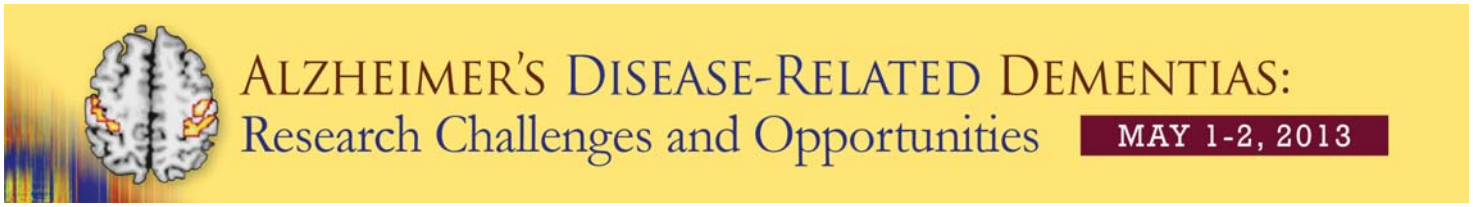

Conference and Recommendations Report to the NINDS Council

12 September 2013

Scientific Chair Thomas Montine, MD, PhD

1. INTRODUCTION

Background. This document reports to the NINDS Council the results of the "Alzheimer's Disease-Related Dementias: Research Challenges and Opportunities" conference, held on May 1-2, 2013. The report, if approved, will be delivered to the National Alzheimer's Project Act (NAPA) Council, at the Department of Health and Human Services (DHHS), for its October 2013 NAPA Council meeting. The conference complements the National Institute on Aging's "Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention." Both conferences respond to the National Alzheimer's Project Act that was signed into law in January 2011, by President Barack Obama. The objective of the conference is to contribute to the National Plan to Address Alzheimer's Disease goal of preventing and effectively treating Alzheimer's disease, including Alzheimer's disease-related dementias, by 2025. Like the 2012 Summit (http://www.nia.nih.gov/about/events/2012/alzheimers-disease-research-summit-2012-path-treatment-and-prevention), the Alzheimer's Disease-Related Dementias steering committee solicited input from internationally recognized experts to develop prioritized recommendations to guide scientific research in the next 5 to 10 yr. Following the 2012 National Plan's guidance on the related dementias, the assembled groups focused on frontotemporal degenerations (FTD), Lewy body dementias (LBD) (including dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD)), vascular cognitive impairment or dementia (VCI/VaD), mixed diseases including the associated diagnostic challenges of multiple etiology dementias (MED), and issues related to health disparities. The Session Chairs included Drs. Dennis Dickson, Maria Glymour, Steven Greenberg, Michael Hutton, David Knopman, Jennifer Manly, Karen Marder, Bruce Miller, William Seeley, and Berislav Zlokovic. Dr. Rod Corriveau was the Workshop Lead, and NINDS members of the Organizing Committee included Drs. Story Landis, Walter Koroshetz, Debra Babcock, Wendy Galpern, Andrey Kuzmichev, Beth-Anne Sieber, Margaret Sutherland, Christine Torborg, and Salina Waddy, and Ms. Marian Emr. Full membership of the conference committees is listed at the end of this document in Appendix 1. The National Institute on Aging was an active collaborator in this endeavor, in particular Drs. Richard Hodes, Tony Phelps, and Nina Silverberg, and sponsors included the FNIH, the Alzheimer's Association, the Alliance for Aging Research: Accelerate Cure/Treatment for Alzheimer's Disease, The Association for Frontotemporal Degeneration, and U.S. Against Alzheimer's Network.

Alzheimer's Disease-Related Dementias (ADRD). Dementia is a syndrome, an overlapping constellation of signs and symptoms caused by multiple diseases, which can be difficult to distinguish clinically. While Alzheimer's disease (AD) is the most common cause of dementia in older adults, in this group of individuals AD commonly co-exists with other diseases that contribute to dementia (termed "multiple etiology dementia" here, but also called "mixed dementia") resulting in, for example, "AD plus LBD" or "AD plus VCI/VaD," although LBD and VCI/VaD each can afflict individuals in the absence of AD. Moreover, although AD is the solitary major cause of dementia in the elderly, this is not the case in middle-aged adults when FTDs and other tauopathies have similar prevalence. The situation is further complicated by the fact that the current evidence base for some of these diseases is sparse, with the existing data derived overwhelmingly from Caucasians.

The diseases that make up ADRDs all are chronic diseases. While this may seem obvious, the significance of this point is that clinical expression of chronic diseases develops over time and includes stages prior to full clinical expression (in this case dementia) that include partial expression of signs and symptoms (prodrome) as well as apparent lack of clinical expression (latency). Some combination of prodrome and latency is often expressed using the term "pre-clinical disease."

We imagine a day in the hopefully not too distant future when the fruits of our research achieve the complementary goals of producing tools that accurately diagnose as early as possible the disease drivers of an individual's cognitive impairment, and of discovering safe, effective, and precise interventions. The complexity of the dementia syndrome

represents a serious challenge to accurate diagnosis, the key decision point in the management of an individual's illness, and often exceeds the expertise of general practitioners and will far exceed the capacity of our nation's specialists workforce unless appropriate steps are taken soon. Complementary to accurate diagnosis of disease drivers in individuals from disparate populations is the essential need to discover safe, effective, and precise interventions. Our knowledge of and experimental models for the molecular mechanisms of these diseases, especially their potential interaction, remains incomplete and is a major barrier to therapeutic development.

Charge. The Alzheimer's Disease-Related Dementias (ADRD) Workshop of 2013 is a component of the work designated by the National Alzheimer's Project Act (NAPA) of 2011 (http://aspe.hhs.gov/daltcp/napa). The law calls for the creation and maintenance of "a national plan to overcome Alzheimer's disease." The first National Plan to Address Alzheimer's Disease was released in May 2012, when the NIH and HHS convened the Alzheimer's Disease Research Summit 2012. Our conference, and the subject of this report, is a specific action item (1.A.4) in this 2012 National Plan.

Work. We organized ourselves into pre-workshop, workshop, and post-workshop sessions to develop the prioritized research recommendations with timelines presented in this report.

Pre-workshop efforts started in the Fall of 2012 when the leadership of NINDS, other officials from NINDS and NIA, and the Scientific Chair developed an overall strategy, five topic areas, and a roster of experts for each topic area. Each committee of 8 to 18 members, including two co-Chairs, (see Appendix 1) was tasked with developing a prioritized list of research recommendations and approximate timeline for its topic area. From December 2012 to April 2013, each committee met many times by teleconference to develop and revise its recommendations. In addition, we had a monthly teleconference of committee co-Chairs, Scientific Chair, NIH officials, and the Conference Steering Committee (Drs. Neil Buckholtz from the NIA; Ron Petersen, Chair of the NAPA Council; Sharon Hesterlee, member of the NINDS Council; David Holtzman, member of the NINDS Council) to ensure alignment and progress. Pre-workshop efforts culminated in a list of up to eight proposed prioritized research recommendations for each of the 5 topic areas, and approximate timelines for completion or full implementation. We distributed the Workshop's agenda and proposed recommendations to meeting registrants and posted the agenda online in April 2013 (https://meetings.ninds.nih.gov/?ID=4077).

