Draft Prioritized Research Recommendations

Session 1:

Multiple Etiology Dementias - Diagnosing Dementia in the 21st Century

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

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

- For all MED recommendations, cognitive impairment refers to memory loss and other forms of cognitive decline including dementia. Cognitive impairment may also be accompanied by behavioral symptoms that occur as a precursor to and with cognitive decline.
- Conduct practical trials to improve the diagnosis of cognitive impairment including dementia that lead to useful outcomes for patients and families. Approaches should focus on the detection and characterization of cognitive impairment syndromes but not, for the purposes of this specific recommendation, differential (etiological) diagnosis. Approaches should be reimbursable, time efficient, and with easy to interpret results and may use existing or new neuropsychological and functional assessment tools.
- Evaluate the impact of interventions to improve diagnosis in different settings where better detection is likely to have benefits for patients, where there is a high frequency of undetected cognitive disorders, and where there is capacity for the practice change. Potential settings include primary care, pre-surgery, and clinics who serve persons with other medical conditions who are at high risk for cognitive decline (e.g., Parkinson's disease, certain metabolic disorders such as diabetes, HIV, cerebrovascular and cardiovascular disease).
- Develop and evaluate interventions that incentivize dementia diagnosis and best practices in everyday clinical settings, for example by enhancing and integrating EHR support related to clinical and administrative workflows that address evaluation, disclosure, psychoeducation, care planning community resources, documentation and billing; that increase the value that primary care providers place on timely dementia detection and management; and that improve basic diagnostic and management skills regarding later-life cognitive disorders.
- Design and assess detection of cognitive impairment based on an evaluation that begins with a self-administered assessment prior to the health care provider appointment. Determine the validity, feasibility, risks and benefits of self-administered cognitive, behavioral and functional assessments, which may include technology-related (e.g., online) assessments, as part of clinical workflows to increase the detection of cognitive

impairment, including dementia. Assessments may be designed for administration at-home, in-clinic, in hospital, or in community settings (e.g., public health screenings – blood pressure, flu vaccine clinics), but should require minimal or no staff time to complete.

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

- Improve clinical diagnostic instruments and educational approaches that increase provider confidence around the recognition and management of common and less complicated presentations of cognitive impairment in everyday clinical and community settings, and for knowing when a referral is needed (i.e., in less common or more complicated presentations).
- Improve diagnostic skills in neurologists, geriatricians, neuropsychologists and geriatric psychiatrists with measurable outcomes, e.g., recognizing and treating an LBD-associated sleep disorder, avoiding contraindicated medications in LBD, treating normal-pressure hydrocephalus, reducing risk of future cerebrovascular events or progression of white matter injury, referring to behavioral interventions and support services with demonstrated efficacy to improve quality of life in people with cognitive disorders.
- Develop community-based clinical evaluation programs for antemortem clinical diagnosis coupled with biomarkers and perform similar clinical and biomarker diagnostic activities in referral centers to remedy referral bias in interpretation of biomarker-assisted diagnoses. A long-term goal is to link clinical activities to subsequent state-of-the-art neuropathological examinations to validate diagnoses.
- Develop new biomarkers (e.gl, imaging and fluid) for people with symptomatic disease - both AD and non-AD dementias and AD/ADRD mimics, including prion disorders - that are integrated into clinical diagnosis.
- Determine the economic impact of earlier diagnosis and care on healthcare systems and patients.

➢ Focus Area 2: Advancing Basic and Clinical Research in MED

Recommendation #3 – Priority 1. Advance basic and clinical research in multi-etiology cognitive impairment (3-7 y).

- Develop improved nomenclature that adequately represents multi-etiology processes and develop terminology to represent these processes across multiple stakeholders, including research and clinical practice.
- Define interactions at the molecular and cellular level of the common pathobiologies of later life cognition including β-amyloidosis, 3R/4R tauopathy 4R tauopathy, TDP43, arteriolosclerosis and other cerebrovascular processes, α-synucleinopathy.
- Develop improved fluid and imaging biomarkers of the common pathobiologies of later life cognition - β-amyloidosis, 3R/4R tauopathy 4R tauopathy, TDP43, arteriolosclerosis and other cerebrovascular processes, α-synucleinopathy - especially those that can be used in tandem with one another in order to obtain a full antemortem etiological profile of persons with cognitive impairment in the context of genetic and behavioral factor risk.

- Promote observations studies in diverse populations that use all available methods to characterize the status of the common pathobiologies of later life cognitive impairment, in both cognitively unimpaired and cognitively impaired individuals, in order to define novel risk factors for each as well as to establish prevalence estimates of each pathobiology as well as their combinations.

➢ Focus Area 3: Increasing the Dementia Capable Workforce

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

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

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

Recommendation #5 – Priority 2. Conduct intervention studies to mitigate reversible causes of cognitive dysfunction in persons with or at-risk for cognitive impairment where etiology may be uncertain or where multiple etiologies appear likely (3-7 y).

- Conduct clinical trials in hospital and community-based settings where risk factors for cognitive decline can be appropriately targeted for intervention. Interventions may include, but are not limited to, exercise, cardiovascular risk reduction, obstructive sleep apnea, use of anti-cholinergic medications, treatment of hearing loss, prevention of delirium, and treatment of mood disorders.
- Studies should include participants at high risk for cognitive decline, from health disparities populations, and Medicare beneficiaries. Studies should elucidate the types of patients most likely to decline and also to benefit from the interventions.

➢ Focus Area 5: Research to Implement Effective Dementia Care

Recommendation #6 – Priority 3. Bridge the science-practice gap for dementia care programs with proven efficacy that support persons with dementia and their caregivers (3-7 y).

