



Draft Prioritized Recommendations

Session 1:

Multiple Etiology Dementias: Diagnosing Dementia in the 21st Century

➤ Focus Area 1: Improved Diagnostic Skills in the Community

Recommendation #1. Detect cognitive impairment when patient or relative voices a concern to health care providers (5-7 y; 2017).

- Develop new educational efforts and practical trials on improved diagnosis that lead to face-valid useful outcomes.
- Develop new approaches (e.g. using computers in the office or ancillary personnel) for using existing *neuropsychological* resources or for using cognitive and functional assessments in primary care setting (meaning that they are reimbursable, time efficient and easy to interpret).
- Develop a more compelling evidence base for value of currently available interventions: Present Centers for Medicare and Medicaid (CMS) with evidence-based examples (either from existing publications or new research) of targetable/reimbursable physician actions that improve quality of life (QOL) for persons with dementia and their families.

Recommendation #2. Develop differential diagnosis of symptomatic cognitive impairment (5-7 y; 2017).

- Improve clinical diagnostic instruments for major dementia/cognitive disorder systems & approaches and practical trials to assess.
- Improve diagnostic skills in neurologists, geriatricians, neuropsychologists and geriatric psychiatrists with measurable outcomes, e.g., treating a DLB sleep disorder or a normal pressure hydrocephalus (NPH). Behavioral interventions to improve quality of life are also essential and dependent on accurate diagnosis of key cognitive and behavioral deficits.
- Develop of community-based programs in antemortem clinical and biomarker diagnosis linked to state of the art neuropathology using currently existing biomarkers.
- Develop tools, including educational and diagnostic, for recognizing cognitively impaired persons with multi-etiology disorders in diverse medical settings.
- Develop new imaging and fluid biomarkers for persons with *symptomatic* disease – both AD and non-AD dementias - that are integrated into clinical diagnosis.

Recommendation #3. Develop diagnostics/biomarkers in asymptomatic individuals (3-5 y for improved biomarkers for non-AD dementias; 2017).

- Develop improved imaging and fluid biomarkers for AD, cerebrovascular, non-AD degenerative dementias.
- Conduct validation studies in *asymptomatic* populations, especially in minority groups and in middle age using population-based studies.
- Validate diagnostic and prognostic value of biomarkers used in asymptomatic persons.

➤ **Focus Area 2: Basic and Clinical Research in Interactions between Dementia Pathophysiologies**

Recommendation #4. Promote basic and clinical research in multi-etiology dementia (5-7 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 and Alzheimer-type mechanisms.
- Define interactions at the molecular and cellular levels between α -synucleinopathy and Alzheimer-type mechanisms.
- Define interactions at the molecular and cellular levels between TDP43 proteinopathy and Alzheimer-type mechanisms.
- Describe quantitatively the clinical synergies between different etiologies.
- Develop approaches to grading clinical relevance of one etiology in the presence of >1 etiologic entity.

➤ **Focus Area 3: Determining the Role for Screening for Cognitive Dysfunction**

Recommendation #5. Screen for clinically relevant cognitive impairment in the absence of a cognitive complaint (indefinite; 2017).

- Conduct observational studies that measure the benefit, if any, 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 to determine if measurable, meaningful outcomes can be identified.
- Develop culturally sensitive instruments for large scale screening with sufficient specificity to minimize impact on a participant, family member, or the health care system of false positives.
- Design screening trials for cognitive impairment in at risk (i.e., older adults [>70 years], multiple comorbidities, functional deficits, etc.), rather than general population. If successful, such trials are more likely to reveal meaningful results, and will be cost effective and easy to implement.
- Evaluate the capacity of the health care system to deal with large number of patients with cognitive disorders, should cognitive screening succeed in identifying patients 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* (a sort of “Brain Health Check”). With the use of advanced technology, neuropsychologists could reach underserved areas for comprehensive, but brief assessments. Such technology-enabled assessments should be tested for their ability to effect meaningful changes in care.