The ADRD Conference was held on 1 and 2 May 2013 on the NIH campus following broad advertisement to the scientific community, government agencies, and non-governmental organizations. There were 567 registrants, of which 322 individuals joined in person; in addition, more than 200 people joined online. The goal of this workshop was to solicit input and feedback on these proposed recommendations and timelines. The two co-Chairs from each committee organized a presentation of the proposed prioritized research targets, the proposed timelines, and the rationale for how each committee reached its recommendations. Each topic session included ample time for exchange with the audience, as well as email input or questions from those participating online. The public portion of the workshop concluded with a review of all suggested additions and revisions with further opportunity for input from all participants. This was followed by a closed executive session during which topic co-Chairs, NIH officials, Steering Committee members, and the Scientific Chair reviewed the proposed revisions and assigned duties to finish the work.

Post-workshop efforts included several meetings among the committees to revise the content, prioritization, and proposed timelines for the research recommendations. Our ultimate conference call among committee co-Chairs, NIH officials, and Scientific Chair to finalize these recommendations was held on 2 July, 2013.

Product. The following report reflects the outcome of our pre-workshop, workshop, and post-workshop efforts. We have divided our prioritized research recommendations and timelines into five topic areas. Two topic areas are fundamental to all ADRDs; and although beyond the scope of our charge, in our opinion, they also are relevant to AD

itself: diagnosis and epidemiology of multiple etiologic dementias, and disparities populations. The other three topic areas are disease-specific: FTD, LBD, and vascular contributions to ADRD (VAS).

The format of prioritized research recommendations differs somewhat among the five topic areas. The decision to allow this was deliberate, and has the goal of not unnecessarily constraining optimal prioritization within each topic area. Timelines were made uniform across topic areas (1-3 yr, 3-7 yr, 7-10 yr, or > 10 yr) and reflect time to completion or achieving fully operational status for the recommendation.

Two points need to be stressed:

- All recommendations in this report are very important research goals. Topic session committees were charged with the difficult task of assigning priority within each area. However, this should not be misinterpreted as indicating that any recommendation is unimportant. Indeed, to be included in this report means that research goal is among the top items in its respective field.
- Our timelines are the interval from now to expected completion or full implementation, and are independent of prioritization. There are several reasons why one recommendation might be expected to take longer than another, *e.g.*, more work needs to done, or other goals need to be accomplished first before full success can be achieved. However, longer time to completion or full implementation does not diminish priority and should not be misconstrued as an option to delay onset of work; in fact, just the opposite.

As Scientific Chair of the ADRD Workshop, I respectfully submit this report to NINDS Council on behalf of all committee co-Chairs and members.

Sincerely,

Thomas J. Montine, MD, PhD

Alvord Professor and Chair

Department of Pathology

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2. EXECUTIVE SUMMARY

Table 1. Stratification of topic areas into focus areas with the number of prioritized research recommendations for each. The recommendations and their timelines are summarized in Table 2 and discussed at greater length in Section 4. Note that the selected Focus Areas are not prioritized, except for LBD (so numbered 1 through 4).

TOPIC AREA	**FOCUS AREA (number of prioritized research recommendations)**			
1. Multiple etiology dementias (MED)	Differential Diagnosis (3)		Epidemiology (3)	
2. Health disparities (HD)	Recruitment (4)		Advancing Treatment and Prevention Strategies (4)	
3. Lewy body dementias (LBD)	1. Establish longitudinal cohorts with common measures, culminating in autopsy studies. (2)	2. Discover disease mechanisms through brain mapping and genetics (2)	3. Develop and validate biological and imaging biomarkers (2)	4. Model disease processes to develop potential symptomatic and disease modifying therapies (2)
4. Frontotemporal dementia and other tauopathies (FTD)	Basic Science: Pathogenesis and Toxicity (4)		Clinical Science: Discovery, tools, and cohorts (4)	
5. Vascular contributions to ADRD - focus on small vessel disease and AD/vascular interactions (VAS)	Basic Mechanisms and Experimental Models (3)		Human-Based Studies (3)	

Table 2 sorts recommendations by priority (high, intermediate, or additional) and timeline for completion or full operation of a continuing activity (1–3 yr, 3–7 yr, 7–10 yr, >10 yr). Within each priority/timeline group, recommendations are listed by Topic Area abbreviated as MED (multiple etiology dementias), HD (health disparities), LBD (Lewy body dementias), FTD (frontotemporal dementia and other tauopathies), and VAS (vascular contributions to ADRD - focus on small vessel disease and AD/vascular interactions) and by Focus Area.

HIGH PRIORITY RECOMMENDATIONS 1–3 yr		
Topic Area	***Focus Area***	***Recommendation***
1—MED	Differential diagnosis	Develop clinical algorithms for detection of prototypical neurodegenerative dementias and VCI in (a) primary care, (b) general neurology, and (c) general psychiatry outpatient settings; and clinical algorithms for referral to specialists in appropriate cases that also might involve consultations using novel technologies.
	Epidemiology	Conduct population-based studies of dementia prevalence and incidence in diverse ethnic groups and age ranges using imaging and fluid biomarkers.
3—LBD	Establish longitudinal cohorts with common measures	Initiate clinical trials for DLB and PDD using existing and newly developed symptomatic therapies that address key symptoms that impact patient function and the burden put on caregivers.
		Create longitudinal clinical, biological, and imaging resources for DLB and PDD from the earliest stages to autopsy studies to improve the 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.
4—FTD	Clinical Science	Expand efforts to genotype patients with FTD and identify new genes.
5—VAS	Human-based studies	Develop noninvasive markers of key vascular processes related to cognitive and neurologic impairment. (Part 1 of 2).
HIGH PRIORITY RECOMMENDATIONS 3–7 yr		
Topic	***Focus area***	***Recommendation***
2—HD	Recruitment	Initiate and leverage ongoing longitudinal community-based cohort studies of incident dementia in diverse populations incorporating imaging, fluid biomarkers, and autopsy.
	Treatment and Prevention Strategies	Enhance the design of all trials of vascular health interventions to improve their application to diverse populations.
4—FTD	Basic Science	Clarify the mechanism of tau pathogenesis and associated neurodegeneration.
5—VAS	Basic Mechanisms and Experimental Models	Develop next-generation experimental models of VCI and VaD.
	Human-based studies	Validate noninvasive markers of key vascular processes related to cognitive and neurologic impairment. (Part 2 of 2).
INTERMEDIATE PRIORITY RECOMMENDATIONS 1–3 yr		
Topic	***Focus area***	***Recommendation***
1—MED	Epidemiology	Develop registries for enumerating and characterizing less common dementias, dementias in younger persons, rapidly progressive dementias, and potentially treatable dementias.
2—HD	Recruitment	Use mixed methodology studies to improve assessment tools for disparities populations.
	Treatment and Prevention	Assess lifecourse risk factors for cognitive decline and ADRDs among disparities populations.
		Estimate disparities in health burden of ADRDs and risk factors among disparities populations.
3—LBD	Discover disease mechanisms through brain mapping and genetics	Using well defined cohorts with DLB or PDD who have come to autopsy, systematically map 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.
4—FTD	Basic Science	Develop better FTD in vivo and cell-based model systems.
	Clinical Science	Create an international FTD clinical trial network.
INTERMEDIATE PRIORITY RECOMMENDATIONS 3–7 yr		
Topic	***Focus area***	***Recommendation***
1—MED	Differential Diagnosis	Develop imaging and fluid biomarker algorithms to detect prototypical versus atypical dementias and expand their accessibility in primary care settings.
2—HD	Recruitment	Use community outreach methods to facilitate recruiting disparities populations into FTD and LBD clinical studies.
3—LBD	Discover disease mechanisms	Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that influence the risk and clinical features of DLB and PDD.
	Develop and validate biological and imaging biomarkers	Develop imaging approaches to enhance the diagnostic accuracy of DLB and PDD, detect latent and prodromal DLB and PDD, and monitor disease progression in natural history and treatment studies by integrating established and new imaging tools.

