marker for the vascular pathology of arteriolosclerosis.
- Perform targeted and agnostic searches for genetic and circulating fluid biomarkers, including systemic (e.g., blood, urine), and central nervous system (CNS) fluids and use of genomic, transcriptomic, proteomic, metabolomics, and epigenetic screening methods. Use Mendelian randomization and temporal course to determine causality of circulating biomarker for brain injury or neurologic dysfunction. Incorporate biomarkers of aging, e.g., methylation clock, miRNA, telomere length, or candidate biomarkers of increased resilience, e.g., circulating growth factors and of NVU damage (e.g., aquaporin 4, neurofilament light chain, SNAP 25).
- Assess 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.
- Pursue cross-directional interdisciplinary studies to validate and explore the links between vascular biomarkers and the key microvascular processes. Determine interactions among biomarkers at more global levels of analysis.
- Incorporate the above pathologically 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. Consider effects of vascular and aging processes across the lifespan, including potential epigenetic effects early in life, cumulative lifetime exposure to vascular risk processes, and specific relationships between risk factors, vascular processes, and neurologic dysfunction in midlife, young old, old, and oldest old life stages.
• Correlate imaging biomarkers of VCID and VCID/AD from animal model to human, including quantitative BOLD MRI, dynamic contrast enhanced MRI.
• Determine validity of candidate biomarkers for use across multiple study sites.

Recommendation 2. Determine interrelationships (cross-sectional and longitudinal) among aging, cerebrovascular disease and risk factors, resilience factors, genetic variants, amyloid, tau, and neurodegeneration (3-7 y; 2018).

• Explore vascular mechanisms 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.
• Characterize the interrelationships among vascular risk factors, cerebrovascular disease, and AD in order to identify and target specific vascular risk factors to reduce the risk of AD, VCID, and multiple etiology dementia. Determine relationships of vascular risk factors and AD biomarkers to biomarkers of cerebrovascular disease, such as endothelial cell function, BBB permeability, vascular stiffness, and other measures of vascular physiology. Analyze biomarkers for VCID, AD, and aging in the context of specific populations with high vascular risk factor or disease burdens (including disproportionately affected disparities populations such as African-American, Hispanic, and Native American populations) or in the setting of environmental factors associated with increased resilience to vascular disease and cognitive impairment (e.g., Mediterranean diet, education, cognitive engagement, physical fitness, social networks, sleep). Identify potential gene-environment interactions.
• Similarly, analyze biomarkers for VCID, AD, and aging in the setting of individuals at increased risk for VCID based on the presence of monogenic conditions (e.g., CADASIL) or GWAS-identified variants associated with cerebrovascular disease (e.g., HDAC9). Determine the association between neuroimaging biomarkers and genomic/proteomic-identified risk factors.
• Determine the link between VCID and the genomic loci associated with AD (e.g., PICALM, CLU, APOE, TREM2) that appear to interact with vascular biology or BBB dysfunction.
• Encourage studies that address the complex pathways leading from vascular risk factors and cerebrovascular disease to changes in cognition, brain structure, Aβ, tauopathy, and neurodegeneration. Such studies may include systems-based approaches incorporating multi-modal imaging, biochemical, genetic and clinical markers to help determine whether risk conditions common to both AD and cerebrovascular disease reflect convergent pathways versus additive effects of independent pathways. Investigate correlation of systemic versus CNS biomarkers. Vascular risk factors are often measured systemically and we have limited knowledge about how they correspond with CNS metabolism. Encourage studies of how diet, exercise, lifestyle, and systemic vascular risk factors affect Aβ, tauopathy, metabolism, inflammation, and oxidative stress.

Recommendation 3. Identify lifestyle and vascular interventions to treat, prevent or postpone VCID (7-10 y; 2022).

• Establish clinical trials to develop surrogate markers for severity of VCID. Such trials could be those relating the burden of VCID 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.
• Currently, there are no known interventions that are specifically geared to VCID. However, there are several interventions that are known to impact general vascular risk factors, including management of hypertension, statins, control of diabetes/metabolic syndrome, diet, exercise,
and other lifestyle interventions. In particular, if we are successful in developing clinical or surrogate markers for diagnosing and quantifying VCID with some specificity, it would be relevant to determine whether or not and to what degree existing vascular interventions may beneficially impact VCID burden. By necessity, these would have to be long-term, longitudinal cohort studies. Consider multimodal clinical trials and modality-specific clinical trials; adding brain imaging, cognition in cardiovascular lifestyle intervention trials.

