



DRAFT RECOMMENDATIONS

Health Equity in AD/ADRD

Recommendation 1 - Priority 1. Advance equity in AD/ADRD research via inclusion science to improve representative sampling and retention of diverse communities. (5 - 7 years)

- Increase the awareness and visibility of the science of recruitment.
- Establish AD/ADRD diversity recruitment and retention centers.
- Build accountability mechanisms for recruitment goals within existing networks
- Prioritize initiation of 2-3 lifespan cohort studies.

Recommendation 2 - Priority 1. Increase training support and capacity of an AD/ADRD scientific workforce of persons historically under-represented in biomedical, behavioral, and social sciences. (1 - 3 years)

- An inclusive and diverse workforce that brings additional perspectives and broadens research scope is a critical and essential component for conducting AD/ADRD research with minoritized populations.
- Ensuring a representative workforce that aligns with diverse community facilitates better communication with community participants and partners, enabling greater validity of data.
- Leverage existing diverse AD/ADRD health equity research groups and organizations to further attract, train, and retool a competent workforce, especially individuals under-represented in science.
- Partner with relevant stakeholders to identify and invest in promising trainees early in the pipeline, including as early as high school.
- Enhance existing systems for tracking and monitoring progress in diversification of the AD/ADRD scientific workforce, including incorporating metrics for barriers to recruitment and retention of diverse scholars.
- Workforce diversity is critical to all aspects of science of AD/ADRD – from neurons to nations – as it affects the quality of the data collected, the knowledge accumulated, and representativeness of future research and the workforce pipeline.
- Implement a robust mentorship and sponsorship system for AD/ADRD trainees that prioritize mentors and institutions to train under-represented scholars.
- Expand the availability of targeted training mechanisms, writing workshops, and other career development resources to support under-represented scholars in obtaining AD/ADRD training, beginning in college and through their advanced research training.

Recommendation 3 - Priority 2. Promote career development of biomedical, behavioral, and social scientists conducting AD/ADRD health equity research. (1 - 3 years)

- Develop an iterative training framework for AD/ADRD health equity research at various training and career stages.
- Retooling and expanding the knowledge base on conducting inclusive science of midcareer and senior scientists attracted to the field of AD/ADRD is essential if progress is to occur in successfully retaining an inclusive and competent research workforce.
- Require training and education in health equity principles, as through Responsible Conduct of Research training, for all scholars, regardless of their background or level.
- Provide training and education in health equity research to all grant reviewers and increase participation on study section of scientists with expertise in healthy equity research, including individuals who are members of under-represented populations. A knowledgeable reviewer pool is essential to achieve the goals of increasing inclusion of populations facing inequities in research and increasing research focused on health equity.
- Increase opportunities for participation in high-level decision-making committees and opportunities for mid-career and senior under-represented scholars.

Recommendation 4 - Priority 2. Assess the social, economic and structural impediments to equity in AD/ADRD assessment, diagnosis, and referrals, and impacts on health and economic outcomes. (3 - 5 years)

- Conduct research on how insurance benefit design and payment and reimbursement policies impact assessment and diagnosis of dementia in diverse populations.
- Determine population generalizable effects of provider specific and health system factors such as access to dementia specialists, role of ethnic/racial concordance, provider and practice-level organization and diagnostic resources on likelihood and quality and validity of assessment and diagnosis in diverse populations.
- Expand research into the sociocultural, behavioral, physical/built environment, economic and health care system factors across all levels from community to societal, that impede assessment, detection, diagnosis, and referrals, as barriers to equitable assessment and diagnosis.
- Develop new research on the effects of assessment, detection, diagnosis, and referrals on health, social and economic outcomes.

Recommendation 5 - Priority 3. Improve AD/ADRD assessment tools (cognitive, biomarkers, -omics) and analytic methods to enhance generalizability and equity of scientific research. (3 - 5 years)

- Cognitive assessment: (a) Consider specific recommendations to develop novel and unbiased normative methods development as well as recommendations/ guidelines/ possible white paper guidance with when to use and when not to use race or ethnic-based norms, for biomarkers and cognitive data; (b) Prioritize establishing 2-3 studies to harmonize cognitive assessment across diverse populations.
- Biomarkers: Develop resources to address the fundamental questions of biomarkers utility in distinct race/ ethnic groups. Existing frameworks may not apply as well in diverse populations given lack of consideration of vascular disease, biomarkers may have different meanings and values in non-White populations.
- Omics: (a) Prioritize studies which characterize genetic risk factors in the context of other (non-genetic) factors). Genetic discoveries need to be examined in the context of environmental, behavioral, and socioeconomic and cultural factors (interventions that are informed by how genetic risk shapes downstream multisystem factors; inform and enable lifestyle interventions tailored to those who would benefit most; and to limit risk of stigmatization of individuals or groups at high genetic risk; (b) Expand the scope of data collection, including multi-omics and other biomarkers of exposures in diverse populations is needed; (c) Prioritize 2-3 large studies of cognitively well-characterized populations that are severely under-represented in -omics (GWAS, WGS, Epigenetic...).
- Enhance inclusion of digital “biomarkers” (e.g., BP, heart rate, sleep data) in existing and prospective diverse population large studies.
- Prioritize establishing 2-3 studies geared towards development of methods for analyzing large scale multidimensional data generated from diverse populations.

Recommendation 6- Priority 3. Apply existing and novel surveillance methods to assess inequities, including trends in inequities, in AD/ADRD prevalence, incidence, diagnosis, treatment and care. (3 - 5 years)

- Documenting inequities by surveilling trends in inequities in AD/ADRD prevalence, incidence, and related outcomes is integral to achieving health equity in AD/ADRD because it informs public health priorities, prevention and treatment strategies.
- Recent studies suggest that dementia incidence rates may be declining, but most of this evidence is based on White persons in Europe and the U.S. Therefore, data are needed to surveil trends in dementia incidence under-represented ethnic/racial minority populations and regionally within the U.S. and internationally.
- Document and monitor inequities in AD/ADRD prevalence, incidence, diagnosis, treatment across a range of social determinants of health, including but not limited to race/ethnicity, nativity, primary language, income and wealth, cultural context, educational background, gender identity and sexual orientation, and neighborhood environment.

- Direct attention to the impact of historic and contemporary policies (e.g., education policy, economic policy, health care policy, urban planning policy) and events (e.g., economic recessions, COVID-19 pandemic) to enable mitigation of AD/ADRD inequities and to achieve AD/ADRD equities.
- Establish new cohorts/registries to accurately estimate the prevalence, incidence, and clinical course of AD/ADRD phenotypes (e.g., Lewy Body, VCID, Frontotemporal dementia, early onset dementia) in populations under-represented in research. Innovative methods for determining prevalence and incidence, particularly of rare dementias, should be adapted from other fields.
- Develop novel approaches to identify and address determinants of under-inclusion in AD/ADRD cohorts and registries, which are a major source of data on inequities and trends in inequities (see Recommendation 1). These determinants might include but are not limited to: recruitment and retention practices, economic barriers and discrimination that reduce access to and quality of healthcare, misinterpretation of early signs of dementia and underdiagnosis by health care providers, and stigma within communities facing inequities.
- Develop valid estimates of AD/ADRD health inequities from samples that are representative of the U.S. population or oversample to adequately power informative research on groups under-represented in research.

Recommendation 7- Priority 4. Identify life course and multi-level mechanisms of and pathways to AD/ADRD inequities and use the discoveries to reduce these inequities. (5 - 7 years)

- Establish as a standard practice, in research on determinants of racial/ethnic and other inequities in AD/ADRD, disclosure of a conceptual model that describes the underlying drivers of those inequities.
- Measure risk factors (both established and novel), over the life course and across generations focusing on appropriate risk periods, and associations of these factors with AD/ADRD including cognitive, pathologic, behavioral, and functional outcomes among populations facing inequity in AD/ADRD and/or inequity in the determinants of AD/ADRD.
- Establish new rigorous and adequately powered AD/ADRD cohort studies or harmonization efforts to augment ongoing cohort studies that evaluate the influence of and interaction between social, environmental, and biological mechanisms in producing AD/ADRD inequities. These mechanisms include but are not limited to:
 - Structural and policy-level factors (e.g., racism in banking and lending, housing, education, occupation, legal/penal system, politics; economic policies present and past)
 - Early-life exposures (e.g., perinatal health, adverse childhood circumstances and events), and epigenetics
 - Exposures to toxicants in the environment (e.g., air/water pollutants)
 - Other characteristics of the neighborhood, housing, schools (e.g., disorder, safety, segregation)
 - Occupational features (e.g., hazards, job security, income)
 - Psychosocial trauma (e.g., interpersonal discrimination, micro/macro-aggressions)
 - Psychosocial exposures and conditions (e.g., stress, depression) and their -omics biomarkers
 - Deep vascular and/or metabolic phenotyping
 - Polygenic risk plus other -omics, including whole genome sequencing, epigenetics, transcriptomics, metabolomics, and proteomics
 - AD/ADRD biomarkers, including but not limited to beta-amyloid, tau, neurodegeneration, and VCID
 - Collect surrogate and diagnostic endpoints including but not limited to MRI, PET, CSF, blood biomarkers, and autopsy when possible
- Develop studies aiming to examine intersectionality (e.g., race and gender, or race and income) in excess risk for an AD/ADRD outcome should entail sufficiently large subpopulations. This may require over-sampling rather than representative sampling alone.
- Apply methods to translate scientific discoveries to the under-represented groups and region(s) from which they are drawn.

Recommendation 8 - Priority 4. Prioritize infrastructure and policy research to understand individual, community, and societal drivers of inequities in cost of and access to treatments and care, and the impact on AD/ADRD outcomes. (5 - 7 years)

- Develop and review national definition/standards for dementia ‘costs’ and ‘health outcomes’ relevant for the US population and populations experiencing health inequities.
- Undertake process to parameterize key-constructs (domains) of a framework that will lead to reliable and valid common data elements for inclusion into a national data repository.
- Identify data sources, data needs and establish a national database for dementia equity research on social, economic, health related factors as drivers of inequities in dementia treatment and high-quality dementia care and their impact on health and non-health outcomes.
- Expand research on the drivers of inequities in pharmacological, non-pharmacological and medical and social service care interventions used in routine clinical care for AD/ADRD and impact on cost and health outcomes.
- Increase research on the impact on health outcomes and care quality of managed care and associated access to, use of expanded non-health and health related benefits in diverse populations.
- New research on the role of supply side factors, such as health system ownership of physician practices, Medicare benefit plan offerings for achieving equity in AD/ADRD treatments and care.
- Catalog existing and develop advanced health economics models of pharmacological, non-pharmacological, and health care intervention access, costs, and outcomes on important and objective outcomes in diverse populations.
- Increase research on the role of sociocultural, behavioral, physical/built environment, economic and health care system factors on equitable access to and use of different care models and pharmaceutical treatments for the cognitive and behavioral symptoms of dementia.
- Identify the impact of adopting telemedicine and mobile-healthcare on reducing financial, communication, structural barriers in access to care and improving access to quality care through remote monitoring and data collection, remote specialist feedback, remote provider-provider decision support from professional network on ADRD outcomes among marginalized communities and populations vulnerable to health inequities.

Frontotemporal Degeneration (FTD)

Here, frontotemporal dementia (FTD) is an umbrella term including clinical presentations of behavioral variant FTD, progressive aphasia, progressive supranuclear palsy - Richardson’s syndrome (PSP-RS), corticobasal syndrome (CBS) as well as neuropathological diagnoses of frontotemporal lobar degeneration (FTLD) with pathology including but not limited to tau or TDP43. It is a priority to understand both sporadic and familial forms of FTD.