		Use existing or new longitudinal case-control studies of individuals with DLB and PDD to develop biomarkers for Lewy-related pathologic changes, disease progression, and the relative amount of concurrent AD. 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 .
4—FTD	Basic Science	Determine the molecular basis for C9ORF72 expansion- and GRN-related neurodegeneration.
	Clinical Science	Develop FTD biomarkers for diagnosis and disease progression.
5—VAS	Basic Mechanisms	Encourage basic science research that investigates the impact of AD risk factors on cerebrovascular function.
	Human-based studies	Determine interrelationships among cerebrovascular disease and risk factors, Aβ, and neurodegeneration.
ADDITIONAL RECOMMENDATIONS 1–3 yr		
Topic	***Focus area***	***Recommendation***
1—MED	Differential diagnosis	Develop clinical, imaging, and fluid biomarker algorithms for the rapidly progressive and potentially treatable dementias to enable recognition and referral to specialists (1-3 yr to initiation).
	Epidemiology	Expand and broaden the accessibility of neuropathology services to cases of cognitive impairment and dementia outside of research centers. Link neuropathologic findings to development of clinical algorithms and biomarkers (timeline 1-3 yr for initiation and ongoing).
ADDITIONAL RECOMMENDATIONS 3–7 yr		
Topic	***Focus area***	***Recommendation***
2—HD	Recruitment	Evaluate under-diagnosis and implement surveillance for ADRDs to detect incidence and monitor trends in disparities populations.
3—LBD	Model disease processes to develop therapies	Recognizing the importance of α-synuclein and AD pathophysiologic processes in DLB and PDD, new animal, cellular, and in vitro models are needed that recapitulate key features of these disorders with the ultimate goal of identifying strategies that can be carried forward into clinical trials.
4—FTD	Basic Science	Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity.
5—VAS	Basic Mechanisms	Encourage basic science research that investigates the impact of cerebrovascular risk factors on AD-related neurodegeneration.
ADDITIONAL RECOMMENDATIONS 7-10 yr		
Topic	***Focus area***	***Recommendation***
3—LBD	Model disease processes to develop therapies	Develop disease-modifying interventions based upon research discoveries.
5—VAS	Human-based studies	Identify next generation vascular interventions to treat or prevent VCI and VaD.
ADDITIONAL RECOMMENDATIONS >10 yr		
Topic	***Focus area***	***Recommendation***
2—HD	Treatment and Prevention	Identify environmental and genetic factors that modify incidence, presentation, and long-term outcomes of ADRDs in disparities populations.
4—FTD	Clinical Science	Understand phenotypic heterogeneity and natural history.

3. OVERLAP

It became clear early in our work that there are shared themes across ADRD, as well as with dementias more generally, including AD itself. We addressed the issue of shared themes in part by including two topic areas that are fundamental not only to all ADRD but also to all diseases that cause dementia: Multiple Etiology Dementias and Health Disparities Research.

- Training and education of researchers and health care providers at all levels is a critical need to meet the coming challenge to our health care systems nationally. Indeed, a shared priority that can be initiated immediately is improved health care professional education at all levels and training of providers of all types including counselors, nurses, general practice, geriatrics, psychiatry, neuropathology, and behavioral neurology. This shared theme is captured as a bullet under **Multiple Etiology Dementias**, Recommendation #1, is essential to improved diagnostics, and is linked with improved caregiver support to enhance quality of life and to fuel patient-based research.
- All recommendations developed for **Health Disparities** can be applied more generally across all diseases that cause dementia.

In addition, our preconference work highlighted several other shared themes. While we discussed these at length and coordinated our concepts, we deliberately eschewed developing overarching or cross-disorder recommendations during our pre-conference work because it was not clear that each would receive the same priority ranking within each topic area. However, one outcome of our conference was consensus to stress the additional major shared themes among topic areas. These are:

- **Fundamental research** to determine the mechanisms of ADRD and the interactions among genetic factors, environment, and aging.
- **Improved diagnostics**, including imaging and biomarkers, to fuel translational and clinical research in ADRD. Special focus needs to be paid to development of validated diagnostics for the earliest stages of disease and for disease progression.
- **Optimized repositories** of tissue, cells, biofluids, and molecules, both in scale and governance, as collaborative resources for fundamental and translational research. This topic is being addressed in other forums, *e.g*., the 2013 NINDS Repository Scientific Liaison Meeting and NIA Biospecimen Best Practices review (in progress).
- All of these efforts ultimately are directed at producing effective rational interventions for ADRD to be evaluated in **clinical trials.**

4. TOPIC AREAS with DETAILED DISCUSSION POINTS

Each Topic Area's prioritized research recommendations reflect that group's consideration of what priorities and timelines chart the best route to prevent, stop, or cure ADRD.

4.1. Topic 1 - Multiple Etiology Dementias: The Public Health Problem and Improving Recognition across the Spectrum. *Focus Area 1 - Differential Diagnosis*

Recommendation 1. Develop clinical algorithms for detection of prototypical neurodegenerative dementias and VCI in (a) primary care, (b) general neurology, and (c) general psychiatry outpatient settings; and clinical algorithms for referral to specialists in appropriate cases that also might involve consultations using novel technologies (1-3 yr).