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

Recommendation #6. Address the inconsistent nomenclature in dementia research and care (3 y; 2017).

- Develop a universal lexicon for characterizing acquired cognitive impairment that spans the needs of therapeutic development (regulatory requirements), clinical researchers, practitioners, patients and caregivers including those from disparity populations, and advocacy groups (representing the “brands” of Alzheimer’s, Frontotemporal Degeneration and Lewy Body Dementia).
- Recommend that a task force that includes representation of all of the above groups be convened to develop a coherent nomenclature for all dementias, such that different stakeholders can utilize shared, unambiguous terms.

Session 2:

Non-Governmental Organizations

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

Recommendation #1. Establish more effective communication between NIH and the NGOs on activities and progress toward the ADRD goals in the off-years between the triennial ADRD Research Summits (ongoing activity; 2016).

- All milestones, implementation plans and success criteria in support of the ADRD goals will be posted publicly on the NAPA site.
- NINDS to have official representation at the NAPA quarterly Council meetings.
- NINDS to present annually to NAPA Council on progress toward the ADRD goals/milestones.
- Hold an annual satellite meeting to the NAPA Council meeting during which NINDS, NIA and NGOs will share activities, funding and progress relevant to the ADRD goals/milestones (consider a ~2 hour meeting, held 6 months opposite the NINDS report).

➤ Focus Area 2: Nomenclature Standards when Discussing Dementia

Recommendation #2. Organize a working group of dementia stakeholders, including founding partnerships with disparities communities, to review the current nomenclature used in public awareness, clinical care and research and to propose strategies to help advance early differential diagnosis and the understanding of dementia and its underlying causes (ongoing activity; 2017).

- Patient/Caregivers/Public considerations include:
 - Differing nomenclature needs by demographic group, i.e., patients; caregivers; health disparities; gender; sex; age; geographic; socioeconomic; education
 - Strategies to reduce stigma
 - Nomenclature for use by all stakeholder groups’ to help:
 - Engage and partner with disparities populations
 - Raise public awareness
 - Drive symptom reporting
 - Increase research participation

- Heighten political support to reduce the impact of dementia on society
- Clinical Care considerations include:
 - Best practices for educating patients and caregivers about the difference between dementia, a particular clinical syndrome and possible underlying etiologies
 - Standardized terms to document cognitive status regardless of etiology (e.g. normal vs. MCI vs. dementia; minor vs. major neurocognitive disorder) to facilitate better communication across care settings
 - 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:
 - Nomenclature standards to differentiate between underlying disease etiology vs. clinical syndromes
 - Standards for defining prodromal, preclinical and clinical syndromes
 - Review regulatory pathway to identify and address barriers related to nomenclature
 - Solutions to nomenclature barriers or challenges in global research, e.g., international diagnostic criteria
- Present strategic recommendations for public comment, including milestones (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, NAPA Council and HHS for inclusion in the NAPA plan.

Session 3:

Health Disparities

➤ Focus Area 1: Treatment and Prevention Strategies

Recommendation #1. Assess epidemiology and mechanistic pathways of disparities in health burden of ADRDs (1-6 y; 2016).

- The prevalence and risk factors of many ADRDs among disparate populations is unknown and must be established to prioritize public health interventions and campaigns.
- Measure changes in risk factors (both traditional and novel) over the lifecourse and across generations to link assessments of adult cognitive status and ADRD outcomes among disparate populations.
- Test the intersection of social, environmental and biological mechanisms of ADRDs to determine if mechanisms differ across populations (e.g., vascular and metabolic processes may play a larger role in disparities populations because of the greater prevalence of these risk factors).
- Strengthen research methods for ADRDs to allow translation of observational evidence to intervention design 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 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 biomarker research must account for social conditions.

- Initiate and leverage ongoing longitudinal community-based cohort studies of incident dementia in diverse populations and incorporate a wide range of risk factors and incorporate cutting-edge imaging and fluid biomarkers (e.g. blood and cerebrospinal fluid) and autopsy.
- Use social, environmental, genetic, and biomarker evidence to identify potential policies, systems, and interventions that could reduce the burden of ADRDs among disparate populations.