Recommendation 1 – Priority 1. Understand FTD epidemiology and genetics in diverse populations, including how socioeconomic and ethnocultural status affects disease risk and manifestations. (1 - 5 years)

- The majority of existing FTD clinical research and genetic data are from non-latin/a/o/x white (NLW) individuals, but increasingly, studies from non-US international cohorts suggest that FTD genetics in these cohorts are significantly different than those documented in current US and EU cohorts. Because little is known about FTD in diverse populations (DP), it is possible that the incidence, prevalence, range of clinical phenotypes and types of symptoms may be different in DP than in NLW and may provide important insight for these and other populations.
- Moreover, unlike AD, FTD is a rare disease with overall much lower prevalence, early age of onset, and initial symptoms that may be less likely to be recognized as part of a neurodegenerative disease. For these reasons, traditional approaches to improving DP participation in AD/ADRD research may not be applicable to FTD and new approaches to DP recruitment and clinical research are needed specifically for FTD.

- Conduct studies to determine the prevalence, incidence, risk and resilience factors for FTD in African American, Latin/a/ox, Asian, Native American, Pacific Islander and other DPs in North America, as well as other DPs worldwide.
- Develop culturally tailored and linguistically appropriate education and outreach tools to both support studies in DP and to reduce inequity in access to diagnosis. Such tools should be deliverable via online, mobile device, print and in person interactions. Clinicians/scientists from diverse populations should be engaged in these efforts.
- Develop and deploy new clinical assessment tools to identify and characterize FTD in diverse populations. These may include surveys, digital biomarkers and health records reviews. Tools must be sensitive to psychiatric/behavioral symptoms, motor (Parkinsonism, motor neuron disease), cognitive and speech/language symptoms of FTD.
- Develop and deploy new biomarkers that can be collected remotely and assessed in geographically remote, resource limited and diverse populations
- Understand the role of socioeconomic, environmental, psychological factors and comorbidities in the etiology of frontotemporal dementia syndromes.
- Develop educational tools and infrastructure to encourage and support brain and biosample donations from diverse populations.

Recommendation 2 – Priority 2. Develop an array of FTD biomarkers for diagnosis, prediction, disease monitoring, target engagement, and patient stratification for clinical trials. (2 - 7 years)

- Diagnosing people with FTD accurately and early in disease progression remains a major challenge for patient care and identification of participants for suitable clinical trials and potential treatments. This need is amplified for DP, who may not have access to certain paradigms used in diagnosis such as PET. In addition, being able to monitor disease progression, target engagement and surrogate measures of clinical benefits of investigational therapies remain major barriers to developing effective treatments. Given the diversity of pathogenic mechanisms in FTD, it is possible that a given molecularly-targeted therapy may only benefit a subset of patients or may only benefit patients at a particular stage of disease progression; patient stratification based on target engagement, disease stage and predictive biomarkers may be critical for effective and efficient clinical trials.
- Increase emphasis on developing easily-accessible biomarkers, including those that can measure clinical and physiologic status and could be derived from remote collection such as blood, peripheral tissue-based biomarkers, and digital biomarkers/tools to measure clinical and physiologic status.
- Develop diagnostic biomarkers to differentiate and characterize different forms of FTD, including FTLD-tau, FTLD-TDP, and FTLD-FUS. Given recent identification of different conformations of these proteins in different clinical presentations, it may be necessary to characterize different forms of the same protein (such as Tau in PSP vs. in bvFTD, or in sporadic vs. inherited forms, etc. using structural biology approaches including cryoEM) to best meet the goals of this recommendation.
- Develop biomarkers (fluid- or molecular imaging-based) for establishing target engagement for emerging treatments directed against Tau, TDP-43, and other targets.
- Develop biomarkers (fluid- or molecular imaging-based) for stratifying participants into groups that are more likely to respond to emerging therapies under investigation.
- Investigate and validate biomarkers in cross-sectional cohorts (for group comparisons) and changes over time as well as predictive value in longitudinal cohorts.
- Develop machine learning approaches and other data-driven approaches to use existing datasets and integrate biomarker data to develop prediction algorithms or other tools to facilitate FTD diagnosis, disease progression modelling, and treatment response / clinical trial simulators.

Recommendation 3 – Priority 3. Accelerate the evaluation of novel FTD treatments by developing new clinical trial resources and FTD-specific designs, and by conducting new trials. (1 - 5 years)

- Given the diversity of pathways leading to FTD, the heterogeneity even within FTD subtypes, and the rarity of FTD in general, new tools and clinical trial approaches are needed to most efficiently and effectively test investigational therapies. There is increasing support from regulatory agencies for innovative approaches to clinical trials in FTD. Travel requirements for enrollees in standard clinical research designs are burdensome and often restrict research participation to participants either in proximity to the specialist sites or with the financial resources, comfort level, and physical fitness for long-distance travel.
- Advance novel clinical trial designs for FTD to increase power, reduce placebo exposure, increase inclusivity to more patient populations (including diverse populations), reduce sample size and/or trial duration to accelerate decision making, and more efficient testing of multiple therapeutic approaches.
- Encourage entry of early stage FTD therapeutics into human proof of concept studies through master protocols and other approaches.
- Build infrastructure to support early stage, as well as pivotal global clinical trials, especially in rare genetic FTD syndromes where global efforts will be necessary to perform adequately powered studies.
- Develop and validate tools to advance decentralized clinical research study designs and measure endpoints remotely.
- Develop and use new clinical trial endpoints that incorporate caregiver burden and FTD specific definitions of clinical meaningfulness based on patient and caregiver reports from DP with distinct linguistic, social, and cultural backgrounds.
- Conduct pragmatic clinical trials in sporadic FTD syndromes to understand current treatment practices and identify potentially beneficial approaches.
- Conduct interventional studies of non-pharmacological therapies for FTD including rehabilitation strategies and caregiver support.

Recommendation 4 - Priority 4. Identify overlapping pathogenic mechanisms between FTD and other neurodegenerative disorders and syndromes. (2 - 7 years)

- Within FTD and other neurodegenerative disorders, there are single upstream genetic causes (e.g., C9orf72 expansion) and unifying pathologies (e.g., TDP-43 proteinopathy) that manifest in multiple distinct clinical pathologies. What explains the diversity of clinical phenotypes? Elucidating the underlying mechanisms for this divergence of clinical phenotypes will be beneficial for prognostic purposes and likely reveal which therapeutic targets are relevant for which form(s) of FTD.
- Likewise, within the FTD spectrum, there are clinical phenotypes (e.g., behavioral variant FTD) with multiple underlying genetic and pathological causes. Elucidating the underlying mechanisms for this convergence in phenotypes (e.g., network-system-level dysfunction, differences in regional vulnerability) will similarly reveal which therapeutic targets are relevant for which form(s) of FTD. These same questions are relevant for sporadic and inherited/familial forms of FTD.
- Identify distinct and overlapping pathogenic mechanisms between FTD, ALS, AD, HD, and other disorders and syndromes. The focus should include not only common pathogenic factors leading to this array of neurodegenerative disorders and FTD (e.g., tauopathies), but also on genetic, environmental and acquired factors that drive phenotypic expression in susceptible individuals, with potentially different underlying pathologies, including differences (where relevant) between sporadic and inherited/familial forms of disease. For example, determining the common mechanisms leading to an ALS phenotype caused by C9orf72, FUS and TARBP mutations, or a hyperkinetic movement disorder caused by HTT and C9orf72 expansions.
- Conduct multi-disease comparative genetic (including transcriptomic and epigenomic), proteomic, metabolomic and lipidomic analyses of FTD-TDP (with ALS, LATE and other disorders), FTD-tau (including MAPT carriers, CBD, PSP and others with AD, CTE) to determine common risk factors and mechanisms.

- Determine whether genetic variants identified in one FTD subset, such as TMEM106B, confer risk/resilience across the FTD spectrum and across diverse populations.
- Expand the scope and precision of human neuropathologic and biomarker studies across the FTD spectrum and related neurodegenerative disorders (FTD, ALS, AD, HD, etc.). At present, regions impacted in FTD are not often included in neuropathologic studies of disorders with possible connections to FTD such as AD, HD, etc. and the collection of this additional information will be helpful in elucidating potential convergent and divergent mechanisms.

Recommendation 5 – Priority 1. Advance understanding of FTD and identify therapeutic targets through the creation, validation, and use of pre-clinical and translational tools and resources. (7 - 10 years)

- While the amount of data and number of tools (often in the form of biological models) are increasing in the FTD research field, there is a need to generate more tools and data across disease stages and harmonize these across diverse datasets and disease subtypes, as well as a need to improve tools/models and their validity for disease mechanism characterization, target identification, validation, and drug development.
- Increase clinical resources to expand and broaden the identification and collection of FTD patient cohorts across all stages and clinical presentation of FTD, include representation from diverse populations, and improve bioinformatics infrastructure for capturing phenotype and genotype information and enable data sharing.
- Develop data and resource infrastructures to support management and collaborative analyses of diverse clinical, imaging, genetic, molecular and biomarker data and resources from FTD basic science and clinical studies. This includes but is not limited to data obtained from use of cell and tissue/fluid resources.
- Create, advertise, and distribute biosamples and data from well-characterized and diverse FTD cohorts, including but not limited to cell models, brain tissue, digital neuropathology, biofluids, neuroimaging, and clinical/cognitive data.
- Enhance molecular characterization of FTDs, including but not limited to proteomics, metabolomics, lipidomics, transcriptomics, epigenomics in tissues and models. Generating data with single cell resolution is particularly valuable.
- Harmonize and integrate these various and diverse ‘omics datasets via computational tools (including through the leveraging of AI) to develop molecular maps of disease pathogenesis, identify disease modifiers, and predict disease progression and/or response to potential interventions via clinical trial simulators.
- Develop cell, animal, and computational models for specific purposes and validate for these specific purposes. For example, animal models may not be able to perfectly recapitulate all aspects of human disease but can be valuable for modelling perturbations or interventions directed at specific molecular pathways that cannot be conducted in other systems. The type of model and specific purpose should be based on the unique attributes of that type of model, combined with other complementary models where appropriate, and validated against human data whenever possible for the specific purpose / context of use (e.g., translational biomarkers).

Recommendation 6 – Priority 2. Accelerate pre-clinical disease-modifying and symptomatic therapeutic development in FTD. (2 - 7 years)

- The field has made significant progress in identifying several potential pathogenic pathways leading to FTD, yet effective therapeutics are still lacking. Increased emphasis on therapeutic development through leveraging existing areas of knowledge or use of mechanism-agnostic approaches such as high-throughput compound screening should be considered. These efforts should further collect IND-enabling information and pursue validation and clinical testing.
- Identify pathways, cell-type specific effects, and the timing of pathogenic processes relative to pre-symptomatic, prodromal, early and late symptomatic stages of disease. Leverage tools to identify drugs/compounds that target these pathways to model and nominate therapeutic strategies.

- Where appropriate, leverage mechanism-agnostic approaches (e.g., high-throughput compound screening) to develop therapies including those based on disease-relevant readouts in appropriate model systems.
- In addition to pursuing disease-modifying approaches, symptomatic therapies should also be pursued including but not limited to electro/magnetic neurostimulation and rehabilitation approaches.