- Identify barriers and facilitators to widespread diffusion and sustainability of interventions with demonstrated benefit for persons with dementia, caregivers, and payers. Test methods to address barriers and leverage facilitators.

- Conduct implementation studies that draw upon science-based models of widespread diffusion or successful examples of health practice change. Sustainability in current payment structures must be tested. Trial designs should be dynamic and guided by input from families, clinicians, health system administrators, and payers. Studies must explicitly address the unique needs of health disparities populations and gender differences.

Session 2:

Health Disparities in AD/ADRD

- **Focus Area 1: Assessment**

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

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

Recommendation 2 – Priority 1. Increase availability and utilization of harmonized culturally- and linguistically-valid assessment tools within ongoing and newly generated studies of AD/ADRD and cognitive health intervention trials (1-3 y).

- Engage and recruit individuals from diverse communities into aging research, regardless of cultural and linguistic factors (e.g., language proficiency).
- Conduct treatment variability analyses across demographic variables.
- Develop criteria by which proposed interventions can be measured to determine whether they are culturally sensitive to ensure their application to diverse populations.

- Generate a repository of assessment tools (i.e., symptom questionnaires, neuropsychological instruments and normative references, and informant-based surveys) validated for use among diverse populations.

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

Recommendation 3 – Priority 2. Test mechanistic pathways that may account for AD/ADRD disparities (3-7 y).

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

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

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

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

Recommendation 5 – Priority 3. Clarify the epidemiology of disparities in AD/ADRD prevalence and incidence by documenting and monitoring trends in disparities in AD/ADRD prevalence and incidence over time (ongoing activity).

- Documenting and monitoring trends in disparities in AD/ADRD prevalence and incidence is an essential step towards achieving health equity in AD/ADRD and is critical for prioritizing public health needs, prevention efforts, and treatment strategies. While some

disparities in AD/ADRD prevalence and incidence have been well documented, the current picture is incomplete or non-existent for many under-represented minority groups and some dementia syndromes.

- Recent studies suggest that dementia incidence rates may be declining, but most of this evidence is based on non-Latino whites, and it is largely unknown whether these trends extend to under-represented minority populations. Monitoring changes in AD/ADRD disparities will provide evidence on the extent to which there has been progress towards reducing AD/ADRD disparities and provide insight into mechanisms.
- Disparities in AD/ADRD should be documented and monitored across a range of social determinants of health, including race/ethnicity, nativity, primary language, income and wealth, educational background, gender identity and sexual orientation, and geographic location.
- Epidemiology and clinical course of many AD/ADRD subtypes (e.g., Lewy Body, frontotemporal dementia, early-onset AD) are largely unknown in disparities populations, in part due to economic barriers and discrimination that reduces access to healthcare, increases misinterpretation of early signs of dementia, and increases stigma within disparities communities. As a result, innovative approaches to diagnosing, documenting, and monitoring AD/ADRD subtypes are needed to understand the magnitude of disparities.
- Valid estimates of AD/ADRD disparities should be obtained from samples that are representative of the U.S. population. Estimates of AD/ADRD disparities from non-representative samples could inaccurately represent disparities in the population of interest (i.e., the U.S. population as a whole or the population in specific geographic locations).

Recommendation 6 – Priority 3. Increase policy-relevant research on disparities in access to care, awareness and stigma, and costs of care for persons living with AD/ADRD and their families and caregivers (ongoing activity).

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

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

Recommendation 7 – Priority 4. Improve and increase training, including for individuals who are members of underrepresented minorities, of scholars of different career levels who conduct health disparities research in AD/ADRD (3-5 y).

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

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

Session 3:

Lewy Body Dementias

- **Focus Area 1: Clinical Science**

Recommendation 1 – Priority 1. Initiate clinical trials to target or prevent LBD symptoms, and prepare for trials which target slowing the course and/or delaying or preventing the onset of disease (1-7 y).

- Initiate clinical trials for motor and non-motor manifestations of a) Lewy body dementia (LBD), which includes both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), b) the LBD pre-dementia disorders including mild cognitive impairment (MCI) of Parkinson's disease (PD) and DLB as well as late-onset psychosis (visual hallucinations and delusions), and c) the LBD prodromal disorders including REM sleep behavior disorder (RBD), anosmia, autonomic dysfunction, etc., and d) those with genetic risk (e.g., LRRK2, SNCA or GBA) in diverse populations using existing and newly developed therapies that address clinically-significant symptoms that have the greatest impact on patient function and caregiver burden. This recommendation also addresses the differentiation of LBD from other etiologies (such as AD, prion diseases, and other neurologic disorders) in the setting of rapidly progressive dementia.
- To accomplish this, engage existing clinical networks and non-governmental organizations to establish new and expand existing networks of relevant clinical investigators, including movement disorder specialists, behavioral and cognitive neurologists, autonomic neurology specialists, psychiatrists, and sleep disorder specialists, to use well-characterized cohorts of established or at-risk LBD for treatment trials with novel therapeutic compounds as well as current FDA-approved drugs. These clinical networks will also engage with the LBD patient/caregiver communities that they serve to help define the highest-priority symptoms (i.e., those responsible for the greatest caregiver/patient distress and burden) to target for trials. It is important that cross-site standardization (e.g., common clinical, imaging, and outcome measures) occur to the greatest extent possible. These efforts will help identify and resolve pre-analytical factors needed to standardize biomarker measurements for use in multicenter

clinical trials. Since LBD is clinically and pathologically heterogeneous and several pathologic and genetic factors likely contribute, biomarkers should be incorporated into trial design for population enrichment or stratification to improve the ability to study more homogenous LBD cohorts in a clinical trial design, thus improving statistical power and likelihood of success.