Recommendation #2. Enhance the design of trials of vascular health interventions to improve their application to aging diverse populations (2-7 y; 2017).

- Evidence exists that vascular health is critical to delaying onset of dementia, potentially not only vascular contributions to cognitive impairment and dementia (VCID), including vascular dementia and VCI, but also LBD and AD, and may be differential across diverse populations.
- 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 sensitive to ensure their application to diverse aging populations.
- Adopt standardized assessments to facilitate meta-analyses and enhance the value of the evidence across these trials.

➤ **Focus Area 2: Monitoring Changes in ADRD Disparities**

Recommendation #3. Develop a system to monitor the magnitude and trends in disparities in incidence of ADRDs (2-8; 2017).

- There is no current data infrastructure that would enable us to evaluate progress towards eliminating health disparities in ADRDs.
- Mechanisms to monitor and confirm 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.
- Data standardization protocols must be developed and validated.
- Small substudies can be used to validate the measurement quality from diverse sources and ensure measures are harmonized for common ADRDs.
- Infrastructure must tie to passive data sources (with very large population bases) to monitor disparities in rare ADRDs.
- A data monitoring system must be put in place to provide stability to collect, clean, and merge the data.

➤ **Focus Area 3: Assessment**

Recommendation #4. Improve tools for assessment of disparities in risks, preclinical disease characteristics, and costs of ADRD among 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 ADRD among disparities populations. (1-4 y; 2016).

- Conduct quantitative and qualitative validity studies of existing and newly generated instruments among diverse patients.
- 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 ADRDs along with 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 ADRD.
- Develop simple, sensitive methods for screening for cognitive impairment and dementia in primary care settings.
- Adopt culturally appropriate, standardized assessments to facilitate meta-analyses and enhance the value of the evidence across research studies and trials that include diverse participants.
- Develop practical guidelines for use of existing assessment and 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 ADRDs and vascular health intervention trials (1-2 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 lifecourse that could contribute to 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 (1-2 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 ADRD dementia syndromes in 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 disparities populations (1-2 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 ADRDs 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 programming 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

- **Focus Area 1: Establish Longitudinal Cohorts with Common Measures, Culminating in Autopsy Studies**

Recommendation #1. Initiate clinical trials for motor and non-motor manifestations of LBD using existing and newly developed symptomatic therapies that address symptoms that have the greatest impact on patient function and caregiver burden (1-3 y; 2016).

- While there have been many therapeutic trials focused on PD, patients with Lewy body dementia (DLB and Parkinson's disease dementia [PDD]) have been excluded. Consequently, there is little information about the efficacy of approved drugs, (e.g., dopamine replacement) and experimental drugs on 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., of clinical, imaging, and outcome measures) be carried out to the greatest extent possible.

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 (5-10 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., of 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 with DLB or PDD 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 database that links clinical, biological, and autopsy data. (3-5 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 (5-7 y; 2016).

- This goal will require genome-wide association studies of large cohorts, as well as whole exome/genome sequencing of families with multiple affected members, on whom

systematic, standardized environmental exposure information is collected. This recommendation also includes identification of genetic and epigenetic factors influencing the risk of developing dementia or LBD in patients with PD or other degenerative diseases. Genetic studies should enable the stratification of patients by phenotype, diagnosis, prognosis, and response to treatment. Studies should be developed that investigate gene-environment interactions.

- 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 (3-5 y; 2016).

- Evaluate the 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. 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 additionally facilitate the development of synergistic multimodal biomarker strategies (e.g. molecular imaging with radiotracers for α -synuclein, amyloid β 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 DLB and PDD, 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 (5-7 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 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, microbiome, others) and biofluids (e.g. blood, CSF, urine, others).