Recommendation 7 – Priority 3. Elucidate the mechanisms of cell type vulnerability and cell-intrinsic and – extrinsic effects on FTD pathogenesis, with the goal of accelerating development of therapeutic targets. (3 - 10 years)

- FTD is distinct from AD and other ADRDs in which brain regions and cell types are affected particularly at early stages of disease. Understanding why this is may reveal unique and novel therapeutic targets. Moreover, the cells that may be particularly vulnerable in FTD may not have correlates in mouse models.
- Roles for various glial cell types as well as non-CNS components such as inflammation and the vasculature are increasingly being identified in FTD, yet much work remains to understand how and to what extent dysfunction in these cell types or systems impacts FTD and particular subtypes.
- Identify, characterize, and recapitulate cell type specificity in FTD, including establishing the cell types most vulnerable in FTD and/or recreating their vulnerability in vitro and in vivo. Approaches to model may include examples such as engineering cell types that lack correlates in mouse models and nonhuman primate models.
- Define and characterize mechanisms by which cell-intrinsic processes, such as protein gain and/or loss of function, dysregulated proteostasis, or dysregulated lipid metabolism lead to cellular vulnerability in FTD.
- Define and characterize mechanisms by which cell-extrinsic processes, such as neuroinflammation, senescence, trans/intercellular spreading of toxic proteins, or vascular dysfunction, contribute to cellular vulnerability in FTD.
- Define mechanisms by which broad organismal processes contribute to FTD such as aging, sleep dysfunction, contribute to cellular vulnerability in FTD.

Recommendation 8 – Priority 4. Define genetic and molecular modifiers of FTD (including in diverse populations). (3 - 10 years)

- While some of the most common autosomal dominant causes of inherited FTD have been identified, rare genetic causes remain uncharacterized and present potential novel insights into disease mechanisms and/or build on to existing pathogenic models.
- In addition, it is a priority to understand the genetic architecture of FTD in DP. Do rare and common variants impact disease risk similarly across populations? Are there variants that confer risk or resilience that are unique within specific populations?
- Identify and functionally annotate risk/resilience loci in Mendelian and sporadic forms of FTD. This includes leveraging functional genomics to map variants and their effects on specific genes within a given loci. Defining the cell-type in which variants confer risk/resilience is critical to understanding the disease mechanism and possible therapeutic approaches.
- Define and functionally characterize the genetic factors that influence onset age and pace of progression in Mendelian and sporadic forms of disease.
- Elucidate how genetic background and environment are linked to the patient's clinico-pathological syndrome in clinical cohorts and modeled in vitro and in vivo.
- 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.

Vascular Contributions to Cognitive Impairment and Dementia (VCID)

Basic mechanisms and experimental models

Recommendation 1 – Priority 1. Establish and refine experimental models and technologies to identify disease-relevant mechanisms underlying VCID. (5 - 8 years)

- Establish and refine experimental models so that they: (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 the pathophysiology of small vessel disease, and develop clinically-relevant manifestations / lesions (examples include microinfarcts, microhemorrhages, superficial siderosis, arteriolosclerosis, atherosclerosis, cerebral amyloid angiopathy, vascular inflammation).
- Generate novel models that will facilitate the study of white matter degeneration. 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 consider incorporating existing and emerging genetic factors of VCID. Examples include, but are not limited to, ApoE, TREM2, Collagen IV, among others.
- Models of VCID should also incorporate common lifestyle, vascular, and metabolic factors associated with aging, including chronic conditions, to investigate the additive effects on pathophysiology. Models should aim to mimic the human condition to the extent possible.
- Incorporation of VCID, AD (amyloid plaques and / or neurofibrillary tangles), as well as other neurodegenerative pathologies, in animal models would be particularly informative for interactions of neurodegenerative and VCID pathophysiologies.
- Use of in vitro and / or iPSC models to study specific molecular mechanisms that are not feasible in animal models.
- Given age remains one of the strongest risk factors for the onset of dementia, age as a biological factor should be considered in experimental model studies. Sex as a biological variable also needs to be incorporated to provide translational insights.
- Validating and aligning existing and new models to human VCID pathologies, incorporating approaches such as multi-omics, neuroimaging, and neuropathology and considering regional specificity.
- Application and development of methods to VCID research, including next-generation technologies such as cognitive / behavioral assessments, deep multiphoton microscopy to allow imaging of subcortical white matter, higher resolution MRI and CT/PET modalities for live animal imaging, and technologies to obtain spatial proteomic and transcriptomic analyses.

Recommendation 2 – Priority 3. Study the neurovascular unit structure and function to establish how it is impacted by VCID. (4 - 6 years)

- Leverage single-cell and spatial technologies to identify cell-type specific changes within the neurovascular unit with VCID pathologies, including endothelial cells, pericytes, astrocytes, perivascular macrophages / microglia, perivascular fibroblasts, oligodendrocytes, and interneurons.
- 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 (arteriole, arteriole-capillary transition/pre-capillary, capillaries and venules), and how VCID pathology affects each of these zones.

- Mechanisms underlying loss of blood-brain barrier integrity must be understood, and the relationship between blood-brain barrier integrity and blood-based biomarkers for neurodegenerative conditions.
- In addition to controlling blood supply, there is known remodeling of the neurovascular unit with aging and VCID. Studies of age and VCID-related changes in capillary angiogenesis, regression, and vascular matrix composition are critical.
- 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.
- Disentangle the relative contributions of clearance mechanisms to VCID, including clearance of metabolic waste? across the blood-brain barrier, perivascular clearance, and phagocytic degradation.
- Understand the anatomical pathways and driving forces for perivascular clearance under normal conditions and during VCID. Delineate the relative contributions of peri-arteriolar, peri-venular, and basement membrane compartments to fluid drainage.
- Studies establishing the contribution of non-neurovascular unit cells including myeloid cells to VCID are essential.
- It is important to establish the impact of normal, biological aging on the neurovascular unit structure and function.

Recommendation 3 – Priority 4. Use experimental models to investigate how aging, cerebrovascular and cardiovascular disease impact myelin, white matter degeneration and neurodegeneration. (5 - 8 years)

- 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 in experimental models.
- Develop tools to characterize the effects of altered cerebrovascular phenotypic cell changes, as they related to different microvascular zones, brain regions and vascular functioning; A focus on understanding endothelial cell molecular and functional disease changes will be critical.
- Apply multi-omics and sophisticated bioinformatics to elucidate disease mechanisms, and also create the opportunity to share data through centralized systems.

Human Studies:

Recommendation 4 – Priority 1. Develop and validate markers of VCID in diverse populations using 1) cognitive, physical, or other functional assessments, and 2) biomarkers of key vascular processes, including in the most common scenario where VCID is accompanied by AD in human studies. (3 - 5 years)

- Develop and validate standardized assessments that include cognitive, behavioral, and functional measures which may also incorporate physical function, non-CNS organ-related (heart, kidney, etc.), and other measures indicating the presence of VCID. This would be an important step towards improving risk assessment, clinical diagnosis, and measurement of clinically meaningful trial outcomes for VCID.
- Identify newer sensitive behavioral and functional outcome measures (e.g., depression, apathy, other behavioral impairments, mild executive dysfunction and altered gait) for human studies that provide novel information relevant to VCID.
- Discover, develop, and validate the clinical utility of candidate non-invasive, lower-cost, systemic markers (e.g., retinal measures, other neurobehavioral measures, remote digital systemic and cognitive assessments) for detecting the presence and progression of VCID.
- Explore the heterogeneity in cerebrovascular disease by identifying and validating fluid, imaging, and multi-omic biomarkers of individual microvascular markers (e.g., lacunar infarcts, ischemic white matter damage, enlarged

perivascular spaces) and processes (e.g., cerebral amyloid angiopathy, BBB dysfunction, impaired neurovascular coupling) related to cognitive/neurologic impairment. These new developments may help refine the understanding of various cerebrovascular disease processes and their contributions to VCID across the lifespan.

- Validate emerging fluid markers, including circulating exosomes. Those identified broadly from VCID and AD/ADRD new basic and translational study data need to be measured: a) use-appropriate clinical and population settings; b) in new clinical neuropathology studies; c) to study influences of systemic disease (e.g., kidney and heart function/failure) on the fluid markers; and d) to compare differences in these measures translationally in human compared to animal model endophenotypes, thus providing more detailed cellular-mechanistic information and translational validation.

Recommendation 5 – Priority 2. Identify and apply 1) interventions (medication, lifestyle or a combination of these) that reduce cardiovascular and cerebrovascular risk and 2) care models to test their efficacy for prevention and treatment of VCID across the spectrum of severity and in diverse populations. (7 - 10 years)

- Establish randomized (Phase I-IV and pragmatic) clinical trials for VCID testing interventions that show efficacy and effectiveness in reducing cardiovascular and cerebrovascular risk. Interventions known to impact general vascular risk factors, including management of hypertension, statins, diabetes/metabolic syndrome; facilitating optimal diet, exercise, sleep; adoption of user-friendly structures and systems, medical devices; environment/neighborhood modification and behavioral interventions may be successful pathways for reducing VCID.
- Consider adding brain imaging and cognition to cardiovascular intervention trials to determine how such interventions influence VCID-relevant outcomes. Utilize as default, whenever feasible and appropriate, study designs that incorporate oversampling of minoritized populations at risk of VCID in clinical trials.
- Conduct early phase clinical trials testing novel interventions shown to be vasoactive or that target specific aspects of dysfunction of the neurovascular unit in VCID, leveraging new translational research discoveries.
- Within current and future large randomized and epidemiological cohort studies of AD/ADRD, include ancillary studies that develop, validate, and apply surrogate non-imaging markers of VCID 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). Promote the incorporation of VCID markers in non-VCID trials in aging and neurodegenerative disorders to control for individual differences in VCID.
- Increase the harmonization and open sharing of VCID data, images, and protocols wherever feasible to permit meta-analyses across trials, following current best practices for VCID trials. Where appropriate, incorporate standardized VCID biomarkers developed and standardized recently.
- Extend pragmatic prevention or treatment trials or initiate studies that test best models for delivering care to persons with ADRD and supporting their caregivers including policy interventions such as paid family leave. Explore VCID treatments in existing studies by determining the possible cause of the emerging trend of lower incidence of age-related dementia reported in North America and Europe and developing better screening methods and design of effective VCID prevention trials.

Recommendation 6 – Priority 4. Understand the impact on VCID of other known dementia risk factors (e.g., aging, genetics) and co-morbid neurodegeneration along the life-course in diverse populations. (7 - 10 years)

- Investigate the life-course and progression of VCID biomarkers in VCID, dementia, and aging studies in the context of specific populations with high vascular risk factors and inequalities in cognitive impairment (including race and ethnic populations that have traditionally been excluded from ADRD research and who may be disproportionately affected by VCID) to inform intervention design. Existing birth cohorts such as those found in statewide health systems or national medical systems have utility in understanding life-course factors contributing to later life VCID.

- Conduct life-course epidemiology investigations including: a) studies on VCID, AD/ADRD, and aging in the context of sex differences and specific populations with high vascular risk factor or disease burdens (including disproportionately affected race and ethnic 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); d) functional pathways of GWAS-identified variants; e) potential gene-environment interactions; and f) detailed focus on links 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. As above, cross-validation of new factors (variables and genes) from basic science needs to be followed closely in clinical-translational research work.
- Conduct studies that address the complex pathways leading from vascular risk factors, cardiovascular disease, and cerebrovascular disease to longitudinal changes in cognition, brain structure, A β , tauopathy, and neurodegeneration. Systems-based approaches, multi-omics, and bioinformatics coupled with multi-modal imaging, biochemical, genetic, and clinical markers can help determine whether risk conditions common to AD, cardiovascular and cerebrovascular disease reflect convergent pathways versus additive effects of independent pathways. Translational cross-validation and detailed evaluation in animal models will be necessary to mechanistically capture critical brain and circulating molecular and cellular phenotypic changes.
- Encourage interaction between scientists working with models of disease and organ system failure (CHF, CKD, microbiome degradation, geroscience) and scientists working with VCID and related forms of AD/ADRD to investigate the links between organ system failure, cardiovascular disease, brain changes and VCID.
- Ensure rigor and reproducibility using appropriate study designs, adequate sample sizes, and use of statistical models and methods to accommodate the high dimensionality and multimodality of the data with the heterogeneity of VCID in the population to identify new specific and biologically relevant VCID targets.
- Establish the generalizability of the sample to the population through evaluation of selection, attrition, and algorithm bias as well as consistency of effects across sub-populations of interest, including women, race/ethnic underrepresented groups, and other pre-specified subgroups of interest.
- Require, foster, and prioritize the adoption of open data, image and specimen sharing principles to promote transparency and facilitate reproducibility and collaboration to promote VCID-ADRD science and medicine.