- Diagnosis of ADRDs can be challenging; however, advances have occurred in the definition of clinically important features that distinguish the dementia of AD from VCI, LBD, behavior variant FTD, primary progressive aphasia, normal pressure hydrocephalus, and prion disease, as well as other rapidly progressive dementias and syndromes with multiple neurodegenerative and vascular elements. "Prototypical" presentations of each of these can be defined on clinical grounds and employed as exemplars.
- Because most people with disorders in the dementia spectrum are not evaluated by specialists and treatments are most effective in the earliest stages of disease, there is a pressing need to translate new advances in diagnoses and care to where the majority of cognitive disorders present: primary care, general neurology, and general psychiatry outpatient practice. Detection of the prototypical presentations by such first line clinicians must be emphasized.
- New approaches to diagnosis of cognitive disorders in primary care should be pursued and evaluated using rigorous criteria for effectiveness. These approaches would include standardized informant-based electronic questionnaires, easily accessible telemedicine consults with specialists, and other electronically supported diagnostic aids.
- There is currently a critical shortage of cognitive specialists and researchers to develop innovative treatments and direct systems of care for persons with dementia. It is therefore imperative to support high quality clinical research training programs that attract physicians and non-physician researchers in geriatrics, behavioral neurology, and geriatric psychiatry.
- Because the problem of dementia crosses multiple disciplines, collaboration among the appropriate planning and funding agencies, both internationally and nationally, including among different Institutes of the NIH, is critical to successfully solve this major public health problem.

Recommendation 2. Develop imaging and fluid biomarker algorithms to detect prototypical versus atypical dementias and expand their accessibility in primary care settings (3-7 yr).

- Despite gains in clinical recognition, clinical diagnostic tools alone will be insufficient to capture the full range of etiologies in many individuals with dementia. Two reasons are that most late life cognitive impairment is multiple etiologic, and specific diseases do not exclusively map to only one clinical presentation. For example, VCI can present with a variety of cognitive syndromes. Additionally, behavior variant FTD may be due to one of several distinct molecular drivers. The field needs to embrace such complexity, as reductionist approaches simply do not fit reality. An improved conceptual framework for, and improved practical approaches to, multiple etiology dementia must be developed.

- Imaging and fluid biomarkers are needed to provide evidence for different etiologies, whose presence might not be provable on clinical grounds alone. Validation of biomarkers will require large-scale testing in well-studied patients.
- A considerable fraction of patients who are clinically diagnosed with AD dementia have other diseases causing dementia alone or in combination with AD. Understanding the contribution of non-AD etiologies to AD pathophysiologic processes is essential.

- Neuroimaging plays a special role in dementia diagnosis. Expertise in the neuroradiology of dementing illnesses is currently limited to tertiary care facilities. Yet methods exist for automating some aspects of neuroimaging. Algorithms for analyzing brain imaging (structural magnetic resonance [MR], single-photon emission computed tomography, positron emission tomography) need to be available for all radiologists and non-radiologists when interpreting brain scans when there is clinical suspicion of dementia. Validation would also need to be provided by neuropathologic evaluation.

Recommendation 3. Develop clinical, imaging, and fluid biomarker algorithms for the rapidly progressive and potentially treatable dementias to enable recognition and referral to specialists (1-3 yr).

- Because of their relative rarity, the rapidly progressive (e.g., prion disease) and potentially treatable (e.g., non-infectious autoimmune encephalopathies, normal pressure hydrocephalus) dementias are very challenging to diagnose outside of specialty settings.
- Particularly with the autoimmune encephalopathies, responsiveness to therapeutic interventions requires timely detection and recognition in the earliest stages by primary care practitioners and general neurologists.
- Algorithms and detection protocols based on a combination of clinical, imaging, and fluid biomarker assessments should be developed for deployment in primary care and general neurology settings. (See Recommendation 1 above for validation of these algorithms and detection protocols).

Focus Area 2 - Epidemiology

Recommendation 1. Conduct population-based studies of dementia prevalence and incidence in diverse ethnic groups and age ranges using imaging and fluid biomarkers (1-3 yr).

- Many of the non-AD dementias occur in people under 70 years-old, and there is considerable uncertainty about the accuracy of current estimates of the prevalence or incidence of behavioral variant FTD, primary progressive aphasia, Lewy body diseases, normal pressure hydrocephalus, and the rapidly progressive dementias.
- Almost all of the currently available estimates of incidence and prevalence of diseases that cause dementia have utilized the single diagnosis model for reporting results. Future studies should develop the capability of reporting prevalence and incidence in terms of multiple etiology.
- The next generation of population-based studies should utilize currently available imaging and fluid biomarker assessments to allow more refined and complete assessments of etiology(ies), and also serve as test-beds for identification and validation of new biomarkers.
- The next generation of population-based studies must involve diverse ethnic groups, due to potential differences in risk factors for dementia and in response to therapies.

Recommendation 2. Develop registries for enumerating and characterizing less common dementias, dementias in younger persons, rapidly progressive dementias, and potentially treatable dementias (1-3 yr).

- Use electronic medical records within large regional health systems to screen populations and develop registries of people with cognitive impairment. This approach complements traditionally designed epidemiological studies by reflecting the actual stress that cognitive disorders place on the healthcare system and expands research opportunities in community settings.
- Efficient data acquisition, supplemented by technologies described in Recommendation 1 in the Differential Diagnosis Focus Area, is a critical design requirement to avoid over-burdening primary care providers.
- Registries should link clinical diagnoses to later neuropathologic findings.

Recommendation 3. Expand and broaden the accessibility of neuropathology services to cases of cognitive impairment and dementia outside of research centers. Link neuropathologic findings to development of clinical algorithms and biomarkers (1-3 yr).

- Until imaging and fluid biomarkers are "qualified" as valid for the diagnosis of specific dementia etiologies, post-mortem neuropathologic examinations remain essential for verifying underlying disease processes when testing imaging and fluid biomarkers and clinical algorithms.
- Because anatomic pathology is grossly underfunded in modern health-care systems, neuropathology as a subspecialty is under great stress. Neuropathology is an absolutely essential core infrastructure for research in neurodegenerative and late-life cerebrovascular diseases, and is the foundation for improving clinical diagnoses and aiding in better understanding the prevalence of the non-AD dementias.

4.2. Topic 2 - Health Disparities. *Focus Area 1 – Recruitment*

Recommendation 1. Initiate and leverage ongoing longitudinal community-based cohort studies of incident dementia in diverse populations incorporating imaging, fluid biomarkers, and autopsy (3-5 yr)

- 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, or leverage prior data collection efforts by building on existing community-based cohort studies by adding careful ADRD assessments and biobanking initiatives.
- Use recruitment strategies that are community-rather than clinic-based to reduce bias, including recruiting persons with 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.
- Assess a wide range of risk factors and incorporate cutting-edge imaging and fluid biomarkers (both blood and CSF) and autopsy when possible.
- Biobank a wide range of ante- and post-mortem biospecimens for future studies.

Recommendation 2. Use mixed methodology studies to improve assessment tools for disparities populations (1-3 yr).