- Clinical tools to track cognitive changes via neuropsychological measures or batteries as well as track problematic symptoms (e.g., cognitive fluctuations, autonomic features, etc.) in LBD are urgently needed. Similar or additional tools to track changes in the pre-dementia, prodromal and at-risk LBD cohorts are also needed. These tools include, but are not limited to, "digital approaches" such as wearable devices, and computerized or app-based cognitive testing.
- Such new or existing methods for detecting and tracking LBD features should undergo multi-center validation, and normative data using the methods should also be generated.
- These efforts build upon the knowledge base that is gained from genetic and environmental studies and from systematic profiling of well-characterized human samples that identify underlying disease mechanisms and biomarkers. The long-range goal is to use therapeutic approaches that prevent or alter the disease processes using 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.
- It is critical that pharma be made aware of efforts to characterize patients and measure disease progression. If the perceived risk around entering into this are can be reduced, there is a much better chance that target-based discovery efforts in pharma will emerge. One idea would be to create a working group of neurology researchers from relevant pharma companies.

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

- Create longitudinal clinical, biological, and imaging resources for LBD from the earliest stages through to autopsy a) to improve accuracy of detection and diagnostic criteria of the LBDs, and at the pre-dementia or prodromal stage of LBD, b) to validate (i.e., Phase 3 studies) biomarkers to predict conversion to dementia, and c) to serve as recruitment source for clinical trials.
- To address the problems of delayed and under-diagnosis, existing or new longitudinal cohorts focused on cognition need to enroll adequate numbers of LBD, pre-dementia LBD, and prodromal or at-risk LBD patients. Active multi-center prospective cohorts should be leveraged.
- There is potential to merge datasets to achieve larger numbers, with increased power to detect clinical and biological markers of diagnosis and prognosis. These resources can also benefit trial recruitment, which is challenging and requires concerted efforts.
- Relevant studies would seek to develop methods to predict time to conversion to LBD or to develop measurable cognitive and motor deficits that may appear before conversion and continue afterwards. Such measures will be critical in order to execute economical disease-modifying trials.
- Although some predictive demographic and clinical factors are known for PDD development, few prospective biomarker studies exist. Recent studies have demonstrated the potential of biomarkers to predict shorter time to dementia, in particular markers of co-morbid AD pathology, but more, broader biomarker work is needed. It is important that cross-site standardization (e.g., clinical, imaging) occur to the greatest extent possible across all LBD resources.

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

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

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

- While there have been efforts by investigators and groups of investigators to develop recommended methods to evaluate the neuropathology of LBD (e.g., Consortium for Dementia with Lewy Bodies), no generally accepted standard exists. Efforts should be made to leverage clinically well-characterized, longitudinal cohorts of LBD and at-risk subjects to increase autopsies, enhance tissue diagnostic consensus standards, and increase tissue sharing.
- A research priority should be to develop best practices in neuropathologic evaluation of LBD as well as standardization of neuropathologic methods for evaluation (e.g., minimal sampling schemes and staining methods) and data collection (e.g., quantitative and semiquantitative data). A starting point might be NIA-AA guidelines for Alzheimer disease neuropathologic change, which includes an LBD module, but it lacks in details and particulars.
- Another priority should be to investigate means to increase autopsies on LBD subjects enrolled in prospective longitudinal studies that utilize standardized evaluations and collection of antemortem biomarkers (biofluid, neuroimaging, others). In addition to symptomatic LBD, autopsies should be sought of patients with mild cognitive impairment and other features of LBD, such as REM sleep behavior disorder (RBD), psychosis (visual hallucinations and delusions) and Parkinsonism. Research is needed on best practices for patient outreach and patient education to emphasize the importance of

brain donation, as well as means to provide logistical support and resources necessary to facilitate brain donations.

- In order to make the greatest research use of autopsy specimens from patients with LBD, a research priority should be on developing a clearinghouse that links scientists to tissue resources. This resource would ideally be an on-line and searchable database that links patient samples with particular clinical and neuropathologic characteristics and an inventory of where samples of this type can be found. Ideally, this clearinghouse would be linked to "-omics" or antemortem biomarker data (including neuroimaging data) that might be linked to the pathological specimens. This research priority will necessitate navigating the issue of blinding of protected health information (PHI). Samples accessible to the general research community will have global unique identifier (GUID), which permits sharing of data specific to a study participant without exposing PHI, as well as providing a tool to match participants across research data repositories.

➢ Focus Area 2: Basic Science

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

- Use new or existing cross-sectional and longitudinal case-control studies of individuals with LBD, longitudinal cohort studies tracking cognitive decline, or studies capturing incident cases of LBD, to develop biomarkers for LBD-related pathologic changes, diagnosis, differential diagnosis, disease progression, and the relative burden of Alzheimer's and other pathologies. As new markers of molecular disease mechanisms are discovered, they should be incorporated into biomarker studies for diagnosis of latent or prodromal disease and for monitoring molecular processes and their response to therapies.
- This recommendation proposes to capitalize on existing longitudinal case-control cohorts to encourage standardization of protocols and common data elements. Analyses of biomarkers in relation to genetic and environmental risk factors, clinical indices, imaging and neuropathology are important components of validation and interpretation of biomarkers.
- Biomarkers should be measured in a diversity of tissues (including, but not limited to, brain, skin, colon, salivary gland biopsies, PBMCs, others) and biofluids (e.g., whole blood, plasma, CSF, urine, microbiome samples, and others).
- Assay and method standardization should be encouraged through sharing and replication of methods and through availability of biosamples.
- Consideration should be given to developing comparable biomarkers in model systems (e.g., transgenic animals; iPSc-derived models, etc.) and in humans.
- This recommendation in conjunction with several others is critical to providing insights on the biological substrates which contribute to the temporal evolution of the major LBD clinical phenotypes (i.e., PD then MCI then dementia compared to MCI then DLB) as well as the variable clinical manifestations within and across individuals (i.e., why some have psychosis early in the course whereas others never experience psychosis).