Translational Studies

Recommendation 7 – Priority 2. Incorporate VCID mechanisms derived from basic science animal/human studies into the design of human trials targeting prevention or treatment of dementia/mild cognitive impairment. (5 - 7 years)

- 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.
- Evaluate mechanisms of amyloid-related imaging abnormalities of the edema and hemorrhagic types (ARIA-E and ARIA-H) associated with amyloid-lowering immunotherapies using both human and experimental models. Determine the impact that VCID co-morbidity has on ARIA incidence and establish potential for mitigating therapies / precision medicine approaches to minimize impact of ARIA with newly approved immunotherapies.
- Incorporate VCID biomarkers and cerebrovascular disease in prior, ongoing, and future clinical trials targeting both cardiovascular and neurodegenerative disorders.
- Incorporate the pathologically validated vascular biomarkers in observational 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, old, and oldest old life stages.

Recommendation 8 – Priority 3. Validate hypothesized mechanisms of VCID in large-scale, including community-based diverse, human studies leveraging existing and in-process biospecimens, genomics, and imaging data. (4 - 6 years)

- Work translationally to characterize the interrelationships of vascular risk factors and AD biomarkers to biomarkers of cerebrovascular disease, such as endothelial, oligodendrocyte, and pericyte cell viability/function, BBB permeability, interstitial clearance, vascular stiffness, and other measures of vascular physiology.
- 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.
- Insights from human studies should be used to guide development of improved models, including cellular, rodent, and non-human primate.
- Studies to examine the fundamental biology underlying CSF and plasma candidate VCID biomarkers are important to establish their physiological function in the brain and their pathophysiological mechanisms underlying VCID.
- Leverage existing biospecimens and imaging from trials to evaluate mechanisms of action of interventions found to alter VCID-relevant outcomes using experimental models of VCID.
- Develop non-invasive human based techniques that will evaluate clearance of disease-relevant biomolecules from the brain to the peripheral compartments including CSF and plasma.

Lewy Body Dementias (LBD)

FOCUS AREA 1: CLINICAL CHARACTERIZATION AND INTERVENTION

Recommendation 1 – Priority 1. Prepare for and initiate clinical trials that aim to alleviate or slow the course of LBD symptoms, and delay or prevent the onset of disease. (1 - 7 years)

- Promote and prepare infrastructure for clinical trials of novel treatments specific to Lewy Body Dementia (LBD). Efforts to develop and test novel therapeutics for LBD must build upon the knowledge base that is gained from genetic and environmental studies and from systematic profiling of well-characterized human samples that identify underlying disease mechanisms and biomarkers. The long-range goal is to use therapeutic approaches that prevent or alter the disease processes using pharmacologic approaches, gene therapy, regenerative medicine, or surgical interventions among others by enhancing clearance of protein aggregates, modulating signaling pathways, reducing the accumulation or transmission of toxic protein aggregates, enhancing synaptic function and resistance to disease pathology, and reducing inflammation (see also recommendations #7 and #8).
- Clinical trials should include persons with either, or both, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), that is LBD. Trials should also be conducted in both the symptomatic and the pre-dementia disease stages, including mild cognitive impairment of Parkinson's disease (MCI-PD) and DLB (MCI-DLB), those at genetic risk (e.g., LRRK2, SNCA or GBA) as well as in persons with isolated rapid eye movement (REM) sleep behavior disorder (RBD) and fully manifest psychosis (hallucinations and delusions). Prodromal disorder/symptoms that could be targeted for symptomatic approaches include RBD, autonomic dysfunction, and depression, clinically significant symptoms that have the greatest impact on patient function and caregiver burden. The participants in trials and the investigators involved in trials will be as inclusive as possible with regards to racial/ethnic, sex, socioeconomic and cultural diversity.
- Promote: 1) therapeutic trial of at least one novel drug targeting known (e.g., alpha-synuclein, APOE, GBA) or emerging genetic or neuropathological targets and mechanisms implicated in LBD; 2) one novel target addressing targets to preserve or restore synaptic function in circuits damaged by DLB pathology; 3) infrastructure to support preclinical drug development including one or more aspects of the pre-clinical development pipeline, e.g. screening, confirmation, lead optimization, preclinical efficacy studies, initial tox studies. In the near-term, at least one novel compound strategy (e.g., novel cholinomimetic agents) and at least one already FDA-approved compound (e.g., anti-amyloid antibody) will enter clinical trials over the upcoming 1-

3 years. In the longer-term, at least one “disease-pathology-modifying” agent and at least three “symptomatic” agents will enter clinical trials over the upcoming 3-5 years.

- Develop and validate DLB-Specific clinical outcome measures. As part of the development of a clinical trial infrastructure, one or more consensus, sensitive, disease-stage specific clinical outcome measures should be developed over the upcoming 2 years to encompass the complex phenomenology inherent to LBD symptomatology, to include cognitive, neuropsychiatric/behavioral, motor, sleep, autonomic, sensory and other clinical domains. 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 (see recommendations #2 and #3). The goal of any composite measure would be to track change over time and be used in clinical trials. A key component or supplement to any such measure must include input from persons/families with LBD on the clinical meaningfulness and relevance to the patient and caregiver experience. Proposed metric: develop consensus proposal for development and validation of one or more clinical outcome measures over the upcoming 3 years. New or existing methods for detecting and tracking LBD features should undergo multi-center validation, and normative data using these new methods should also be generated. New outcome measures should be developed in consultation and collaboration with global regulatory authorities, including FDA, EMA and others.
- To meet the above recommendation, it will be necessary to engage existing clinical and research networks, non-governmental organizations and the pharmaceutical industry to establish new and expand existing networks for well-characterized cohorts of established or at-risk LBD for treatment trials. These 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 (see recommendations #2, #3 and #4). 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 (see also recommendations #2 and #3) should be incorporated into trial design and the required enrollment enriched and with sufficient numbers; or stratified to improve the ability to study more homogenous LBD cohorts in a clinical trial design, thus improving statistical power and likelihood of success. Proposed metrics: 1) develop a robust infrastructure, including consensus protocol elements, for the conduction of numerous multisite LBD clinical trials over the upcoming 2 years (see recommendation #4) 2) develop one or more working groups of investigators from relevant pharma companies, medical and research community, and general public over the upcoming year 1 to address barriers to clinical trials in LBD.

Recommendation 2 – Priority 2. Develop and refine neuroimaging biomarkers that track progression, assist in differential diagnosis, provide therapeutic target engagement, and relate to pathology. (2 - 7 years)

- Develop imaging approaches within the next 3-5 years to: a) enhance the differential diagnostic accuracy of LBD compared to other dementing illnesses and parkinsonisms; b) detect preclinical and prodromal LBD; c) establish reproducibility and the expected change over time relevant for clinical trials (see recommendation #1); d) characterize and monitor disease progression in natural history and genetic studies (see recommendations #4 and #6) by integrating established and new imaging tools; and e) validate these tools against postmortem neuropathology (see recommendation #5) using both in vivo and ex vivo imaging.
- Develop at least one α -synuclein tracer within the next 7 years that is sensitive and specific to α -synuclein in the human brain, and that can be measured safely. Establish the biochemical and biophysical features of the tracers as well as safety and efficacy in human trials. Validate α -synuclein tracers against postmortem neuropathology using both in vivo and ex vivo imaging and utilize this technology as the standard to develop assays for measuring α -synuclein in blood and CSF (see recommendation #3). Compare performance of α -synuclein tracers

with alternative approaches such as nigrostriatal dopaminergic imaging or myocardial sympathetic innervation imaging in LBD and other neurodegenerative dementias and parkinsonian disorders.

- Repurpose currently available imaging tools for the diagnosis and classification of LBD within the next 5 years. For example, molecular imaging of neurotransmitter receptors can be considered. Emphasis should be placed on imaging modalities demonstrating high reproducibility across populations, imaging sites, and imaging platforms. Imaging tools should be categorized by their scalability to clinical trials (see recommendation #1), and for possible clinical use, including availability and cost. Evaluate feasibility of imaging biomarkers developed in the research setting for use in clinical trials where imaging resources may be limited or heterogeneous across sites. Tools should be accessible in diverse settings, including historically underserved populations, and imaging tools should be evaluated in racially and ethnically diverse cohorts, incorporating sex differences.
- Determine the feasibility of emerging technologies or analytical approaches through in vivo and ex vivo imaging for value added to natural history studies and multicenter therapeutic trials within the next 5 years. Utilize a multi-center approach to determine scalability of techniques and prepare for Phase 3 trials. Incorporate multimodal analyses, including EEG, systems-level biomarkers or biofluid biomarkers to enhance accuracy of diagnosis and reliability of prediction of disease progression. Establish large datasets to enable machine learning and AI approaches. For these approaches to be successful, protocol harmonization and data sharing are essential (see recommendation #4) however post-acquisition harmonization of legacy data should also be considered.
- Investigate imaging biomarkers' potential for sensitivity/specificity to the contributions of α -synuclein, beta-amyloid, TDP-43, tau and other protein deposits as well as vascular disease lesions to LBD disease heterogeneity and clinical phenotypes within the next 5 years. Determine pathophysiologic underpinnings of core clinical features of LBD with imaging biomarkers. Utilize established and new imaging tools to determine the evolution of the multi-proteinopathy including synergistic interactions of proteins across brain regions and across time in LBD. This approach will facilitate the development of synergistic multi-modal biomarker strategies to enhance the accuracy of diagnosis and the reliability of progression measurements during all stages of disease. Safety is a priority in terms of radiotracer research.

Recommendation 3 – Priority 3. Develop and refine biomarkers for diagnosis, prediction, and prognosis utilizing biofluids, tissues, and digital and electrophysiological methods. (2 - 7 years)

- Biomarkers should be developed by capitalizing on existing or new cross-sectional, case-control and longitudinal studies of individuals throughout the course of LBD (including prodromal stages), in which symptoms of cognitive and/or motor decline, neuropsychiatric and autonomic changes are tracked (see recommendation #4). Building on and extending existing cohort studies and establishing new cohorts will support these aspects of biomarker discovery and validation portfolio over the next 5-7 years.
- A panel of biomarkers should reflect pathophysiological changes related to LBD (e.g., synaptic, lysosomal, and other processes related to α -synuclein pathology) as well as changes due to other proteinopathies (such as amyloid, tau, and TDP43) and vascular pathology. During biomarker development, the context of use should be defined and validated, such as diagnosis (including prodromal disease), prediction and prognosis, or use in clinical trials, including stratification and enrichment, monitoring response to therapies and measuring outcomes (see recommendation #1 & #4). Normative data for biomarkers should be obtained on well-phenotyped and demographically comparable control subjects and/or appropriate disease controls, with attention to race/ethnicity. At least one panel of biomarkers reflecting the multiple proteinopathies and vascular changes in LBD will undergo validation as having diagnostic and/or predictive/prognostic value. Prioritize studies of biomarkers and panels with the goal of eventual CLIA and FDA-approval within 2-7 years.
- Where appropriate, biomarker discovery and evaluation should be carried out in multiple tissues (e.g., skin, colon, salivary gland, PBMCs, others) and biofluids (e.g., whole blood, plasma, CSF, urine, saliva, tears, microbiome samples, others). Novel biomarkers or biomarkers in different tissues should be compared to gold

standards wherever possible. Targeted as well as -omic approaches to biomarker discovery and development should be pursued. Collection and biomarker analysis of samples from at least CSF, blood, and skin biopsies from participants of at least 2 cohorts need to be accomplished. A catalog and database of cohorts and samples available at government and non-government organizations should be developed (1-2 years, see also recommendations #1 and #4), and biomarker data generated will be deposited into this database to allow sharing of well-curated samples and data.