- Harmonize protocols across trials wherever feasible to permit meta-analyses. Develop clinical trials using outcome markers developed in parallel with animal models. This will allow direct ties to be drawn between the results of animal- and human-based interventions. Human-based clinical trials also should seek to develop and validate standardized cognitive test batteries for VCID as a potential step towards improving clinical diagnosis and measurement of clinically meaningful trial outcomes.
Table 1: ADRD Summit 2016 Non-Federal Committee Members

<table>
<thead>
<tr>
<th>Topic Area</th>
<th>Panelist name</th>
<th>Title and Affiliation</th>
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<tbody>
<tr>
<td>Multiple Etiology Dementias (MED)</td>
<td>David Bennett, MD (co-chair)</td>
<td>Director, Rush Alzheimer’s Disease Center, Rush University Medical Center</td>
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<td></td>
<td>David Knopman, MD (co-chair)</td>
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<td></td>
<td>Sanjay Asthana, MD</td>
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<td></td>
<td>Lisa Barnes, PhD</td>
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<td></td>
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<td></td>
<td>Helena Chui, MD</td>
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<td>Neil Graff-Radford, MBBCH, FRCP</td>
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<td>Chiadi Onyike, MD</td>
<td>Associate Professor, Psychiatry and Behavioral Sciences, Johns Hopkins University</td>
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<td></td>
<td>Sandy Weintraub, PhD</td>
<td>Professor, Cognitive Neurology and Alzheimer’s Disease Center, Northwestern Feinberg School of Medicine</td>
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<tr>
<td>Non-Governmental Organizations (NGO)</td>
<td>Susan Dickinson (co-chair)</td>
<td>Executive Director, the Association for Frontotemporal Degeneration</td>
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<td></td>
<td>Howard Fillit, MD (co-chair)</td>
<td>Executive Director and Chief Science Officer, Alzheimer’s Drug Discovery Foundation</td>
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<td></td>
<td>Maria Carrillo, PhD</td>
<td>Vice President, Medical and Scientific Relations, Alzheimer’s Association</td>
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<td>Guy Eakin, PhD</td>
<td>Vice President, Scientific Affairs, BrightFocus Foundation</td>
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<td>Rodney Pearlman, PhD</td>
<td>President, the Bluefield Project to Cure FTD</td>
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<td>Simon Ridley, PhD</td>
<td>Director of Research, Alzheimer’s Research UK</td>
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<td>Todd Sherer, PhD</td>
<td>Chief Executive Officer, the Michael J. Fox Foundation</td>
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<td></td>
<td>Angela Taylor</td>
<td>Director of Programs, Lewy Body Dementia Association</td>
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<tr>
<td>Health Disparities (HD)</td>
<td>Jennifer Manly, PhD (chair)</td>
<td>Associate Professor, Neuropsychology in Neurology, Columbia University Medical Center</td>
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<td></td>
<td>Maria Glymour, ScD</td>
<td>Associate Professor, Epidemiology and Statistics, University of California, San Francisco</td>
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<td>Hector Gonzalez, PhD</td>
<td>Associate Professor of Epidemiology and Biostatistics, Michigan State University</td>
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<td>Virginia G. Wadley, PhD</td>
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<tr>
<td><strong>Lewy Body Dementias (LBD)</strong></td>
<td>Sid O'Bryant, PhD</td>
<td>Departmental Chair, Department of Molecular Neuroscience, Reta Lila Weston Research Laboratories, University College London Institute of Neurology</td>
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<td></td>
<td>Dennis Dickson, MD (co-chair)</td>
<td>Professor, Neuroscience, Mayo Clinic</td>
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<td>Karen Marder, MD (co-chair)</td>
<td>Sally Kerlin Professor of Neurology, Columbia University Medical Center</td>
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<td></td>
<td>James Galvin, MD</td>
<td>Professor of Integrated Medical Sciences, Associate Dean for Clinical Research, Florida Atlantic University</td>
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<td>Todd Golde, MD, PhD</td>
<td>Professor, Neuroscience, Director, Center for Translational Research in Neurodegenerative Disease, University of Florida College of Medicine</td>
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<td></td>
<td>Jennifer Goldman, MD</td>
<td>Associate Professor, Neurological Sciences, Rush University Medical Center</td>
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<td></td>
<td>Eliezer Masliah, MD</td>
<td>Professor, Neuroscience and Pathology, University of California, San Diego</td>
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<td>Joel Perlmutter, MD</td>
<td>Professor, Neurology, Washington University, St. Louis</td>
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<td>Clemens Scherzer, MD</td>
<td>Associate Professor, Neurology, Harvard Medical School</td>
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<td></td>
<td>Carlie Tanner, MD, PhD</td>
<td>Professor in Residence, Neurology, University of California, San Francisco</td>
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<tr>
<td><strong>Frontotemporal Degeneration (FTD)</strong></td>
<td>Michael Hutton, PhD (co-chair)</td>
<td>Chief Scientific Officer, Neurodegenerative Disease, Eli Lilly and Company</td>
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<td></td>
<td>William Seeley, MD (co-chair)</td>
<td>Associate Professor, Department of Neurology, University of California, San Francisco</td>
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<td></td>
<td>Adam Boxer, MD, PhD</td>
<td>Associate Professor, Neurology, Memory and Aging Center, University of California, San Francisco</td>
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<td>Bradley Boeve, MD</td>