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

- Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that impact the risk for and clinical features of LBD.
- This goal will require single nucleotide polymorphism (SNP) genome-wide association studies, as well as whole exome sequencing, whole genome sequencing, and

expression studies of large cohorts of LBD on whom systematic, standardized environmental exposure information is also collected, as well as studies of families with multiple affected members. This recommendation also includes identification of genetic and epigenetic factors influencing the risk of developing DLB and of dementia in patients with pre-existing PD. Genetic studies should enable stratification of patients by phenotype, diagnosis, prognosis, and response to treatment.

- Studies should include diverse populations and incorporate measures of environmental factors that may vary across these populations and reflect healthy disparities. Examination of gene-environment interactions is essential.
- Although some success has been achieved with the execution of large-scale association, genome-wide association and whole exome sequencing studies, limitations exist around pursuing these aims further with existing data, most of which relate to genetic, clinical, biological, pathological, environmental, and other large-scale data. This recommendation also includes a need to support modern data-driven approaches, such as machine learning on complex genomic data, to facilitate identification and understanding of abnormal pathways.
- There is a need for a central knowledge platform to allow easy data sharing (e.g., via cloud), to generate and harmonize high-dimensional data sets, to visualize complex data, and to create a framework for comparative analyses between LBD and molecularly closely related neurodegenerative diseases.

Recommendation 7 – Priority 3. Understanding the molecular biology of α-synuclein in the context of non-motor brain areas (2-4 y).

- While the fundamental biology of α-synuclein has been extensively studied in many experimental paradigms, particularly in the context of motor systems, the function of this protein in areas vulnerable to the broader set of LBDs remains underexplored. The effect of small molecules therapies meant to target motor systems on non-motor systems (e.g., cognition) is unknown. This recommendation is therefore aimed at improving our knowledge of the role of α-synuclein non-motor systems. These experiments will aim to inform current clinical development by identifying potential safety concerns.
- Understanding the fundamental biology of α-synuclein in the context of the broadest numbers of neurons that are vulnerable to LBD will be important. Questions to be asked, mainly using animal models, will relate to cellular and regional physiology of neurons when α-synuclein expression is modified. Identifying sequelae of the removal of α-synuclein from the mature brain across multiple regions, in terms of neuronal health and function, will be an important component of this investigation.
- Additional models, which should include human-derived materials such as induced pluripotent stem cells, should integrate genetic discoveries from human population studies that have identified pathways relevant to disease risk and progression with the directed goal of identifying biological pathways and networks that ultimately regulate expression of the SNCA gene and other risk factors for disease. Both Mendelian alleles and non-mendelian pathways, such as genetic risk scores, should be considered in a continuum of genetic risks for LBDs.
- Understanding the regulation of α-synuclein protein levels, as a product of both regulation of expression discussed above and of post-transcriptional regulation within cells, will be important to provide tractable hypotheses relevant to both genetic risk of LBDs. This recommendation should also be considered in the context of the aging brain, which will be discussed further below. This consideration should improve our thinking about which human subjects might benefit from modification of α-synuclein, or other

targets, in LBDs and may inform clinical action around measurement of target engagement.

- It is clear that aging contributes substantially, and critically, to LBD risk. The role of aging should be interrogated further using model systems that allow for modeling this risk factor and also in the analysis of available resources such as high volume 'omics' datasets, including novel methods such as mRNA expression, proteomics, metabolomics, etc. Such studies can expand on knowledge gained from AMP-AD and AMP-PD.
- Identification of biological mechanisms that explain both sex differences and resilience in LBD, as identified in human pathological studies, will be of high value. Inclusion of both male and female samples at appropriate number to support well-powered analyses of both sexes is required.

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

- A major recent conceptual framework for how we think about neurodegenerative diseases is the proposal that many diseases can spread between brain regions in a prion-like manner. Whether α-synuclein has the ability to spread in general or only across certain types of cells (resulting in selective vulnerability) is unknown. It is also unclear whether α-synuclein interacts with other proteins (e.g., β-amyloid, TDP-43, tau) to trigger LBD pathology. Research to understand how LBD pathology develops and proliferates is critical for the development of animal models and therapeutics. These studies would move forward new mechanistically tractable targets that could be engaged for clinical studies.
- This recommendation recognizes the need to develop more complete animal and cellular models of the molecular pathology and symptomatology of LBDs. New models are needed that identify key processes involved in neuronal damage and protein deposition. Such models will need to be able to identify the key pathways mediating the propagation of toxic protein assemblies between cells in appropriate, physiologically relevant, context.
- A more complete understanding of why some neurons are vulnerable to toxicity evoked by spreading of α-synuclein assemblies while others remain resistant (i.e., selective vulnerability) is needed. These studies should be used to identify the anatomical underpinnings of brain regional differences in Lewy body pathology associated with variable behavioral outputs in animal models that are relevant to human clinical phenotypes. Where feasible, validation of findings from this type of research should use data from humans, including PDD and DLB.
- Identifying mechanisms by which α-synuclein and β-amyloid pathologies interact in the intact brain is a critical step towards a fuller picture of the complex pathology of LBDs. Development of models in which both pathologies are present either within the same cells or in proximate cell populations should be supported.