- Due to language differences, varied cultural 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 great need for assessment tools developed for and validated among disparities populations.
- Generate a repository of assessment tools (i.e., questionnaires, neuropsychological instruments and normative references, and informant-based surveys) validated for use among diverse populations.
- Pool existing (global and item-level) data from ongoing or previously conducted studies of aging that include diverse populations for 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 ADRDs along with appropriate methods for collecting informant-based assessments of daily functioning levels.
- Conduct validity studies of newly generated instruments among diverse patients.
- Embed culturally- and linguistically-appropriate assessment tools within ongoing and newly generated studies of ADRDs.

Recommendation 3. Use community outreach methods to facilitate recruiting disparities populations into FTD and LBD clinical studies (5-7 yr).

- 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.
- 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.

- Develop simple, sensitive methods for screening for cognitive impairment and dementia in primary care settings.
- Leverage local initiatives/agencies sponsoring collaborative, community-driven plans that are focused on health outcomes in disparities populations.

Recommendation 4. Evaluate under-diagnosis and implement surveillance for ADRDs to detect incidence and monitor trends in disparities populations (5-7 yr).

- Identify barriers to diagnosis to understand the burden of disease for ADRDs, for example via research on predictors of under-diagnosis, evaluate whether disparities populations have similar diagnosis rates.
- Develop surveillance approaches using information gained from these studies.
- Build these studies into other research approaches, provided data linkages are available and time-to-diagnosis questions are implemented.

Focus Area 2 - Advancing Treatment and Prevention Strategies

Recommendation 1. Enhance the design of all trials of vascular health interventions to improve their application to diverse populations (5-7 yr).

- Evidence exists that vascular health is critical to delaying onset of dementia, potentially not only VCI/VaD but also LBD and AD, and may be differential across diverse populations.
- Intervention trials for cardiovascular and stroke outcomes could 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 sensitive to ensure their application to diverse populations.
- Prioritize diversity recruitment, with over-representation of certain populations to permit stratified or effect modification analyses.
- Adopt standardized assessments to facilitate meta-analyses and enhance the value of the evidence across these trials.

Recommendation 2. Assess lifecourse risk factors for cognitive decline and ADRDs among disparities populations (1-3 yr).

- Cognitive decline appears to be greater for disparities populations where there are well-established higher risk factor profiles, but much observational research does not define exposures that closely correspond with potential treatments or interventions.
- Measure changes in risk factors (both traditional and novel) over the lifecourse and link to assessments of adult cognitive status and ADRD outcomes.
- Assess whether interventions that change the risk factors predict reduced rates of cognitive decline or risk of dementia across dimensions of race/ethnicity, socio-economic status, and rural living.

Recommendation 3. Estimate disparities in health burden of ADRDs and risk factors among disparities populations (1-3 yr).

- To prioritize public health interventions and campaigns, obtain estimates of incidence of ADRDs and the population-attributable fractions for specific risk factors.
- Both the prevalence and impact of many risk factors may differ across disparities populations.
- It is currently unknown whether vascular disease makes a larger contribution to all-cause dementia in disparities populations; however, this is likely to be the case because prevalence of several vascular risk factors and stroke differs across groups.

Recommendation 4. Identify environmental and genetic factors that modify incidence, presentation, and long-term outcomes of ADRDs in disparities populations (>10 yr).

- Environmental contexts often differ markedly across all disparities populations.

- Prevalence of some risk genetic alleles may differ by race/ethnicity and the impact of the same genetic locus on ADRD outcomes may differ across social context.
- Test the intersection of social and biological mechanisms of dementias to see if mechanisms differ across populations (*e.g.*, vascular processes may play a larger role in disparities populations because of the greater prevalence of many vascular risk factors).
- Genetic studies should include diverse populations and incorporate measures of environmental 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 ADRD outcomes so genetic research must account for social conditions.
- Use this genetic research to identify opportunities to prevent or treat the dementias.

4.3. Topic 3 - Lewy Body Dementias (LBD): Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD). ***Focus area 1 - Establish longitudinal cohorts with common measures, culminating in autopsy studies.***

Recommendation 1. Initiate clinical trials for DLB and PDD using existing and newly developed symptomatic therapies that address key symptoms that impact patient function and the burden put on caregivers (1-3 yr).

- While there have been many therapeutic trials focused on PD, patients with dementia (DLB and PDD) have been excluded. Consequently, there is little information about the efficacy of approved drugs, (*e.g.*, dopamine replacement) and experimental drugs on DLB and PDD. The aim of this recommendation is to engage existing clinical networks, such as the Alzheimer's Disease Cooperative Study, Parkinson Study Group, or NeuroNEXT, and to establish new networks of clinicians, including movement disorder specialists, behavioral neurologists, psychiatrists or sleep disorder specialists, to use well-characterized cohorts of DLB and PDD for treatment trials with current Food and Drug Administration-approved drugs.

Recommendation 2. Create longitudinal clinical, biological, and imaging resources for DLB and PDD from the earliest stages to autopsy studies to improve the 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 (1-3 yr).

- 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, such as the Alzheimer's Disease Neuroimaging Initiative, 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 and non-amnestic 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 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.

Focus area 2 - Discover disease mechanisms through brain mapping and genetics

Recommendation 3. Using well defined cohorts with DLB or PDD who have come to autopsy, systematically map 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 (1-3 yr).

- Require that data generated in this mapping initiative be incorporated into an open-access database that links clinical, biological and autopsy data.

Recommendation 4. Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that influence the risk and clinical features of DLB and PDD (5-7 yr).

- This goal will require genome wide association studies of large cohorts, as well as whole exome/genome sequencing of families with multiple affected members. This recommendation also includes identification of genetic and epigenetic factors influencing the risk of developing dementia or Lewy body disease in patients with PD, or other degenerative diseases. Genetic studies should lead to the development of diagnostics, such as a panel of common genetic variants or gene expression profiling, to enable the stratification of patients by diagnosis, and with respect to prognosis and response to treatment. Studies should also be developed that study gene-environment interactions.

Focus area 3 - Develop and validate biological and imaging biomarkers

Recommendation 5. Develop imaging approaches to enhance the diagnostic accuracy of DLB and PDD, detect latent and prodromal DLB and PDD, and monitor disease progression in natural history and treatment studies by integrating established and new imaging tools (5-7 yr).

- Evaluate role of currently available imaging tools in the diagnosis and classification of these disorders with emphasis on imaging modalities demonstrating high reproducibility across populations, scanning sites, and imaging platforms.
- Develop parallel strategies to evaluate emerging technologies or analytical approaches for feasibility and value added in a multicenter trial environment. This approach will additionally facilitate the development of synergistic multi-modal biomarker strategies (e.g., α-synuclein binding agent) in combination with systems-level functional biomarkers of disease severity to enhance the accuracy of diagnosis and the reliability of progression measurements early in disease course.

Recommendation 6. Use existing or new longitudinal case-control studies of individuals with DLB and PDD to develop biomarkers for Lewy-related pathologic changes, disease progression, and the relative amount of concurrent AD. 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 (5-7 yr).