<td>Professor, Neurology, Mayo Clinic</td>
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<td></td>
<td>Brad Dickerson, MD</td>
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<td>John Hardy, PhD</td>
<td>Chair, Molecular Biology of Neurological Disease, Department of Molecular Neuroscience, University College London</td>
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<td></td>
<td>Virginia Lee, PhD</td>
<td>John H. Ware 3rd Endowed Professor in Alzheimer’s Research, Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania</td>
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<td></td>
<td>Manuela Neumann, MD, PhD</td>
<td>Head of Department, Neuropathology, University of Tuebingen</td>
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<td>Leonard Petrucelli, PhD</td>
<td>Chair and Ralph B. and Ruth K. Abrams Professor, Neurosciences, Mayo Clinic</td>
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<td></td>
<td>Rosa Rademakers, PhD</td>
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<tr>
<td>Erik Roberson, MD, PhD</td>
<td>Associate Professor, Neurology, University of Alabama at Birmingham</td>
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<tr>
<td>Jonathan Rohrer, MD, PhD</td>
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<tr>
<td>S. Thomas Carmichael, MD, PhD (co-chair)</td>
<td>Professor, Neurology and Neurobiology, David Geffen School of Medicine, University of California, Los Angeles</td>
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<tr>
<td>Steven Greenberg, MD, PhD (co-chair)</td>
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<td>Geert Jan Biessels, MD, PhD</td>
<td>Professor, Neurology, University Medical Center Utrecht</td>
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<td>Roxana Carare, MD</td>
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<td>Suzanne Craft, PhD</td>
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<tr>
<td>Martin Dichgans, MD</td>
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<tr>
<td>Atticus Hainsworth, PhD</td>
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<td>Constantino Iadecola, MD</td>
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<tr>
<td>David Kleinfeld, PhD</td>
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<td>Jin-Moo Lee, MD, PhD</td>
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<td>Gary Rosenberg, MD</td>
<td>Professor and Chairman, Neurology, University of New Mexico</td>
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<tr>
<td>Julie Schneider, MD</td>
<td>Professor, Associate Director, Pathology, Rush Alzheimer’s Disease Center</td>
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<td>Sudha Seshadri, MD</td>
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<td>Eric Smith, MD</td>
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<td>Heather Snyder, PhD</td>
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<tr>
<td>Donna Wilcock, PhD</td>
<td>Associate Professor, Sanders-Brown Center on Aging, University of Kentucky</td>
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Vascular Contributions to Cognitive Impairment and Dementia (VCID)
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<tr>
<th>Panelist name</th>
<th>Title and Affiliation</th>
<th>Role</th>
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<tbody>
<tr>
<td>Walter Koroshetz, MD</td>
<td>Director, NINDS</td>
<td>Steering (ex officio member)</td>
</tr>
<tr>
<td>Roderick Corriveau, PhD</td>
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<tr>
<td>Patricia Walicke, MD, PhD</td>
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<tr>
<td>Debra Babcock, MD, PhD</td>
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<tr>
<td>Francesca Bosetti, PhD</td>
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<tr>
<td>Irene Dankwa-Mullan, MD, MPH</td>
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<tr>
<td>Marian Emr</td>
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<tr>
<td>Robert Finkelstein, PhD</td>
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<tr>
<td>Jordan Gladman, PhD</td>
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<tr>
<td>Amelie Gubitz, PhD</td>
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<tr>
<td>Carl Hill, PhD, MPH</td>
<td>Director, NIA Office of Special Populations, Office of the Director, NIA</td>
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<tr>
<td>Sophia Jeon, PhD</td>
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<tr>
<td>Jim Koenig, PhD</td>
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<tr>
<td>Claudia Moy, PhD</td>
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<tr>
<td>Margaret Ochocinska, PhD</td>
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<tr>
<td>Lisa A. Opanashuk, PhD</td>
<td>Scientific Program Manager, Office of Research and Development Dept. of Veterans Affairs Central Office</td>
<td>Organizing Committee</td>
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<tr>
<td>David Owens, PhD</td>
<td>Acting Deputy Director, Division of Extramural Research, NINDS</td>
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<tr>
<td>Anthony Pacifico, PhD</td>
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<td>Suzana Petanceska, PhD</td>
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<td>Creighton Phelps, PhD</td>
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<td>Steering, NIH Session Lead</td>
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<tr>
<td>Name</td>
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<td>Role (Organizing Committee/NIH Session Lead)</td>
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<tr>
<td>Paul Scott, PhD</td>
<td>Director, Office of Science Policy and Planning, NINDS</td>
<td>Organizing Committee</td>
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<td>Beth-Anne Sieber, PhD</td>
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<td>Nina Silverberg, PhD</td>
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<tr>
<td>Luke Stoeckel, PhD</td>
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<td>Margaret Sutherland, PhD</td>
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<td>Christine Torborg, PhD</td>
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<td>Salina Waddy, MD</td>
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