- For validated biomarkers, approaches to disclosure of results in symptomatic and at risk populations and consequences of revealing this information should be studied. Studies of disclosure can be initiated in 1-5 years.
- Efforts should be made to develop comparable biomarkers in model systems (e.g., transgenic animals; iPSc-derived models, etc.) to those biomarkers identified in human studies; this process may be bidirectional and accomplished within 2-5 years.
- Digital and electrophysiological approaches to biomarkers, including wearables, electroencephalogram and polysomnography, computerized testing, home-based monitoring of lifestyle, behavior, cognition, neuropsychiatric symptoms, autonomic function, activity and sleep should be developed and validated across all stages of LBD. Regardless of the approach, attention should be paid to optimizing the assessment to be as unobtrusive or ambient as possible to maximize the ecological validity of the data captured. Attention to feasibility, acceptability of methods to participants and compliance is essential. Defining the psychometric properties and validating these approaches for diagnosis and to track progression is critical. Quantitative approaches should be adapted for telehealth and clinical trials. At least 2 electrophysiological studies (EEG and sleep) are initiated in early stage or prodromal LBD cohorts; at least one digital biomarker study is initiated in 2-5 years. Workshops should develop metrics of feasibility, acceptability and compliance to be applied to studies during the next 1-2 years. A workshop should explore how to make data shareable from open-source vs proprietary biomarkers and analytical methods in 1-2 years.
- Protocols and common data elements should be harmonized to facilitate analyses of biomarkers in relation to genetic and environmental risk factors, clinical measures, sex differences, medical comorbidity and phenotypes of DLB vs PDD (discussed in recommendation #4). While detailed phenotyping through the DLB module is carried out in some studies, harmonization of key phenotypic domains will support larger scale integration of data. Imaging and neuropathology data should be incorporated, where available, to help to interpret and validate biomarkers. A workshop to harmonize definitions and approaches to common data elements (CDEs) should be held within 1-2 years. One or more integrative studies of biomarkers with an investigative team requiring multidisciplinary teams of investigators (clinical, biomarker, biology, statistician and others) will be initiated in 2-5 years.

Recommendation 4 – Priority 4. Expand existing and new longitudinal LBD study cohorts, including diverse populations, from pre-symptomatic disease to autopsy to support diagnostic, epidemiologic, and therapeutic studies. (1 - 7 years)

- Virtually all of the LBD recommendations require access to well-characterized and deeply phenotyped LBD subjects and their associated imaging, biofluid biomarker, genetic, and neuropathologic characterization. This includes recruitment to clinical trials, materials and data for biofluid biomarker, imaging, genetic and neuropathologic investigation, and for translational research. Thus, continued prioritization is needed for efforts to expand longitudinal LBD cohorts with deep phenotyping, uploading of clinical, genetic, biofluid biomarker and imaging data into a central database, and biofluids into a biofluid repository to allow for broad utilization by the LBD research community. Deep phenotyping would include characterization of cognitive, motor and behavioral change over time, quality of life and function, comorbid health conditions and risk factors. Utilization of digital biomarkers would assist with phenotyping across diverse subject cohorts (see also Recommendation #3). Double current or proposed cohorts' sizes and associated clinical characterization including imaging, biofluid collection and support of autopsy data.

- An imperative for Recommendation #4 is a focus on increasing diversity of participants in LBD research cohorts to allow investigation and validity across racial, cultural and sex differences. Twenty percent of subject cohorts fulfilling criteria for diverse populations or female sex.
- Sufficiently large longitudinal and compatible cohorts are needed to allow for the development of predictive models for clinical conversion, rate of decline, and clinical heterogeneity in LBD. This effort would be enhanced by common phenotyping, imaging and biofluid collection methods across cohorts, including diverse populations and non-US based LBD research-based programs. To accomplish this goal, we recommend the development of the potential to harmonize and merge datasets across existing and future study cohorts, including cognitive, behavioral, motor and biomarker data (including non-US based programs). Convene a meeting to develop and publish common data elements and collection protocols (see also proposals from other recommendations) that allow for collaboration and utilization of data and biological specimens across sites.

FOCUS AREA 2: PATHOGENESIS AND MECHANISMS OF TOXICITY

Recommendation 5 – Priority 1. Delineate genetic loci and their functions contributing to the onset and progression of LBDs using genetic, transcriptomic, epigenetic, and environmental characterization analyses. (1 - 7 years)

- Discover and replicate genetic variants associated with LBDs within the next 3 years. Initial success has been achieved with the execution of large-scale association studies. Systematic identification of novel genetic, epigenetic, and environmental determinants associated with risk for LBDs; or with core clinical or neuropathological features of LBDs remains a major goal. This goal will require genome-wide cross-sectional and longitudinal association studies, whole-genome sequencing, genome-wide methylation mapping, and expression studies. This recommendation also includes the identification of genetic and epigenetic factors influencing the risk of developing LBDs in patients with pre-existing PD or other prodromal LBDs syndromes. There is a related need to develop polygenic scores for longitudinal prediction of risk of LBDs and for clinical trials, e.g., for enrichment and stratification. Examination of gene-environment interactions is also important.
- To advance this research, large cross-sectional and longitudinal cohorts and LBDs families are needed (see recommendation #4). This includes expanding follow-up, recruitment, or phenotyping for existing cohorts; and establishing new cohorts. Some cohorts could span the prodromal to terminal disease stages. Cohorts should emphasize harmonized, longitudinal clinical, molecular and biomarker characterizations, environmental factors, and include diverse populations. Promote inclusive participation, transparency, and diversity in all aspects of this endeavor.
- There is a need to translate LBDs-associated genetic variants into mechanisms, therapeutic targets, and biomarkers. This should emphasize analyses of specific types of brain cells and single brain cells from human autopsy brains using single-cell multi-omics approaches. Clarifying the putative causal variants underlying genetic association signals is also important. Proposed metric: the functional mechanism of at least one novel genetic locus linked to risk of LBDs will be established over the upcoming 5 years (see recommendation #7).
- Clarifying the divergences and convergences in the genetic, molecular, neuropathological, and clinical landscape of LBDs and related neurodegenerative diseases is important. LBDs are clinically and neuropathologically heterogeneous (e.g., showing Lewy bodies, amyloid plaques, tangles, etc.) and there is a need to identify aspects of the genetic architecture that may be shared with or different from other neurodegenerative diseases and dementias. This requires innovative analytical approaches and existing and new data sets suitable for these analyses across LBDs and related neurodegenerative diseases.
- Data platforms and analytics. This recommendation also prioritizes innovative data analytics and data platforms. Although progress has been made on central knowledge, there remains a need to expand on existing platforms; develop new solutions for easier and more user-friendly data platforms and analytics. There is a need to facilitate data sharing, 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 6 – Priority 2. Enhance and standardize the techniques for neuropathologic characterization of LBD and the use of LBD pathology cohorts including more diverse cohorts. (2 - 7 years)

- Within the next 4 years develop best practices for neuropathologic evaluation of LBD as well as standardization of neuropathologic methods (e.g., minimal sampling schemes and staining methods) and data collection (e.g., quantitative and semiquantitative data). This should include emerging digital image analysis and open-source deep learning techniques to detect and quantify histopathological features for clinicopathological correlation and diagnosis (see recommendations #1 through #4). Techniques should be tested for scalability, feasibility, and generalizability across multiple cohorts, anatomical areas, and histologic methods.
- Within the next 3 years develop tissue processing and sampling strategies for LBD associated pathologies to study the pathologic bases of cognitive, non-motor and motor dysfunction in LBD, especially for the neuroanatomy associated with core LBD clinical features, including REM sleep behavior disorder, cognitive fluctuations, and visual hallucinations (see recommendation #2 for validation of imaging measures).
- Within the next 5 years develop cost-effective scalable methods to assess integrity and quality of human tissue samples across multiple cohorts used in molecular, neurochemical, and genetic research (see recommendations #7 and #8).
- Encourage and enhance infrastructure for collection of peripheral tissue samples (fixed and frozen) from autopsies, including skin, salivary gland, gastrointestinal, and solid organ tissues outside the central nervous system for detection of non-CNS α -synuclein. Analysis of central and peripheral tissues would include emerging seeding aggregation assays (see recommendation #3).
- Within the next 5 years increase autopsies on subjects at-risk for LBD, including those currently enrolled in prospective longitudinal studies who have standardized collection of demographic and clinical data (see recommendation #4). Autopsies should be sought of individuals with mild cognitive impairment and other pre-symptomatic, core or related features of LBD, such as REM sleep behavior disorder (RBD), pure autonomic failure, anosmia, and Parkinsonism.
- Provide outreach and education to underrepresented groups, including studies on barriers to autopsy, importance of brain donation, as well as logistical support and resources necessary to facilitate brain donations. This would include individuals who may not be included in formal research studies of LBD or prodromal LBD. Increase autopsies on subjects from diverse backgrounds representative of the diversity of the US, including minority groups (Native American, Asian, Hispanic/Latino, and African American).
- Within the next 3 years create a publicly available portal linking scientists or other investigators to LBD tissue resources (see recommendation #4). Integrate a universal unique identifying number (e.g., GUID) to provide a link between molecular (e.g., genomic, transcriptomic and proteomic) data and the specific autopsy samples with these data. This resource would include an on-line and searchable database that links fixed and frozen autopsy samples, as well as slides and digitized images to samples with specific clinical, neuroimaging and antemortem biomarkers in the networked repositories (discussed in recommendation #4).

Recommendation 7 – Priority 3. Develop models to understand the pathophysiology and normal molecular and cellular functions of α -synuclein to support drug discovery. (5 - 7 years)

- The fundamental biology of α -synuclein has been extensively studied in many experimental paradigms, particularly in the context of motor systems, while the normal function and misfolding of this protein in areas vulnerable to the broader set of LBDs remains underexplored. It is unknown if small molecule therapies targeting motor systems will have meaningful effects on non-motor systems (e.g., cognition). This recommendation is aimed at improving our knowledge of the normal function of α -synuclein and role of α -synuclein in non-motor systems. Specifically, studies that inform current clinical therapeutic development by identifying potential safety concerns and new targets are encouraged.