- This recommendation proposes to capitalize on existing longitudinal case-control cohorts to encourage standardization of protocols and core 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 detect PD but also PD pathologic changes, markers of neurodegeneration, and markers of disease risk (5-7 yr).

Focus area 4 - Model disease processes to develop potential symptomatic and disease modifying therapies

Recommendation 7. Recognizing the importance of α-synuclein and AD pathophysiologic processes in DLB and PDD, new animal, cellular, and in vitro models are needed that recapitulate key features of these disorders with the ultimate goal of identifying strategies that can be carried forward into clinical trials (3-7 yr).

- This recommendation recognizes the need to develop models that fit not only what is known about the molecular pathology of DLB and PDD based upon current evidence, but also what can be learned from proposed systematic mapping and biomarker studies. New models will enhance understanding of selective vulnerability; mechanisms of neurotoxicity; factors that determine disease progression, transmission or propagation; and 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 cells (iPS cells) from subjects enrolled in clinical, genetic or biomarkers studies.

Recommendation 8. Develop disease-modifying interventions based upon research discoveries (7-10 yr).

- This recommendation builds upon the knowledge base that is gained from genetic studies and from systematic profiling of well-characterized patient samples that identify underlying disease mechanisms. 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.

4.4. Topic 4 - FTD and Related Tauopathies. *Focus Area 1 - Basic Science: Pathogenesis and Toxicity*

Recommendation 1. Clarify the mechanism of tau pathogenesis and associated neurodegeneration (3-7 yr)

- 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 (post-translational tau modifications, aggregation, microtubule dysfunction, interneuronal spread, or other tau (dys)functions) represent the most human-relevant, deleterious, and targetable processes?
- Innovative cell-based, animal model, and human post-mortem studies are the recommended approaches to determine pathogenic events that promote tau toxicity and spread. Genetic models should be complemented with other methods that may simulate aspects of sporadic disease (inoculation studies, iPSCs, etc).

Recommendation 2. Develop better FTD in vivo and cell-based model systems (1-3 yr)

- There is a need to improve the tools for disease mechanism and target identification, validation, and drug development. Do existing FTD models reproduce the formation of pathological lesions, associated neurodegeneration, and behavioral impairment?
- The recommended approach is to prioritize development of robust models to study TDP-43/FUS, GRN haploinsufficiency, and C9ORF72 expansion disease, using emerging behavioral and pathological features of human disease as the standard for comparison once those features are systematically defined. In addition, continue to evaluate transgenic models of tauopathy and revisit genomic tau transgenes and knock-in models, emphasize 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 molecular dissection of pathogenesis.

Recommendation 3. Determine the molecular basis for C9ORF72 expansion- and GRN-related neurodegeneration (3-7 yr)

- There is need to identify the predominant mechanism(s) of *C9ORF72* FTD/ALS pathogenesis: loss of gene function, RNA toxicity, dipeptide repeat toxicity, TDP-43 proteinopathy or other factors, and to determine the mechanisms of neurodegeneration in *GRN*-related FTD: 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 pathologic features correlate best with neurodegeneration. In addition, compare human findings with those derived from animal and cell-based models and test treatments for different aspects of mutation-related pathogenesis in model systems, for example by exploring RNA lowering strategies for *C9ORF72*-related disease or anti-inflammatory approaches to GRN-related disease. Finally, determine the normal function of progranulin, especially during the response to brain injury, how haploinsufficiency leads to neurodegeneration, and identify therapeutic approaches designed to replace/increase GRN.

Recommendation 4. Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity (3-7 yr)

- There is need to clarify fundamental disease mechanisms associated with the TDP-43 and FUS proteinopathies. Do TDP-43/FUS represent toxic, spreading disease proteins? Does loss of protein

function play a significant role? Is intraneuronal progression unified across TDP-43 pathologies and what is the sequence of events?

- Our recommended approach is to expand the scope and precision of human neuropathologic studies, focusing on early-stage disease, define the sequence of molecular changes associated with pathogenesis from loss of nuclear localization to the formation of assemblies, and continue to study and define the normal cellular functions of TDP-43 and FUS.

Focus Area 2 - Clinical Science: FTD clinical discovery, tools, and cohorts

Recommendation 1. Expand efforts to genotype patients with FTD and identify new genes (1-3 yr)

- There is need to accelerate discovery of new familial FTD genes and provide genotyping support for research on patients with known genetic profiles, whether or not a disease-causing mutation is present.
- Our recommended approach is to provide increased clinical resources to identify and collect FTD families with a range of phenotypes, create core service for FTD genotyping and banking DNA where any researcher can send samples, receive genotype information, or request data/samples from large cohorts. Improve access and cost of screening for FTD genes, and support GWAS with deep sequencing around subthreshold peaks. These efforts should include amyotrophic lateral sclerosis (ALS) kindreds in gene discovery studies.

Recommendation 2. Develop FTD biomarkers for diagnosis and disease progression (3-7 yr)

- There is need for better tools to detect early stage disease, establishing molecular diagnosis, 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, with a priority on tau. These efforts will segment clinical trial cohorts and ultimately enable tailored FTD therapy. These studies should be complemented by efforts to define the most sensitive systems-level surrogate outcome biomarkers (MRI/fMRI/PET/EEG/clinical) 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 need to identify the most meaningful clinical endpoints for Phase III trials, determine whether recently identified tau PET tracers will detect tau pathology in FTD and related tauopathies, as well as in AD, and pursue deeper motor phenotyping to detect emergence of motor neuron disease (MND), as this will impact natural history.

Recommendation 3. Create an international FTD clinical trial network (1-3 yr)

- 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.
- We recommended prioritization of clinical studies with therapies designed to replace/increase GRN.

Recommendation 4. Understand phenotypic heterogeneity and natural history (>10 yr)

- There is need to understand how genetic background, brain development, and environment are linked to the patient's clinico-pathologic syndrome and what factors influence onset age and pace of progression. Understanding these factors may enhance trial design by accounting for variations in anatomical and temporal progression across cohorts and will aid interpretation of trial outcomes.
- Our recommended approach is to conduct natural history studies of preclinical inherited FTD (especially *MAPT*, *GRN*, and *C9ORF72*-related FTD) by following 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-pathologic

correlation is high (*e.g.,* progressive supranuclear palsy and tau, semantic variant primary progressive aphasia and TDP-43 Type C, FTD with MND and TDP-43 Type B). We recommend seeking genetic, anatomic, and environmental disease modifiers that influence clinico-pathologic 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.

4.5. Topic 5 - Vascular Contributions to ADRD: Focus on Small Vessel Disease and AD/Vascular Interactions. *Focus Area 1 - Basic Mechanisms and Experimental Models*

Recommendation 1. Develop next-generation experimental models of VCI and VaD (3-7y).