➤ **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 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

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

Recommendation #1. Clarify the mechanism of tau pathogenesis and associated neurodegeneration (2-5 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 (post-translational tau modifications, microtubule dysfunction, interneuronal spread, or other tau [dys]functions) represent the most human-relevant, deleterious, and targetable processes? How and why does the process of tau aggregation begin? A focused effort to fully understand the mechanism of interneuronal spreading of aggregated tau is a priority.

- Innovative cell-based, animal model, and human post-mortem studies are the recommended approaches to determine pathogenic events that promote tau toxicity and pathology spreading. Genetic models should be complemented with other methods that mimic aspects of sporadic disease (inoculation studies, iPSCs, etc.).

Recommendation #2. Determine the molecular basis for C9ORF72 expansion- and GRN mutation-related neurodegeneration (3-10 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 FTD: 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 pathologic features correlate best with neurodegeneration. For example, more comprehensive studies are needed to understand the relationship between RAN-translated dipeptide repeat protein accumulation, TDP-43 aggregation, RNA foci and neurodegeneration in *C9ORF72* carriers. The field should compare human findings with those derived from animal and cell-based models. Mechanistic hypotheses should be tested in appropriate models to drive therapeutic development. An important goal is also to understand the normal function of progranulin, especially during the response to brain injury. This effort should include determining the role of GRN and the modifying factor TMEM106B in lysosomal function. The link between GRN haploinsufficiency and the initiation of TDP-43 pathology also needs to be identified via this approach. Finally the field should continue to identify therapeutic approaches designed to replace/increase GRN function.

Recommendation #3. Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity (3-10 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 upstream events that precede TDP-43/FUS aggregation?
- Our recommended approach is to expand the scope and precision of human neuropathologic studies, focusing on early-stage disease, define the sequence of molecular changes associated with TDP-43/FUS pathogenesis from loss of nuclear localization to the formation of assemblies, and continue to study and define the normal cellular functions of TDP-43 and FUS. Expand 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 or 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 FTD 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 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 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 molecular dissection of pathogenesis.

➤ **Focus Area 2 – Clinical Science**

Recommendation #1. Expand efforts to genotype patients with FTD and identify new genes (1-3 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. Continue to build core services for FTD genotyping and banking DNA where any researcher can send samples, receive genotype information, or request data/samples from large cohorts. Pursue a focused effort to find additional genetic causes and risk factors for FTD through deep sequencing approaches, initially in small families and expanding into large cohorts of unrelated FTD patients to confirm pathogenicity. Improve bioinformatics infrastructure for capturing phenotype and genotype information and enabling data sharing. Include families with combined FTD and 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 FTLT-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 FTD 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 clinico-pathological syndrome and what factors influence onset age and pace of progression. Understanding these factors may enhance trial design by accounting for variations in anatomical and temporal progression across cohorts and will aid interpretation of trial outcomes. For sporadic FTD, innovative approaches are needed to clarify the 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 with MND and TDP-43 Type B). We recommend seeking genetic, anatomical, and environmental disease modifiers that influence clinico-pathological heterogeneity across inherited and sporadic cohorts. 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 (1-7 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 neurovascular unit (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 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.
- Explicitly incorporate aging into animal models, e.g. explore interaction between age and other risk factors introduced by animal model (hypertension, diabetes, 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 neurovascular unit, 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 A β -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 A β -mediated effects on cerebrovascular function, including all cells involved in the neurovascular unit. 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 A β -mediated effects on hemostasis, including blood clotting and fibrinolysis.
- Investigate the contributions of additional risk factors for AD, including diabetes, 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 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 A β - and tau-related disease processes, both separately and together.
- Develop tools for cell- (endothelial, smooth muscle, pericyte, etc.) and region- (gray vs. white matter, cortex vs. striatum, etc.) specific characterization of the effects of altered cerebrovascular and neurovascular unit (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 neurovascular unit 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 possible explanation for emerging trend of lower age-specific incidence of dementia 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, blood brain barrier 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, A β , 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 A β , 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, 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.