- Furthermore, studies are needed to improve knowledge on pathological α -synuclein by isolating Lewy Bodies from LBD, PD and PDD patients and characterize them biochemically and biophysically, to determine if unique features of specific LB α -synuclein strains exist. Understanding the fundamental biology of α -synuclein in the context of the broadest numbers of neurons vulnerable to LBD will be important. Questions to be asked, mainly using animal models that mimic key clinical and/or pathophysiological components of bona fide disease, will relate to cellular, regional physiology, and pathophysiology of neurons when α -synuclein expression is modified. Identifying sequelae of α -synuclein removal from mature brain across multiple regions, in terms of neuronal health and function, is an important component and will guide therapeutic development. More specifically, the goal of this approach is to promote discovery of at least one novel target to preserve or restore synaptic function in circuits damaged by alpha-synuclein and associated pathology.
- Additional focuses should include in-vitro models utilizing human-derived materials such as induced pluripotent stem cells, integrating genetic discoveries from human population studies that have identified pathways relevant to LBD risk and progression with the directed goal of identifying biological pathways and networks that ultimately regulate gene expression and other disease risk factors hypothesized to be causative of LBD. These models can be used to screen and identify potential therapeutic agents. Both Mendelian alleles and non-mendelian pathways, such as genetic risk scores, should also be considered.
- Understanding the regulation of α -synuclein protein levels and its aggregation, as a product of both regulation of expression, misfolding, and clearance. In addition, post-transcriptional regulation within cells, will be important to provide tractable hypotheses relevant to LBD genetic risk. This recommendation should also be considered in the context of the aging human brain. This consideration should improve thinking about which human subjects might benefit from α -synuclein modification, or other targets, in LBDs and may inform clinical action around measurement of target engagement. Studies are encouraged to examine lysosomal function and glucocerebrosidase (GBA) genetics/function with α -synuclein accumulation and spread. These can inform the development and implementation of emerging therapeutics targeting GBA/autophagy in GBA carriers and potentially sporadic disease.
- It is clear aging contributes substantially, and critically, to LBD risk. The role of aging should be interrogated further using LBD relevant model systems that allow for modeling this risk factor and also in analyses of available resources such as high volume 'omics' datasets, including novel methods such as mRNA expression, proteomics, metabolomics, etc.
- Identification of biological mechanisms explaining both sex differences and resilience in LBD across numerous demographic backgrounds (i.e., diverse cohorts), as identified in human pathological studies, will be of high value. Inclusion of samples from all genders/sex at appropriate number to support well-powered analyses of all groups is required.
- Overall, the overarching goal of the pre-clinical basic science and translational work in this recommendation is to prioritize the discovery of at least one novel drug targeting known (e.g., alpha-synuclein, APOE, GBA) or emerging genetic or neuropathological targets and mechanisms implicated in LBD.

Recommendation 8 – Priority 4. Identify mechanisms of selective vulnerability, disease heterogeneity, disease spread/propagation, and interaction with other age-related pathologies as therapeutic targets. (5-7 years)

- A major recent conceptual framework for how we think about neurodegenerative diseases is the proposal that many of these disease proteins can undergo cell-to-cell spread between brain regions in wild type animal models in the context of LBD, and some human studies even suggest they may spread to the peripheral nervous system. Thus, roles of genetic risk factors from genome-wide association and exome sequencing studies can be interrogated in animal models where the levels of these genetic risk factors are manipulated. Whether α -synuclein has the ability to spread in general or only across certain types of cells is unknown. Further, the molecular mechanisms for the uptake, intracellular trafficking, degradation, and release of α -synuclein preformed fibrils versus LB and -GCI α -synuclein strains in neurons and oligodendrocytes are unknown, as well

as brain vs. periphery. It is also unclear whether α -synuclein directly interacts with other proteins that are known to aggregate (e.g., β -amyloid, TDP-43, tau) and/or vascular pathology to trigger LBD pathology. Research to understand how LBD pathology develops and progresses is critical for development of LBD specific animal models and therapeutics. These studies would move forward new mechanistically tractable targets that could be engaged for clinical studies.

- This recommendation recognizes the need to develop more complete animal and cellular models of the molecular pathology and symptomatology of LBDs. New models are needed that identify key processes involved in neuronal damage, vascular changes, and protein deposition (see recommendation 1) having synergistic translatability to human studies on LBD. Such models will need to be able to identify the key pathways mediating the propagation of toxic protein assemblies between cells in appropriate, physiologically relevant, context.
- A more complete understanding of why some neurons are vulnerable to toxicity evoked by α -synuclein assemblies while others remain resistant (i.e., selective vulnerability) is needed. Studies should identify the anatomical, biochemical, and molecular underpinnings of brain regional differences in LB pathology associated with variable behavioral outputs in human brain as well as animal models that are relevant to human clinical phenotypes. Where feasible, biospecimens and data from humans, including PDD and DLB patients should be used for validation of findings (see recommendations #1, #2, and #3) for important preclinical work in therapeutic development
- Identifying mechanisms by which α -synuclein, tau, and β -amyloid pathologies interact in the intact brain is a critical step towards a fuller picture of the complex pathophysiology of LBDs. Development of LBD models in which more than one pathology is present either within the same cells or in proximate cell populations should be prioritized. These studies should also account for potential interaction and/or additional independent association of aging and related factors (see recommendation #2). This preclinical work will inform the potential role for therapeutic strategies targeting multiple pathologies in LBD.
- Studies of genetic and molecular interactions of α -synuclein and tau cross-seeding and resultant spread patterns of both pathologies will inform selective vulnerability in human brain. (See recommendation #6)
- Contributions of immune-mediated mechanisms and inflammation in LBD pathogenesis and cellular vulnerability should be investigated and agents that alter or reduce central inflammation should be tested in model systems described here.
- There is a need for use of one or more preclinical models to explore potential efficacy of newly discovered and developed compounds, including systems based on human neurons and/or organoids derived from patient stem cells and suitable animal model systems that mimic the multi-proteinopathy substrate of the LBD spectrum.
- There is also a need for enhancing and leveraging infrastructure for scalable, efficient means to support preclinical drug development that arise from these mechanistic studies, This infrastructure that includes screening, confirmation, lead optimization, efficiency and/or toxicology evaluations should be designed to account for the selective vulnerability, disease heterogeneity, disease spread/propagation, and/or interaction with other age-related pathologies that encompass the full spectrum of LBD.

Multiple Etiology Dementias (MED)

Detection and Diagnosis of Cognitive Impairment and MED

Recommendation 1 – Priority 1. Evaluate pragmatic approaches to objectively detect cognitive impairment and link to quality care when a patient, care partner, or clinician reports cognitive, behavioral or functional changes. (3 - 5 years)

- Conduct pragmatic trials to improve the detection of cognitive impairment, including mild cognitive impairment and dementia, for patients and their families in primary care and other clinical settings. Approaches should focus on the detection and characterization of cognitive impairment syndromes but not, for the purposes of this

specific recommendation, differential (etiological) diagnosis. Paradigms being studied should be practical (e.g., time efficient and with easy to interpret results) and may use existing or new neuropsychological and functional assessment tools. Trials must also include methodology to ensure that cognitive impairment detection is linked to quality care, including, but not limited to, diagnostic services, specialty referrals and caregiver support. While most studies should be conducted in primary care, evaluation of detection paradigms may also be conducted in other clinical or home and community-based settings where there is a high prevalence of undetected cognitive impairment, and where improved detection is likely to have benefits for patients and their families. Trials must be adequately powered and include populations with known health disparities as a central focus.

- Develop and evaluate interventions that expand the capacity of primary care and home and community-based service organizations to improve care during and immediately after a diagnosis is made in primary care. Interventions may include electronic health record (EHR) decision support for the diagnosing provider, clinical services designed to fill gaps in diagnostic care (e.g., involving consultation to the family by a nurse, social worker, or community health worker), and primary care education that improves basic diagnostic and management skills regarding later-life cognitive disorders.
- Conduct research to identify and address structural barriers to the timely detection, diagnosis and care for populations experiencing health disparities and for individuals with pre-existing conditions that may alter performance on brief assessments (e.g., brain injury, Down syndrome, serious mental illness, sensory impairment). In addition, conduct research on the social and cultural differences across populations that can inform how best to detect, diagnosis, and support individuals and families.

Recommendation 2 – Priority 4. Evaluate the benefits, burdens, and harms of screening for cognitive impairment in older adults in the absence of a patient, care partner or clinician report of cognitive, behavioral or functional changes. (5 - 7 years)

- Evaluate the impact of screening community-dwelling older adults without recognized signs or symptoms of cognitive impairment during the Annual Wellness Visit or other clinical encounters on important patient, caregiver, and societal outcomes, including psychological well-being, decision-making, advance care planning, healthcare costs and utilization, and caregiver outcomes.
- Studies evaluating the impact of screening must include methodology to ensure that patients who screen positive are linked to diagnostic services and quality care, and should compare the impact of different diagnosis and care strategies on outcomes (benefits, burdens, and harms).
- Conduct trials that could help determine which populations optimally benefit from screening, as well as those who may be more likely to experience harms, including a comparison of adults with and without report of cognitive/behavioral/functional changes.
- Whenever possible, include primary or secondary outcomes from family members, caregivers, health care providers, health care systems, payers, and other stakeholders in screening studies to evaluate the breadth and diversity of impact on population screening for cognitive impairment.
- Conduct validation studies on brief cognitive assessments in primary care and home and community-based settings that minimize the referral biases inherent in validation studies conducted in specialist and other referred settings. The tools selected for these studies must have strong evidence for accurate early detection (e.g., mild cognitive impairment) in diverse populations, and clear feasibility for primary care workflows.

Recommendation 3 – Priority 3. Conduct multimodal clinical and translational research to support the identification of multiple etiologies in diverse populations. (5 - 7 years)

- Promote observational studies with deep phenotyping in diverse populations to characterize the status of the common pathobiologies of later life underlying cognitive impairment, including their combinations, and to map novel pathobiological entities using neuropathological studies.

- Conduct studies to identify risk factors (including infectious disease, metabolic disorders, and traumatic brain injury), prevalence estimates, sex-specific mechanisms, genetic ancestry, and clinical phenotypes of each pathobiology as well as their combinations. Life course factors, including social and environmental determinants of health, must be measured systematically and evaluated for their impact on disease risk and prevalence estimates. Studies must preferentially include populations most at risk for AD/ADRD and disparities in diagnosis and care, including racial/ethnic minorities and people with Down syndrome.
- Validate multi-biomarker approaches to obtain a full antemortem etiological profile of persons with cognitive impairment that also incorporates genetic modifiers, the effects of sex, and social, environmental, and behavioral factors.
- Develop and implement clinical pathways that identify clinically actionable signs and symptoms of multiple etiologies, prioritize the early and appropriate identification and stratification of patients for disease-specific therapies and clinical trials, facilitate access to differential diagnosis for non-AD dementias including prion disorders, and track progression over time. Prioritize approaches with potential for scale and to reduce inequities in access to diagnosis in AD/ADRD for racial and ethnic minority populations that are at higher risk for disease. Studies must engage community partners and may be primarily based in community settings to foster inclusive enrollment but are also encouraged to prioritize participation in deep phenotyping (e.g., multimodal imaging, neuropathological examinations, and other diagnostic tests) that may only be available at specialist centers. The economic impact of earlier differential diagnosis should be evaluated.

Basic Research in MED

Recommendation 4 – Priority 2. Advance basic research on the common and interacting risk factors and mechanisms of multiple etiology cognitive impairment and dementia in diverse populations. (3 - 7 years)

- Define interactions at the molecular and cellular level of the common and newly identified pathobiologies of later life cognitive impairment including proteinopathies, inflamm-ageing, immunosenescence, prion-like seeding/spreading and other factors that lead to cognitive decline (e.g., psychiatric disorders, substance abuse, traumatic brain injury, metabolic disorders, sleep abnormalities, social disadvantage, and more) in diverse population.
- Define molecular signatures of vulnerable vs. resilient neuronal populations as an approach to inform on mechanisms of cell vulnerability.
- Prioritize innovation to address technological gaps that represent barriers to progress in basic research on common mechanisms of MED (e.g., human iPSCs).
- Prioritize creation of multi-disciplinary, multi-sector, multi-career stage teams to address both the heterogeneity and common mechanism questions of MED.