- 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 VCI/VaD 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 breakdown such as those caused by disrupted endothelial-pericyte or endothelial-astrocyte signaling and models of hypoperfusion.
- Such rodent models should also easily be applied to AD research, so VCI/VaD 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.
- Use such animal models to increase our knowledge of lifestyle risk factors.
- Develop new tools for cell- (endothelial, smooth muscle, pericyte, etc.) and region- (gray vs. white matter, cortex vs. striatum, etc.) specific genotyping and phenotyping of the cerebrovascular tree and neurovascular unit (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.

Recommendation 2. Encourage basic science research that investigates the impact of AD risk factors on cerebrovascular function (3-7 y).

- 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 Aβ-mediated effects in young to middle-aged mice fed a far healthier diet than most North Americans consume. Key areas for further research include:
    - Investigate Aβ-mediated effects on cerebrovascular function, including all cells involved in the neurovascular unit.
    - Investigate Aβ-mediated effects on hemostasis, including blood clotting and fibrinolysis.
    - Investigate the contributions of additional risk factors for AD, including diabetes, lipid metabolism, hypertension, diet, exercise, 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 GWAS 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 on AD-related neurodegeneration (3-7 y).

- 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 Aβ- and tau-related disease processes, both separately and together.
- 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. 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 neurovascular unit leading to secondary neurodegeneration in Aβ-independent and tau-independent pathways, and within the Aβ pathway and the tau pathway (e.g., receptor for advanced glycation end products (RAGE), lipoprotein receptors, endothelial and pericyte cell-specific gene deletion and expression).
- Cognitive and behavioral tests should, when modeling VCI/VaD, include functional testing of brain regions impacted by cerebrovascular disease.

Focus Area 2 - Human-Based Studies

Recommendation 1. Develop (1-3 y) and validate (3-7 y) noninvasive markers of key vascular processes related to cognitive and neurologic impairment.

- Identify biomarkers of key microvascular processes related to cognitive and neurologic impairment, including biomarkers of tissue injury (*e.g.,* microinfarcts, ischemic white matter damage); vessel disease (e.g. cerebral amyloid angiopathy, arteriosclerosis); and other vascular alterations such as blood brain barrier dysfunction, vascular reactivity, and hypoperfusion. Modalities may include but are not limited to neuroimaging, systemic (blood/urine), and central nervous system (CNS) fluids.
- Pursue cross-directional interdisciplinary studies to validate and explore the links between vascular biomarkers and the key microvascular processes.
- Incorporate the above pathologically validated vascular biomarkers in clinical studies to determine their association with risk factors and cognitive/neurologic impairment and decline in human subjects.

Recommendation 2. Determine interrelationships among cerebrovascular disease and risk factors, Aβ, and neurodegeneration (3-7 y).

- 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, VCI, and multiple etiology dementia.
- Determine relationships of vascular risk factors and AD biomarkers to biomarkers of cerebrovascular disease, such as endothelial cell function, blood brain barrier permeability, vascular stiffness, and other measures of vascular physiology.
- 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 vs. 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 next generation vascular interventions to treat or prevent VCI and VaD (7-10 y).

- Establish clinical trials to develop surrogate markers for severity of VCI and VaD. Such trials could be those relating the burden of VCI 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 VCI and VaD. However, there are several interventions that are known to impact general vascular risk factors, including management of hypertension, statins, control of diabetes, diet, exercise, and other lifestyle interventions. In particular, if we are successful in developing clinical or surrogate markers for diagnosing and quantifying VCI and VaD with some specificity, it would be relevant to determine whether or not and to what degree existing vascular interventions may beneficially impact VCI burden. By necessity, these would have to be long-term, longitudinal cohort studies.
- 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 VCI as a potential step towards improving clinical diagnosis and measurement of clinically meaningful trial outcomes.

Appendix 1: ADRD Committee Members

Topic Area	Panelist name	Title and Affiliation
1. Multiple etiology dementias (MED)	David Knopman, M.D. (co-chair, also FTD panelist)	Professor, Department of Neurology, Mayo Clinic
	Bruce Miller, M.D. (co-chair)	Professor, Department of Neurology, Sandler Neurosciences Center, University of California, San Francisco
	David Bennett, M.D. (also HD)	Director, Rush Alzheimer's Disease Center, Rush University Medical Center
	Bradley Boeve, M.D. (also LBD, FTD; pre-workshop discussions only)	Professor of Neurology, Department of Neurology, Mayo Clinic
	Cynthia Carlsson, M.D.	Associate Professor of Medicine, Medicine/Geriatrics, Alzheimer's Disease Research Center, University of Wisconsin
	Michael Geschwind, M.D., Ph.D.	Associate Professor of Neurology, Memory and Aging Center, University of California, San Francisco
	Ted Huey, M.D.	Assistant Professor, Depts. of Psychiatry & Neurology, Taub Institute for Research on Alzheimer's Disease, Columbia University
	Richard O'Brien, M.D., Ph.D.	Professor of Neurology, Associate Dean of Research, Johns Hopkins Bayview Medical Center, Johns Hopkins Medical Institute
2. Health disparities (HD)	M. Maria Glymour, Sc.D. (co-chair)	Assistant Professor, Social and Behavioral Sciences, Harvard School of Public Health
	Jennifer Manly, Ph.D. (co-chair)	Associate Professor of Neuropsychology, Columbia University Medical Center
	Lisa Barnes, Ph.D.	Professor, Neurological Sciences, Rush Alzheimer's Disease Center, Rush University Medical Center
	David Bennett, M.D. (also MED)	Director, Rush Alzheimer's Disease Center, Rush University Medical Center
	James Galvin, M.D., M.P.H. (also LBD)	Professor, Department of Neurology, New York University
	Virginia J. Howard, Ph.D.	Professor, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham
	Lori L. Jervis, Ph.D.	Associate Professor, Department of Anthropology, Center for Applied Social Research, University of Oklahoma
	Thomas Mosley, Ph.D.	Professor of Geriatrics/Gerontology, University of Mississippi Medical Center
	Sid O'Bryant, Ph.D.	Associate Professor, Internal Medicine, University of North Texas Health Science Center
	Chiadi Onyike, M.D., M.H.S.	Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine
	Ralph Lewis Sacco, M.D.	Professor and Chairman, Department of Neurology, University of Miami Miller School of Medicine
	Lon White, M.D., M.P.H.	Senior Neuroepidemiologist, Pacific Health Research and Education Institute
	Keith Whitfield, Ph.D.	Vice Provost and Professor, Duke University