Session 4:

Dementia Nomenclature

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

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

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

- **Part B – Form a Clinical Practice Working Group** to consider the Research Working Group recommendations towards terminology for common clinical practice needs and for the multiple stakeholders within the medical practice community.
  - Nomenclature should reflect the underlying disease process and convey the diagnosis, stage and progression of the disease to affected individuals and concerned parties (family, caregivers, payers). Nomenclature must also be able to translate what is talked about in research into terms that patients and caregivers can understand and that translate into recommendations. This is important for the determination of program eligibility and insurance coverage for services.
  - The Clinical Practice Working Group should include clinicians (primary care and specialty) and representation from the other dementia nomenclature working groups to review current terminology used to translate science/research to their patients and caregivers and identify potential areas of improvement for terminology for the benefit of advancing care and practice.
  - Solicit input from cross-cutting stakeholders, such as payors, health systems and electronic health record vendors, on the impact of changing terminology (e.g. coding, reimbursement and quality measurement)
  - Consider the implications of changing terminology on public health science and the education of healthcare professionals, including physicians, nurses, speech, occupational and physical therapists, social work and other care providers, and the public.

- **Part C** – **Form a Public Stakeholder Working Group** to assess the potential to develop nomenclature that is not stigmatizing, while being transparent, scientifically accurate, clinically useful and easy to understand.
  - Current terms (i.e. dementia, demented) can have pejorative/negative connotations, though it is unknown whether the term "dementia" is an insurmountable obstacle or a failure to educate the public about the health implications of dementia and the opportunities for care. Communication to the public about dementia needs to be transparent and accompanied by public education about the complexities of dementia and its various causes, treatment, services and supports.
  - The Public Stakeholders Working Group should include experts in stigma, health disparities and ethics, people living with dementia and their caregivers, advocacy groups and representation from the other dementia nomenclature working groups, as well as cross-cutting stakeholders including and communications professionals to gather expertise and consultation from groups dealing with terminology in and communications with the public
  - Convene diverse groups, including representation from health disparity communities, to develop an understanding of how the public stakeholders (those living with, at risk for, or assisting someone with dementia, as well as people who see themselves as at risk) view the usefulness of and sensitivities to today's terminologies.
  - Define the role current terminology plays in contributing to stigma and preventing or delaying the pursuit of clinical care; based on the findings, develop strategies to educate the public about dementia that reduce stigma and promote early symptom reporting, which may include identifying potential changes in existing terminology.

➢ Focus Area 2: Integration and Interoperability of Dementia Nomenclature

Recommendation 2 – Priority 1. Integrate and refine recommendations from the Research, Clinical Practice, and Public Stakeholder Working Groups into standardized, acceptable and accurate nomenclature that works across the spectrum of stakeholders (2-4 y).

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

Session 5:

Vascular Contributions to Cognitive Impairment and Dementia

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

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

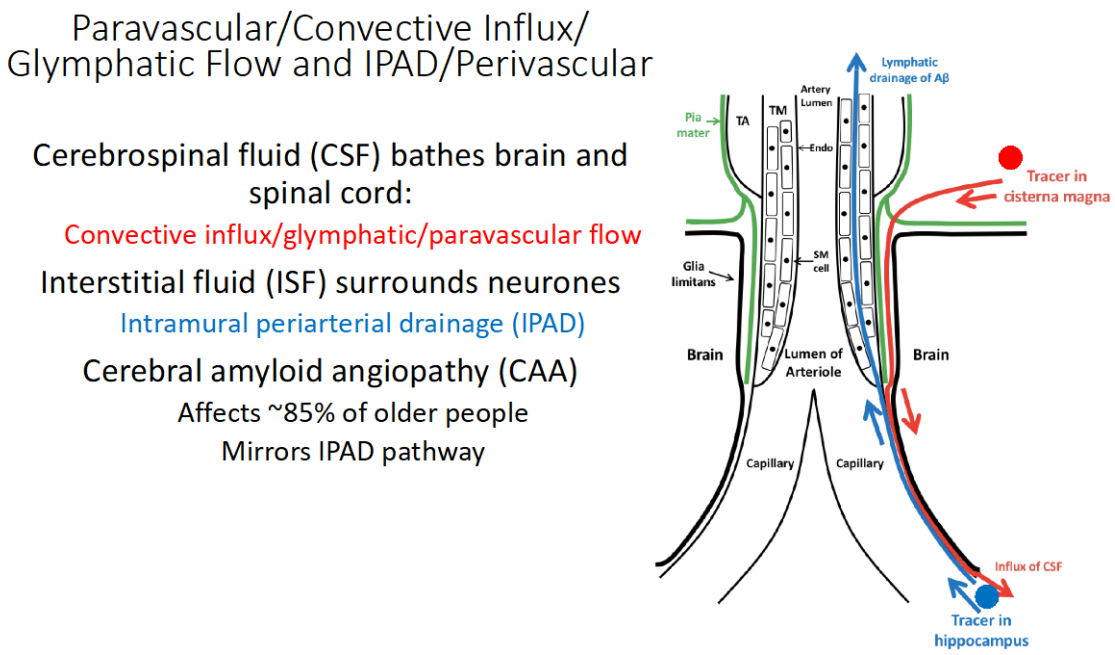
- Establish new animal models that: (i) reproduce small vessel disease and other key pathogenic processes thought to result in cognitive impairment; (ii) are easily applicable to both VCID and AD research for advances in mixed etiology dementias; (iii) address vascular contributions to damage of both white matter and grey matter or (iv) include genetic and acquired conditions that are associated with VCID.
- Because of the pathogenic diversity of VCID syndromes, multiple models, each recapitulating key features of a specific human disease process, are needed.
- In particular, models should be established that reproduce small vessel disease.
- White matter degeneration is a pathologic process that currently lacks suitable animal models for mechanistic studies.
- Studies are encouraged that leverage existing models of systemic cardiovascular disease such as cardiac failure, atrial fibrillation, or renal disease, to examine the brain for pathological signatures of VCID.
- Models should incorporate lifestyle and genetic factors of VCID, including HDAC9, collagen IV, and MFSD2a. Lifestyle factors include diabetes, hypertension, and hyperhomocysteinemia.
- Incorporation of VCID pathologies with AD pathologies in animal models would be particularly informative for interactions of AD and VCID pathological processes.
- New tools will need to be developed to study the models with an eye to identifying key molecular mechanisms of VCID. Suggested tools for development include enhanced in vivo microscopy to allow imaging of deep structures such as subcortical white matter, higher resolution MRI and CT/PET modalities for live animal imaging, and ex vivo technologies that improve translation of cellular models to the in vivo system.