Interventions and Treatments for MED

Recommendation 5 – Priority 1. Conduct clinical studies on approved or promising interventions and treatments to mitigate risk for cognitive decline. (5 - 10 years)

- Conduct inclusive and pragmatic clinical trials in hospital and community-based settings where risk factors for cognitive decline can be appropriately targeted for intervention. Interventions may target, but are not limited to, exercise, cardiovascular risk reduction, sleep disorders, use of anti-cholinergic medications, treatment of hearing loss, prevention of delirium, allostatic load, and treatment of mood disorders. Studies should include participants at high risk for cognitive decline as well as individuals at earlier phases of risk, 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.
- Prioritize the development of practice-based research networks to facilitate the translation of effective assessment and intervention strategies into practice at a large scale, to achieve greater diversity in research

participation, to target communities with the highest prevalence of risk factors, and to generate research results that are more generalizable to the real-world.

- Evaluate the health risk and effectiveness of AD therapeutics in MED (e.g., anti-amyloid therapies) among patients with diverse cultural and socioeconomic backgrounds, accounting for genetics and comorbidities.

Recommendation 6 – Priority 4. Implement and evaluate outcomes for effective dementia care programs that support persons living with dementia and their caregivers, including those of socially, ethnically and racially diverse populations. (3 - 7 years)

- 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, leverage facilitators, foster community engagement, achieve greater health equity, evaluate care quality, and impact outcomes that are identified as most important by people and families living with dementia and with attention to distinct social and cultural populations.
- Conduct implementation studies in multiple and varied real-world settings 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 identify and address sex and gender differences and the unique needs of populations experiencing health disparities.
- Develop and evaluate payment models that will promote dissemination and sustainability of effective dementia care programs in fee-for-service Medicare, Medicare Advantage, and Alternative Payment Models, including provision of needed services by community-based organizations.
- Develop and evaluate core components of culturally sensitive collaborative dementia care models that deliver high quality care.

Dementia Capable Workforce

Recommendation 7 – Priority 2. Promote education and training on multiple etiology cognitive impairment and dementia to increase the dementia capable workforce, advance researchers including from groups underrepresented in science, and foster inclusive research practices. (5 - 10 years)

- Develop, implement, and evaluate training programs in different dementia syndromes for the current and emerging generation of all healthcare professionals who work with older adults, with the goal of increasing the dementia-capable workforce across disciplines. Training programs should deepen understanding in the heterogeneity of cognitive impairment and dementia and its distinct causes.
- Prioritize mentorship and provide research opportunities in multiple etiology cognitive impairment and dementia for the current and emerging generation of researchers including from groups underrepresented in science, in ways that promote their integration and inclusion into a multicultural educational setting.
- Promote education of researchers in recruiting and retaining diverse research participants from populations that experience health disparities into research studies on multiple etiologies.

Data Harmonization

Recommendation 8 - Priority 3. Conduct research to improve pre- and post-data collection harmonization and sharing practices across multiple etiology cognitive impairment and dementia studies. (5 - 10 years)

- Develop and evaluate common data elements and standardized consent language required for multiple etiology dementia for inclusion in ongoing and future studies. Development should synergize with other ongoing efforts, such as in TBI.
- Identify barriers and facilitators to widespread incorporation of common data element usage and sharing of data and findings to the broader community.

- Promote incorporation of common data elements into data collection for observation and intervention studies that incorporate phenotypic data. Document and promote neuroimaging acquisition protocols. Promote biospecimen processing and storage protocols to align data capture across studies, as appropriate, including sample processing, sample storage and assays. Promote inclusion of forms, instruction manuals and data dictionaries to accompany any data sharing/ centralized reporting of data. Examine pragmatic, streamlined tools that protect participant rights and privacy while enabling the tracking of research participation of individuals across centers and studies.
- Use harmonized data to investigate differences in dementia risk factors, dementia phenotypes, and dementia outcomes in clinic- and community-based studies and with a focus on multiple etiologies.
- Develop and evaluate training opportunities to promote methodologically rigorous and efficient data-sharing for current and emerging generations of researchers, focused on foundational and advanced data harmonization methods to promote the use of shared data to generate new insights and findings across multiple etiology dementia.

Special Topic: Post-TBI AD/ADRD

Recommendation 1 – Priority 1. Promote collaboration among TBI and dementia researchers through working groups, retrospective and prospective data and measurement harmonization, and interdisciplinary research. (1 - 3 years)

- Convene a working group of stakeholders from the TBI & Multiple-etiology dementia communities to evaluate the extent to which current knowledge (e.g., mechanistic pathways, environmental and genetic risk factors, independent and interactive effects of multiple proteinopathies on pathological proliferation and AD/ADRD clinical manifestation) in AD/ADRD can be applied to the study of dementia after TBI, and how TBI (an AD/ADRD risk factor with a “time zero”) contributes to AD/ADRD.
- Harmonize existing data across longitudinal TBI outcome studies and TBI-AD/ADRD studies using data harmonization and advanced psychometric methods; improve data annotation in existing studies to facilitate cross-study comparisons.
- Maximize measurement harmonization across longitudinal TBI and dementia clinical cohort studies by establishing and prospectively collecting common data elements (CDEs; clinical, psychometric, neuroimaging, fluid biomarkers) to facilitate comparisons and data sharing.
- Encourage collaboration between clinical researchers, biostatisticians, epidemiologists, data scientists, and implementation scientists to incorporate multidimensional/multimodal data, employ causal inference methodologies, and maximize clinical translatability in the study of TBI-AD/ADRD.

Recommendation 2 – Priority 2. Characterize the heterogeneous clinical phenotypes and time course of progressive dementia following varied TBI exposure histories by developing methods to quantify lifetime head trauma exposure and diagnose post-TBI dementias. (1 - 10 years)

- Establish and validate a quantitative index of lifetime head trauma exposure.
- Establish and validate a provisional clinical definition of post-TBI dementia(s) that distinguishes chronic static TBI-related symptoms from a progressive neurodegenerative disease as measured by clinical decline and changes in clinically accessible biofluid and imaging biomarkers.
- Conduct longitudinal studies to characterize the clinical phenotype, phenotypic heterogeneity, clinical course, environmental and genetic protective factors, and effect modifiers (e.g., post-traumatic stress disorder, sleep disorders, etc.) of post-TBI AD/ADRDs in samples of men and women from diverse backgrounds with a range of exposure histories, as characterized by age at injury, severity, mechanism, and chronicity.
- Develop and validate TBI-AD/ADRD biomarkers (e.g., psychometric, wearable sensors, imaging and biofluid) to non-invasively identify progressive post-TBI AD/ADRD pathologies, monitor disease progression over time,

elucidate pathological substrates of domain-specific clinical decline, and predict resilience to cognitive decline and to behavioral disorders.

Recommendation 3 – Priority 3. Establish research infrastructure, including multimodal longitudinal studies with autopsy endpoints that employ standardized CDEs and methodologies, to study post-TBI AD/ADRD. (1 - 3 years)

- Enrich the design of longitudinal TBI studies to include multimodal clinical and biological/biochemical endpoints relevant to neurodegenerative diseases and incident dementia diagnostics. Similarly, enrich AD/ADRD studies with expanded lifetime TBI ascertainment methods.
- Establish clinic- and community-based prospective studies of individuals with diverse head trauma exposure histories (e.g., single TBI, repetitive head trauma in the contexts of contact sports, military service, domestic violence, and intimate partner violence (IPV)) for longitudinal study using multimodal clinical evaluations and neuroimaging and neuropathological endpoints to inform clinically actionable diagnostics for post-TBI AD/ADRD.
- Expand efforts to build and enhance existing brain biorepositories to include optimally preserved tissues from individuals with diverse head trauma exposure histories (e.g., a history of participation in contact sports or military service, single or repetitive TBI of all severities) and clinical and/or postmortem neuroimaging, medical records, and CDE structured post-mortem interview data.
- Launch nationwide inter-agency efforts to expand and standardize the use of NINDS CDEs for Human Neuropathological Studies in TBI for harmonized neuropathological evaluation and postmortem clinical characterization across tissue banking centers. Promote tissue sharing and develop digital pathology infrastructure to facilitate research across tissue banks.

Recommendation 4 – Priority 4. Basic and translational research to elucidate the mechanistic pathways, development, and progression of post-TBI AD/ADRD neuro-pathologies to better understand clinical symptom expression. (7 - 10 years)

- Promote collaboration between clinical and translational researchers to accelerate development, standardization, and validation of clinically relevant experimental models of TBI that accommodate diversity of injury biomechanics and accurately reproduce their distinct and interactive acute and chronic neuropathological and behavioral sequelae.
- Deploy traditional, quantitative, and/or molecular (omics) approaches to deeply characterize post-TBI neuropathologies, identify selectively vulnerable/resilient cells/regions, and determine underlying pathological mechanisms common with, or unique from, other multi-etiology dementias and neurodegenerative disorders.
- Determine how the relative extent, distribution and temporal progression of individual neuropathologies (and their potential interactions) contribute to the clinical manifestation of dementia following TBI. Identify how TBI exposure history (e.g., mechanism and severity of injury, number of exposures etc.) influences the nature and evolution of autonomic and central nervous system pathologies in humans and experimental models.
- Identify intrinsic (e.g., genetic, proteomic) and environmental (e.g., socioeconomic, educational, lifestyle) factors that confer resilience to cognitive decline and behavioral disorders after TBI and during aging.

Special Topic: LATE (TDP-43 in Common Late-Onset Dementias)

Recommendation 1 – Priority 1. Define LATE (pathologic, clinical, genetic, molecular) classification and diagnostic boundaries across FTLD-TDP, AD and other dementia related pathologies and their syndromes to enhance diagnosis, research, and awareness. (2 - 7 years)

- Develop definitions and classification for distinguishing LATE from other TDP-43 proteinopathy related disorders including FTLD-TDP.
 - Using data-driven methods, define the pathologic boundaries to aid disease classification and to enhance basic and translational research.
 - Develop LATE biomarkers that can specifically refine clinical boundaries.

- Contrast TDP-43 disorders through clinical, pathologic and basic science studies to determine commonalities/differences across TDP43 proteinopathy disorders.
- Study clinical and pathologic intersections (including known pathologies such as ADNC and vascular disease), across differing TDP-43 proteinopathy diseases.
- Study ultrastructure to determine TDP-43 proteinopathy conformations/alterations that differ between disorders.
- Investigate genetic variants and molecular changes associated with LATE-NC (e.g., GWAS, differential gene expression).
- Compare disease classes using genetics and other -omic studies to provide insights on the classification/boundaries across TDP-43 proteinopathy diseases.
- Define the relationships between LATE and non-TDP43 dementia pathologies including ADNC, Lewy body disease, and cerebrovascular disease
 - Identify shared and distinct features of LATE and AD, using multiple avenues including genetic, molecular, epidemiologic, pathologic, and clinical approaches
 - Clarify the relationship of LATE with LBD and vascular disease, using genetic, molecular, epidemiologic, pathologic, and clinical approaches
 - Investigate determinants of comorbid LATE-NC in individuals with ADNC
- Increase awareness of LATE across both research and clinical practice including trials and basic patient management.
 - Increase awareness of LATE with respect to clinical and pathologic AD
 - Encourage LATE clinical trials and incorporate awareness of LATE into clinical trials for other dementia disorders
 - Encourage both human and other disease models to inform one another on the clinical and biological features of LATE.