3. Lewy body dementias (LBD)	Dennis Dickson, M.D. (co-chair)	Professor, Department of Neuroscience, Mayo Clinic
	Karen Marder, M.D., M.P.H. (co-chair)	Professor of Neurology, Taub Institute, Columbia University Medical Center
	Dag Aarsland, M.D., Ph.D.	Stavanger University Hospital
	Bradley Boeve, M.D. (also MED, FTD)	Professor of Neurology, Department of Neurology, Mayo Clinic
	David Eidelberg, M.D.	Director, Center for Neurosciences, Feinstein Institute for Medical Research
	James Galvin, M.D., M.P.H. (also HD)	Professor, Department of Neurology, New York University
	John Hardy, Ph.D. (FTD)	Departmental Chair, Department of Molecular Neuroscience, Reta Lila Weston Research Laboratories, University College London Institute of Neurology
	Carol Lippa, M.D.	Professor , Department of Neurology, Drexel University College of Medicine
	Eliezer Masliah, M.D.	Professor, Neurosciences and Pathology, University of California, San Diego
	Ian McKeith, FMedSci, M.D., FRCPsych	Professor of Old Age Psychiatry, Institute for Ageing and Health, Newcastle University
	Pamela McLean, Ph.D.	Associate Professor , Department of Neuroscience, Mayo Clinic
	Bernard Ravina, M.D., MSCE	Medical Director, Clinical Development, Neurodegeneration and Experimental Medicine, Biogen Idec
	Clemens Scherzer, M.D.	Associate Professor of Neurology, Harvard Medical School/Brigham & Women's Hospital
	Ellen Sidransky, M.D.	Chief of the Section of Molecular Genetics, National Human Genome Research Institute, National Institutes of Health
	David Simon, M.D., Ph.D.	Associate Professor of Neurology, Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School
4. Frontotemporal dementia and other tauopathies (FTD)	Michael Hutton, Ph.D. (co-chair)	Chief Scientific Officer for Neurodegenerative Disease, Eli Lilly and Company
	William Seeley, M.D. (co-chair)	Associate Professor, Department of Neurology, University of California, San Francisco
	Karen Ashe, M.D., Ph.D.	Professor, Department of Neurology, University of Minnesota
	Bradley Boeve, M.D. (MED, LBD; pre-workshop discussions only)	Professor of Neurology, Department of Neurology, Mayo Clinic
	Adam Boxer, M.D., Ph.D.	Associate Professor, Memory and Aging Center, Sandler Neurosciences Center, University of California, San Francisco
	Nigel Cairns, Ph.D., FRCPath	Professor of Neurology, Department of Neurology, Washington University School of Medicine
	Thomas Cooper, M.D.	Professor, Department of Pathology and Immunology, Baylor College of Medicine
	Marc Diamond, M.D.	Professor, Department of Neurology, Washington University School of Medicine
	Karen Duff, Ph.D.	Professor, Taub Institute, Columbia University

	Howard Feldman, M.D., FRCP (C)	Professor, University of British Columbia
	Alison Goate, D.Phil.	Professor, Department of Psychiatry, Washington University School of Medicine
	John Hardy, Ph.D. (also LBD)	Departmental Chair, Department of Molecular Neuroscience, Reta Lila Weston Research Laboratories, University College London Institute of Neurology
	David Knopman, M.D. (also, MED)	Professor, Department of Neurology, Mayo Clinic
	Leonard Petrucelli, Ph.D.	Chair and Professor, Department of Neuroscience, Mayo Clinic
	Erik Roberson, M.D., Ph.D.	Associate Professor, Departments of Neurology and Neurobiology, University of Alabama at Birmingham
	Stephen Strittmatter, M.D., Ph.D.	Professor, Cellular Neuroscience, Neurodegeneration and Repair Program, Yale University
	Bryan Traynor, M.D., Ph.D.	Investigator, National Institute on Aging, National Institutes of Health
	John Van Swieten, M.D., Ph.D.	Erasmus Medical Center
5. Vascular contributions to ADRD - focus on small vessel disease and AD/vascular interactions (VAS)	Steven Greenberg, M.D., Ph.D. (co-chair)	Director, Hemorrhagic Stroke Research Program; Neurology, Massachusetts General Hospital / Harvard Medical School
	Berislav Zlokovic, M.D., Ph.D. (co-chair)	Director, Zilkha Neurogenetic Institute, University of Southern California
	Geert Jan Biessels, M.D., Ph.D.	Professor of Neurology, Department of Neurology, University Medical Center Utrecht
	Monique Breteler, M.D.	Director of Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Professor of Population Health Sciences, University of Bonn, Professor of Epidemiology (Adjunct), Harvard University School of Public Health
	Helena C. Chui, M.D.	Professor, Department of Neurology, University of Southern California
	Suzanne Craft, Ph.D.	Professor, Gerontology and Geriatric Medicine, Wake Forest University School of Medicine, Roena B. Kulynych Geriatric Research Center
	Costantino Iadecola, M.D.	Professor of Neurology and Neuroscience, Brain and Mind Research Institute, Weill Cornell Medical College
	Eng H. Lo, Ph.D. (pre-workshop discussions only)	Professor of Neurology and Radiology, Massachusetts General Hospital
	Julie A. Schneider, M.D., M.S.	Associate Professor, Pathology/Neurology, Rush University Medical Center
	Sidney Strickland, Ph.D.	Professor, The Rockefeller University
	Michael Tymianski, M.D., Ph.D.	Professor of Neurosurgery, Toronto Western Hospital
	Cheryl Wellington, Ph.D.	Professor, Department of Pathology and Laboratory Medicine, University of British Columbia
	Donna Wilcock, Ph.D.	Assistant Professor, Sanders-Brown Center on Aging, University of Kentucky

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DATE: September 23, 2013

TO: NAPA Council

FROM: Director, NINDS

SUBJECT: Alzheimer's Disease-Related Dementias (ADRD) Conference Recommendations to the NINDS Council

The Chair of the recent Alzheimer's Disease-Related Dementias (ADRD) Conference presented the recommendations of that meeting to the NINDS Council, which is a FACA committee. The NINDS Council discussed and approved the ADRD Conference 2013 Report on September 12, 2013. The recommendations emerged from a year-long iterative process involving more than 80 national and international expert scientists, including a steering committee with 2 NINDS Council members (David Holtzman, Sharon Hesterlee), the Chair of the NAPA Council (Ron Petersen), and representation from the NIA (Neil Buckholtz). Additional input from scientists as well as the public, including patients and their advocate, was provided at the Conference.

NINDS Council members recognized that the ADRD 2013 Report represents a consensus document and that setting priorities is very difficult, given the lack of understanding of the underlying mechanisms responsible for these diseases and the lack of treatments. Nonetheless, during discussion that resulted in approval, several NINDS Council members considered the Lewy body dementia (LBD) and frontotemporal dementia (FTD) sections of the Report, and provided comments that are summarized as follows:

a) Biomarker and mechanistic discoveries for synucleinopathy, tauopathy, TDP-43opathy, etc., are critically important for FTD and LBD, as they are for vascular contributions to dementia, since advances in these areas are necessary to inform the design of cohort studies and clinical trials.

b) For FTD, efforts designed to increase understanding of the mechanisms underlying TDP-43opathy, FUS and C9orf72-related neurodegeneration are as important as efforts to increase understanding of mechanisms underlying tauopathy.

Story Landis

Story C. Landis, Ph.D.