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

- Understand the factors influencing “paravascular” clearance of CSF alongside brain vessels, and “perivascular” clearance of CSF within the vascular basement membrane. Delineate the relative contributions of these pathways to cerebrospinal fluid and interstitial fluid drainage under normal physiologic conditions and during VCID (see figure 1 below).
- Of critical importance is the study of peri- and paravascular clearance pathways and how these pathways contribute to proteostasis, immune cell trafficking, and lymphatics in the brain.
- Continued investigation of how the neurovascular unit contributes to regulation of neurovascular coupling and basal blood flow. In particular, studies are encouraged that dissect vascular function and blood flow control across different microvascular zones (arterioles, capillaries and venules), and how VCID pathology affects each of these zones.

- Recent data indicates blood-brain barrier integrity is affected early in the pathological process of both VCID and pathological AD. Understanding the mechanisms underlying the integrity loss of the neurovascular unit is important.
- In addition to controlling blood supply, cells of the neurovascular unit release molecules with significant contribution to the trophic environment in the brain. Establishing how this function is affected in VCID is recommended.
- Understanding how the normal function of the neurovascular unit is impacted by risk factors of VCID such as aging, cardiovascular and cerebrovascular disease, AD pathology and genetics, will be critical for understanding disease mechanisms.
- Investigate the neurovascular unit as a site of interaction between AD and VCID pathologies.
- Investigate the contribution of risk factors for the clinical syndrome of AD, including diabetes, obesity, lipid metabolism, hypertension, diet, exercise, sleep, head injury, and aging, on the neurovascular unit function.

Figure 1



<u>Recommendation 3 – Priority 4.</u> Encourage basic science research on clinical dementia-related neurodegeneration and myelin biology to determine the impact of cardiovascular / cerebrovascular risk factors and genes (5-7 y).

- White matter changes are characteristic of some VCID processes, yet oligodendrocyte biology in the context of cerebrovascular and cardiovascular disease remains poorly understood. Therefore, studies are encouraged to establish these mechanisms.
- The high co-morbidity of cerebrovascular disease with AD pathology necessitates the study of these two processes together.
- Studies should be encouraged that will examine common cerebrovascular disease risk factors in AD animal models. These studies should cover both beta-amyloid, and tau-related disease processes, both separately and together.

- Develop tools to characterize the effects of altered cerebrovascular function on specific vascular cell types, microvascular zones, and brain regions.
- Apply multiomics and sophisticated bioinformatics to elucidate disease mechanisms.

➢ Focus Area 2: Human-Based Studies

Recommendation 4 – Priority 1. Develop, validate and longitudinally track 1) cognitive, physical, or other functional assessment components that indicate the presence of VCID, and 2) biomarkers of key vascular processes that indicate the presence of VCID, including in the most common scenario where VCID is accompanied by AD (3-5 y).

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

Recommendation 5 – Priority 2. Identify 1) interventions (medication, lifestyle or a combination of these) with proven efficacy for reducing cardiovascular and cerebrovascular risk and 2) care models to test their efficacy for prevention and treatment of VCID across the spectrum of severity (3-5 y).

- Establish additional clinical trials testing interventions that have shown efficacy in reducing cardiovascular and cerebrovascular risk. Interventions known to impact general vascular risk factors, including management of hypertension, statins, control of diabetes/metabolic syndrome, diet, exercise, and other lifestyle interventions may be successful pathways for reducing VCID. Consider multimodal clinical trials and modality-specific clinical trials; adding brain imaging, cognition in cardiovascular intervention trials.
- Within current and future large randomized and epidemiological cohort studies, develop or confirm surrogate markers in blood, urine or CSF for severity of VCID, particularly those that are more strongly associated with persons having both a high cardiovascular and/or cerebrovascular disease burden who also develop dementia. Such studies should also relate the burden of cardiovascular disease to imaging markers such as the frequency or distribution of lacunar strokes, neurophysiological markers such as cerebrovascular reserve or functional imaging, or molecular biomarkers obtainable from the subjects such as genetic or proteomic measures.
- Increase the harmonization of protocols across trials wherever feasible in order to permit meta-analyses.

- Extend prevention or treatment trials or initiate studies that test best models for delivering the care of persons with AD/ADRD and supporting their caregivers.