Recommendation 2 – Priority 2. Develop biomarkers, classifiers, and risk profiles to establish in-vivo diagnostic criteria for LATE in persons without cognitive symptoms and in persons with amnesic or other relevant late-life dementia syndromes. (2 - 7 years)

- Develop, harmonize and expand community cohorts combining neuroimaging, biofluids, and genetics with autopsy to promote clinical-pathological studies that will better establish phenotypic patterns associated with LATE-NC.
- Identify distinguishing cognitive and behavioral features associated with LATE-NC alone or in the presence of co-pathology.
- In the absence of a biomarker specific to the molecular pathology of LATE-NC (i.e., TDP-43), develop classifiers that provide probabilistic metrics of the presence of LATE-NC leveraging one or more existing modalities (e.g., MRI, PET, biofluids).
- Define and incorporate genetic associations of LATE/LATE-NC in the setting of LATE-NC alone or with co-pathology in risk models and/or classifiers.
- Ultimately develop biofluid (e.g., blood or CSF) or neuroimaging (e.g., MRI, PET) biomarkers that show good discrimination of the molecular pathology of LATE-NC (i.e., TDP-43).

Recommendation 3 – Priority 3. Build new experimental models that incorporate aging with behavioral, pathologic, and molecular phenotypes of TDP-43 proteinopathy or hippocampal sclerosis, to advance knowledge and enable testing of therapeutics. (5 - 8 years)

- Develop and characterize models that incorporate aging designed to simulate LATE-NC, i.e. TDP-43-dependent, clinical, pathologic and molecular phenotypes in common dementias. This may include
 - virally transduced animal models using aged animals

- Knock-in, gene-edited or stress induced models.
- Transgenic animal models that express wild-type or mutant TDP-43 or develop hippocampal sclerosis. Consider using inducible promoters to drive transgene expression in the disease relevant cell type(s) with attention to appropriate time of life of the animal.
- Vascular contributions to TDP-43 proteinopathy and/or hippocampal sclerosis
- Interaction between TDP-43 and tau, alpha synuclein, amyloid proteinopathies and other pathologic proteins.
- Glial/neuron inflammatory contributions to TDP-43 proteinopathy, specifically in aging
- Study prion-like transmission of pathological TDP-43 species that simulate anatomical progression of LATE-NC, TDP-43 pathology in common dementias.
- Develop translationally actionable cellular and animal models to enable preclinical therapeutic development and testing pipelines in LATE-NC.

Recommendation 4 – Priority 4. Study the intersection of hippocampal sclerosis (HS) and LATE-NC, within and across all disciplines (clinical, pathologic, diagnostic, genetic, molecular, etc.) and consider the roles of vasculopathy, senescence, and other potential contributing factors. (2 - 7 years)

- Develop a clear definition and consensus-based protocol for pathological categorization of HS (because of important association with LATE-NC) to provide “gold standard” for pathologic categorization, and a rigorous foundation for future study of HS via genetics, clinical-pathologic, and imaging studies.
- Study LATE with versus without HS via clinical-pathological and genetic correlations.
- Develop standardized and biomarkers/risk profiles to identify HS clinically.
 - For a clinical biomarker, antemortem and postmortem imaging studies may link specific MTL MRI changes (shape, signal, texture) with HS.
 - Biomarker/risk profiles for HS should be compared with other pathologically confirmed causes of MTL pathology.
 - Risk profiles could include other modalities including genetic polymorphisms, risk factors, plasma biomarkers.
- Identify molecular, genetic, clinical and pathologic drivers of LATE-NC, with versus without HS, and with or without vasculopathy, and the role of senescence.
 - Determine the nature of the small vessel and vessel wall constituent changes seen in LATE+/-HS if this differs from SVD without LATE +/- HS.
 - Explore the mechanism for the common co-occurrence of LATE-NC, SVD, and HS, and determine if TDP-43 proteinopathy promotes vasculopathy "upstream" of HS or vasculopathy promotes both LATE-NC and HS or is there an alternative mechanistic pathway.
 - Study vasculopathy in LATE+HS and its link to aging and senescence mechanisms.
 - Explore common interconnected risk factors for LATE-NC, HS, vasculopathy.

Special Topic: Impact of COVID-19 on AD/ADRD Risk and Outcomes

Recommendation 1 – Priority 1. Establish research infrastructure enabling clinical, epidemiological and basic research studies of COVID-19 impact on AD/ADRD risk and outcomes, prioritizing disproportionately affected populations and clinical trials readiness. (1 - 3 years)

- Establish new and leverage existing clinical cohorts for longitudinal prospective studies to examine the impact of COVID-19 on AD/ADRD risk and outcomes, prioritizing cohorts that oversample minoritized groups that have been disproportionately affected by both COVID-19 and AD/ADRD, and prepare these cohorts for clinical trials with repurposed or newly developed treatments. Studies should center the experiences of groups that have been historically marginalized and include careful ascertainment of prevalent circulating virus variants in the community at the time of infection.

- Define common data elements (including multilingual), develop a database and data and material sharing avenues, and harmonize collection of social and structural determinants, clinical, neuropsychometric, and imaging data and biosamples (including dried blood spot, plasma, serum, PBMCs, CSF supernatant, CSF cell pellet, saliva, DNA and RNA) using best practices for tissue collection across cohorts to facilitate analyses across various populations.
- Encourage national autopsy, brain donation and fibroblast collection programs from persons infected with SARS-CoV-2 with and without chronic neuropsychiatric sequelae to study the molecular, pathological and epigenetic consequences of infection and factors underlying, markers of susceptibility and resilience.
- Design and validate protocols that (i) examine brain regions and systems known to be especially vulnerable to acute and post-acute sequelae of SARS-CoV-2 (PASC) (e.g. olfactory bulb, autonomic nervous system, cerebral vasculature), (ii) facilitate high quality research among linguistic, racial, and cultural groups that have been disproportionately affected, incorporating individual and internalized (e.g. coping mechanisms, behavior, genetics) and systemic/structural (e.g. racialized policies and institutions, social supports, access to medical care, vaccines, built environment, occupational exposures) factors, (iii) permit accurate assessment of diagnosis and extent and type of cognitive impairment and brain injury, and iv) consider comorbid symptoms that could impact cognitive assessment such as dyspnea and fatigue.

Recommendation 2 – Priority 2. Characterize the clinical phenotype and develop diagnostic criteria for neurocognitive impairment and dementia associated with COVID-19 in those with and without neurocognitive impairment/dementia prior to infection. (1 - 7 years)

- Evaluate the direct and indirect impact of SARS-CoV-2 infection on brain structure and function utilizing neuroimaging, blood and CSF biomarkers. We recommend a special emphasis on (i) persistent cognitive, behavioral, and mood impairments, (ii) amplification and acceleration of dementia risk, and (iii) assessment of smell/taste due to high prevalence of persistent hyposmia, anosmia and dysgeusia in survivors.
- Define and describe the temporal progression of clinical neurocognitive impairment and dementia (CID), including the wide spectrum of acute and delayed objective and subjective neurological manifestations (e.g., “brain fog”), in the presence and absence of other PASC symptoms.
- Determine neuropsychological profiles (e.g., dysexecutive vs. amnesic) as well as stress, behavioral and mood changes in CID associated with COVID-19 in older adults with AD/ABDRD biomarker information.
- Include cognitively unimpaired persons, as well as persons with prior diagnosis of mild cognitive impairment (MCI) and/or dementia into the future studies, since morbidity, mortality, and other impacts may differ between these groups.
- Examine role, if any, of covert and overt (clinically symptomatic) AD/ABDRD pathology on modifying the risk and severity of COVID-19 infection (e.g., role of genetic factors underlying susceptibility to both SARS-CoV-2 and ABDRD such as APOE4, OAS1 and TMEM106B).
- Examine if type and severity of CID and acceleration of cognitive decline in persons with AD/ABDRD (including VCID) relate to severity of acute illness, vaccination type and status, and treatment.
- Examine role of structural, social, environmental and behavioral factors on characteristics of CID and risk of AD/ABDRD after SARS-CoV-2 infection.

Recommendation 3 – Priority 3. Explore interaction of social, structural, and systemic inequalities, comorbidities and social and medical interventions with risk and neurocognitive sequelae of COVID-19. (1 - 5 years)

- Prioritize evaluation of structural and social determinants of health and research to understand and eliminate disparities in CID and other neurological sequelae of COVID-19 by race, ethnicity and gender, with engagement and inclusion of historically marginalized populations at higher risk for COVID-19 infection and sequelae.
- Include careful ascertainment of exposure to SARS-CoV-2, infection, illness and treatment details, access to care, pandemic-related and unrelated barriers to access, social support, environmental factors in ongoing cohort

studies of cardiovascular, cerebrovascular, and other neurological conditions such as brain aging, AD/ADRD, VCID and stroke.

- Include culturally and linguistically valid, harmonized assessments of neurological, cognitive and psychiatric consequences in ongoing clinical trials of COVID-19 preventive interventions and treatments.
- Facilitate electronic health record collation and analyses to identify unsuspected, potentially beneficial or harmful effects of medications administered for other conditions (e.g., ACEI, ARBs) on risk of ADRD in post-COVID setting.
- Examine the impact of policy interventions such as caregiver support, paid family leave, access to health care, housing (e.g., rent abatement, evictions protections, household energy insecurity), and non-pharmacological supports on risk and progression of CID after COVID-19 infection.
- Understand the role of availability, access, uptake, barriers, and effectiveness of innovative health technologies including telemedicine and artificial intelligence-based solutions with focus on reducing racial and geographic disparities in impact of COVID-19 on AD/ADRD.

Recommendation 4 – Priority 4. Advance understanding of basic mechanisms underlying neurocognitive impairment and dementia due to COVID-19 in order to develop biomarkers, risk profiles, and the foundation for early interventional trials. (1 - 7 years)

- Understand the biological pathways implicated in CID including (i) direct and indirect effects of SARS-CoV-2, (ii) similarities and differences between response to this virus compared to other corona viruses and response to systemic infections and illnesses of comparable severity, and (iii) similarities and differences in pathophysiology of subacute "long COVID" and CID (both elements of PASC).
- Develop model systems corresponding to various clinical presentations of SARS-CoV-2 infection to explore pathophysiology and possible interventions.
- Explore model systems enabling SARS-CoV-2 infection in existing AD/ADRD models to determine direct and indirect effects of viral infection on molecular changes at the cellular and tissue levels and on brain structure, cognitive and behavioral outcomes.
- Conduct long-term studies of COVID-19 survivors from racial, ethnic, economic, and geographic groups who were put at higher risk for COVID-19, and survivors of severity-matched non-COVID illness, to compare and contrast brain injury (as assessed by CSF and blood biomarkers, brain imaging including 3T MRI protocols, MR spectroscopy, and 7T MRI, and PET imaging including for classic AD markers of amyloid/tau and markers of synaptic density and microglial activation for assessment of neuroinflammation, neurodegeneration, blood brain barrier, endothelial and microvascular injury) and to correlate these markers of brain injuries with sensorimotor, cognitive, behavioral symptoms, either persistent or progressive.
- Explore the age, sex, genetic, biomarker (circulating, multi-omic, imaging), behavioral, psychosocial (including family and social network, occupation, income, access to medical care and support, early life exposures), environmental, immune, vascular, metabolic factors, as well as viral variant, vaccination, treatment, social (neighborhood safety and cohesion, housing and food insecurity, transportation infrastructure, educational quality) and structural (e.g., racism, sexism, classism, homophobia, able-ism) factors and policies that increase or mitigate risk of CID and subsequent AD/ADRD.
- Develop and study potential interventions against an adverse SARS-CoV-2 impact on AD/ADRD, based on early translational studies, including targeting neuroinflammation, amyloid and/or tau aggregation, viral persistence, and other mechanisms that emerge as the data accumulate.
- Facilitate rapid implementation of candidate drug screening, discovery and treatment trials to mitigate impact of COVID-19 on AD/ADRD risk and progression.