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

- Explore CVD and cerebrovascular disease mechanisms and treatments as a possible explanation that may underlie the emerging trend of lower incidence of age-related dementia that has been reported in North America and Europe.
- Conduct life-course epidemiology investigations including a) studies on VCID, the clinical syndrome of AD, pathological AD, and aging in the context of specific populations with high vascular risk factor or disease burdens (including disproportionately affected populations such as African-American, Hispanic, and Native American populations), b)environmental factors associated with increased resilience to vascular disease and cognitive impairment (e.g., Mediterranean diet, education, cognitive engagement, physical fitness, social networks, sleep, c) factors that increase risk for VCID based on the presence of monogenic conditions (e.g., CADASIL) or GWAS-identified variants associated with cerebrovascular disease (e.g., HDAC9) and d) potential gene-environment interactions.
- Analyses that advance ability to determine the link between VCID and the genomic loci associated with AD (e.g., PICALM, CLU, APOE, TREM2) that appear to interact with vascular biology or BBB dysfunction.
- Encourage analytic studies that address the complex pathways leading from vascular risk factors CVD and cerebrovascular disease to changes in cognition, brain structure, Aβ, tauopathy, and neurodegeneration. Such studies may include systems-based approaches, multiomics, and bioinformatics, incorporating multi-modal imaging, biochemical, genetic and clinical markers to help determine whether risk conditions common to both the clinical syndrome of AD and cerebrovascular and cardiovascular disease reflect convergent pathways versus additive effects of independent pathways.
- Encourage interaction between scientists working with models of disease and organ system failure (CHF, CKD, microbiome degradation) and scientists working with VCID and related forms of AD/ADRD

➢ Focus Area 3: Translational Studies

Recommendation 7 – Priority 2. Use existing and in-process biospecimens, genomics, and imaging data from large-scale human studies to test hypothesized mechanisms of VCID derived from basic science animal/human studies (3-5 y).

- Work translationally to characterize the interrelationships of vascular risk factors and pathological AD biomarkers to biomarkers of cerebrovascular disease, such as endothelial, oligodendrocyte, and pericyte cell function, BBB permeability, interstitial clearance, vascular stiffness, and other measures of vascular physiology.
- Translationally characterize the influence of vascular risk factors and vascular-mediated pathways on cognitive, physical, and other function.
- The gut-brain axis is emerging as an important factor in many neurological disorders. Translational studies are encouraged to examine systemic factors including gut-brain axis in relation to VCID.

- Information from human studies should be used to guide development of improved models, including cellular, rodent, and non-human primate

Recommendation 8 – Priority 3. Incorporate VCID mechanisms derived from basic science animal/human studies into the design of human trials targeting dementia/MCI as primary outcomes (5-7 y).

- Include in clinical trials outcomes developed in parallel with animal models, while conversely ensuring that animal models include readouts informed by clinically relevant highly valued patient outcomes. This will allow direct ties to be drawn between the results of animal- and human-based interventions.
- Incorporate the 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, considering effects of vascular and aging processes across the lifespan specific relationships in young adult, midlife, young old, old, and oldest old life stages.

Session 6:

Frontotemporal Lobar Degeneration

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

Recommendation 1 – Priority 1. Clarify unique and converging cellular mechanisms related to tau pathogenesis, C9orf72 expansion, GRN mutations, and other targets and pathways contributing to FTD neurodegeneration (2-10 y).

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

pathologic features correlate best with neurodegeneration. For example, more comprehensive studies are needed to understand the relationship between RAN-translated dipeptide repeat protein accumulation, TDP-43 aggregation, RNA foci and neurodegeneration in C9orf72 carriers. The field should compare human findings with those derived from animal and cell-based models. Mechanistic hypotheses should be tested in appropriate models to drive therapeutic development. An important goal is also to understand the normal function of progranulin, especially during the response to brain injury. This effort should include determining the role of GRN and the modifying factor TMEM106B in lysosomal function. The link between GRN haploinsufficiency and the initiation of TDP-43 pathology also needs to be identified via this approach. Finally, the field should continue to identify therapeutic approaches designed to replace/increase GRN function.

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

- There is a need to clarify fundamental mechanisms associated with the TDP-43 and FUS proteinopathies and to more fully understand the normal function of these proteins. Do TDP-43/FUS represent toxic, spreading disease proteins? Does loss of normal protein function play a significant role? Is intracellular progression unified across TDP-43 pathological subtypes and what is the sequence of events? What are the upstream events that precede TDP-43/FUS aggregation?
- Our recommended approach is to expand the scope and precision of human neuropathologic studies, focusing on early-stage disease, define the sequence of molecular changes associated with TDP-43/FUS pathogenesis from loss of nuclear localization to the formation of assemblies, and continue to study and define the normal cellular functions of TDP-43 and FUS. Expand research efforts to understand the role of TDP-43/FUS in RNA biology and the potential importance of this function in pathogenesis (e.g. formation of RNA granules or seeding 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 3 – Priority 3. Develop data and resource infrastructures to support management and collaborative analysis of diverse clinical, imaging, genetic, molecular and biomarker data and resources from FTD basic science and clinical studies (1-3 y).

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

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

- There is a need to improve the tools for disease mechanism and target identification, validation, and drug development. Do existing FTD models reproduce the formation of pathological lesions, associated neurodegeneration, and behavioral impairment?
- The recommended approach is to prioritize development of robust models to study TDP-43, FUS, GRN haploinsufficiency, and C9orf72 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 5 – Priority 1. Develop FTD biomarkers for diagnosis, prediction and disease monitoring (2-7 y).

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

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

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

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

- The most common familial FTD genes have been identified, but genetic modifiers and risk factors for both familial and sporadic FTD are not well understood. Providing genotyping support to enable research on patients with a known genetic status remains a priority.
- Our recommended approach is to provide increased clinical resources to identify and collect FTD patient cohorts, including any remaining genetically unexplained FTD families, with a range of phenotypes. Continue to build core services for FTD genotyping and banking DNA where any researcher can send samples, receive genotype information, or request data/samples from large cohorts. Pursue a focused effort to find additional genetic causes and risk factors for FTD through deep sequencing and epigenetic approaches, initially in small families and expanding into large cohorts of unrelated FTD patients to confirm pathogenicity. Improve bioinformatics infrastructure for capturing phenotype and genotype information and enabling data sharing. Include families with combined FTD and ALS phenotypes in gene discovery studies. Conduct community outreach efforts to capture genetic causes of and risk factors for FTD in underserved and minority populations.

Recommendation 8 – Priority 4. Understand phenotypic heterogeneity and natural history (>10 y).

- There is need to understand how genetic background, brain development, and environment are linked to the patient's clinico-pathological syndrome and what factors influence onset age and pace of progression. Understanding these factors may enhance trial design by accounting for variations in anatomical and temporal progression across cohorts and will aid interpretation of trial outcomes. For sporadic FTD, innovative approaches are needed to clarify the pre-symptomatic and prodromal stages of disease in the face of low prevalence.
- Our recommended approach is to conduct natural history studies of preclinical autosomal dominant FTD (especially MAPT, GRN, and C9orf72 mutation carriers) by

following cohorts of individuals from health to disease. Such studies should employ clinical, biofluid, MRI and other novel assessment tools. In addition, we recommend pursuing parallel longitudinal studies of patients with sporadic FTD, starting from early symptomatic FTD and prioritizing clinical syndromes for which the clinico-pathological correlation is high (e.g., PSP and tau, semantic variant primary progressive aphasia and TDP-43 Type C, FTD with MND and TDP-43 Type B). We recommend seeking genetic, anatomical, and environmental disease modifiers that influence clinico-pathological heterogeneity across inherited and sporadic cohorts. Conduct community outreach efforts to capture underserved and minority populations for inclusion in natural history studies, enabling a more comprehensive picture of disease modifying factors.

Session 7:

Emerging Scientific Topics

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

Recommendation 1 – Priority 1. Develop biomarker and risk profiles to establish in-vivo diagnostic criteria for TDP-43 pathology in persons without cognitive symptoms and in persons with amnestic syndromes, e.g. amnestic MCI and AD clinical syndrome (5-7 y).

- Develop biomarkers (e.g. imaging, biofluids, etc.) of TDP-43 pathology in pre-symptomatic and common dementias – these may or may not be similar to those that are established in FTLD/TDP research.
- Investigate genetic drivers of TDP-43 pathology in common dementias including GWAS, specific genes (GRN, TMEM106B, ABCC9, KCNMB2, and APOE) and other genetic profiling.
- Identify risk factors for TDP-43 pathology in pre-symptomatic and common dementias including but not limited to autoimmune disease link/inflammatory connection/thyroid antibodies, vascular disease, traumatic brain injury.
- Identify cognitive, behavioral, and longitudinal phenotypic profiles of TDP-43 pathology in common dementias.

Recommendation 2 – Priority 2. Determine underlying pathobiologic and molecular mechanisms of cellular TDP-43 displacement, phosphorylation, and pathology in pre-symptomatic and common dementias (3-5 y).

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

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

- Investigate the value of differing methodologies and the potential for harmonization for the pathologic assessment of TDP-43 pathology including the type of stain (phospho vs. nonphosho antibodies), pathologic assessment (nuclear clearing vs. proteinopathy), TDP-43 inclusion morphology (with analogy to the TDP-43 sub-types of pathology in FTLD-TDP) value of different staging methodologies and burden assessments of TDP-43 pathology in common dementias.
- Study TDP-43 pathology in presymptomatic and common dementias compared to FTLD/ALS. Specifically, investigate cellular phenotypes, subtyping, distribution, and hippocampal pathology.
- Investigate hippocampal phenotypes and progression to hippocampal sclerosis associated with TDP-43 pathology pre-symptomatic persons and those with common dementias.

Recommendation 4 – Priority 4. Develop animal models (conventional and novel) that reproduce clinical-pathologic-molecular aspects of the human TDP-43 pathology in common dementias, capitalizing on lessons learned from animal models in FTLD/ALS, AD and other diseases (7-10 y).

- Develop animals expressing wild type TDP-43 as a transgene and mutant animal models that simulate the TDP-43 clinical-pathologic phenotype in common dementias.
- Use RP promotors/ and toxicity models to model the TDP-43 clinical-pathologic phenotype in common dementias.
- Develop Knock-ins that model TDP-43 clinical-pathologic phenotype in common dementias.
- Study transmission/trans-axonal models that simulate TDP-43 pathology anatomical progression in TDP-43 in common dementias.

➢ Focus Area 1: TBI and AD/ADRD Risk

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

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

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

- Establish diverse longitudinal prospective studies of individuals with TBI and unexposed controls with harmonized multimodal clinical evaluations and autopsy endpoints.
- Expand efforts to collect brain tissue from individuals with diverse TBI histories (e.g., a history of participation in contact sports, or diagnosed single and repetitive mild-severe TBI) in regards to age at injury, severity, mechanism, and chronicity.

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

- Identify mechanisms that initiate progressive neuropathological processes after TBI.
- Characterize TBI-induced neuropathologies and identify similarities and differences in comparison with other neurodegenerative disorders.
- Identify potential neuropathological substrates of dementia in TBI. Characterize the relative burden of individual pathologies related to the extent of symptoms.

Recommendation 8 – Priority 4. Promote basic and clinical research examining the development and progression of TBI AD/ADRD neuropathologies and clinical symptoms (2-10 y).

- Establish and validate a provisional clinical definition of TBI-associated dementia(s).
- Conduct clinical studies to characterize the clinical phenotype, phenotypic heterogeneity, and clinical course of post-traumatic dementia in comparison to known dementia subtypes.
- Investigate associations between clinical dementia phenotypes and pathological markers of TBI-AD/ADRD to begin to characterize relative contributions of distinct pathological substrates to clinical features and disease progression.
- Develop TBI-AD/ADRD biomarkers (e.g., imaging and blood) to non-invasively identify the development of TBI-AD/ADRD pathologies and track their progression over time in relation to dementia.