Alzheimer's Disease-Related Dementias (ADRD) Conference 2013
Prioritized Research Recommendation Milestones

Topic 1: Multiple Etiology Dementias: The Public Health Problem and Improving Recognition across the Spectrum		
Focus Area 1: Differential Diagnosis		
Milestone Recommendation	Success Criteria	Timeline[1]
1. Develop clinical algorithms for detection of neurodegenerative dementias and vascular contributions to cognitive impairment and dementia (VCID) in (a) primary care, (b) general neurology, and (c) general psychiatry outpatient settings; and clinical algorithms for referral to specialists in appropriate cases that also might involve consultations using novel technologies.	1. Develop and/or apply clinical algorithms for detecting primary dementias in outpatient general neurology. The algorithms should also be applicable to a primary care setting, and should yield appropriate referral guidance. Include a training component to support high quality clinical training for physicians and non-physicians.	1-3 years
2. Develop imaging and fluid biomarker algorithms to detect and differentiate AD and other dementias, and expand access to these algorithms in primary care settings.	1. Develop and/or apply one or more biomarker algorithms to detect and differentiate among AD and other dementias (e.g. but not limited to FTD, VCID, LBD) in a general neurology setting. This algorithm should also be applicable to primary care settings.	3-7 years
3. Develop clinical, imaging, and fluid biomarker algorithms for the rapidly progressive and potentially treatable dementias to enable recognition and referral to specialists.	1. Initiate at least one research study to develop biomarker algorithms for rapidly progressive dementias, and one study to develop biomarker algorithms for potentially treatable dementias, to enable recognition in general neurology and primary care settings and facilitate referral to specialists.	1-3 years
Focus Area 2: Epidemiology		
Milestone Recommendation	Success Criteria	Timeline[1]
1. Conduct population-based studies of dementia prevalence and incidence in diverse ethnic groups and age ranges using imaging and fluid biomarkers.	1. Initiate at least one research study using biomarkers or contributing to biomarkers discovery within a health disparities population that specifically examines dementia prevalence and incidence.	1-3 years
2. Develop registries for enumerating and characterizing less common dementias, dementias in younger persons, rapidly progressive dementias, and potentially treatable dementias.	1. Establish at least one registry for enumerating and characterizing less common dementias, dementias in younger persons, rapidly progressive dementias, and potentially treatable dementias. The registry should implement efficient data acquisition and, when possible, leverage existing electronic medical records, for example, within large regional health care systems.	1-3 years

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3. Expand and broaden the accessibility of neuropathology services to cases of cognitive impairment and dementia outside of research centers. Link neuropathologic findings to development of clinical algorithms and biomarkers.	1. Develop and implement procedures to increase access by external sites to neuropathology services at specialized research centers. 2. Document increased number of research brain autopsies referred by external sites to specialized research centers. 3. Leverage this collaborative infrastructure to link neuropathologic findings to diagnostic and/or biomarker advances.	1-3 years

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Topic 2: Health Disparities		
Focus Area 1: Recruitment		
Milestone Recommendation	Success Criteria	Timeline
1. Initiate and leverage ongoing longitudinal community-based cohort studies of incident dementia in diverse populations incorporating imaging, fluid biomarkers, and autopsy.	1a. Identify and catalog ongoing diversity research cohorts, including associated biospecimens and clinical data, as well as potential diversity cohorts (e.g., cross sectional studies amenable to follow-up) that would strengthen research in the ADRDs, e.g. based on, but not limited to, race/ethnicity, socioeconomic status, or geography. Assess what steps are needed to assess and follow disparities in incident dementia in these cohorts/potential cohorts. 1b. Maximize diverse representation in dementia research by embedding sample collection (e.g. blood, CSF, & autopsy tissue) and clinical data in high impact research cohorts among those identified. To increase the range of co-morbidities represented, when possible, collection should emphasize samples based on the community or population, rather than memory clinics or other specialized medical settings. Facilitate wide sharing of the samples and clinical data for biomarkers discovery and other research. 1c. Enhance the power of diversity community-based research studies of middle age and older adults by developing, within the identified research cohorts, assessment tools for cognitive impairment and dementia and for neuropsychiatric status in diversity populations (guided by evidence from mixed methods studies to evaluate and improve population appropriate measures). These efforts should contribute to and be informed by leading edge development of best practices for assessing cognitive function, cognitive impairment, and dementia in diverse populations.	1.a: 1-3 years 1b, 1c: 3-5 years

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2. Use mixed methodology studies to improve assessment tools for disparities populations.	1. Use diverse community-based research cohorts and mixed methodology (e.g. including but not limited to clinical assessment, questionnaires, neuropsychiatric instruments, informant-based surveys, and adaptive psychometric tests) to develop best practices for assessing cognitive function, cognitive impairment, and dementia in diverse populations. These best practices will include validated tools for assessing AD and ADRD and tracking disease progression over time, and methodology for documenting salient symptoms and for understanding disease burden to individuals and family members/caregivers. Key priorities are that tools operate the same across time and populations, and that they facilitate harmonized comparison of assessment data among diverse populations, and, optimally, between existing and legacy assessment data. These best practices will reflect and account for how diverse populations understand and recognize dementias, and should address needs in primary care, specialized care, and for surveillance. 2. Facilitate harmonized comparisons among assessments of cognitive function, cognitive impairment, and dementia in diverse populations by developing and making available normative references for these developed using best practices for assessing cognitive function, cognitive impairment, and dementia in diverse populations.	3-5 years
3. Use community outreach methods to facilitate recruiting disparities populations into FTD and LBD clinical studies.	1. Conduct mixed methods research to develop strategies (e.g., specific language and outreach mechanisms/venues) to recruit study participants in diverse populations, based on how each population understands and recognizes AD and ADRD. 2. Develop guidelines for increasing diverse participation in ADRD clinical research. Such guidelines should address logistical barriers, e.g., transportation, cultural issues, and should suggest how to identify and leverage local initiatives, institutions, agencies, and other organizations focused on health outcomes in disparities populations.	5-7 years

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4. Evaluate under-diagnosis and implement surveillance for ADRDs to detect incidence and monitor trends in disparities populations.	1. Complete at least one study embedded within large scale community-based health surveillance systems, including potentially primary care, designed to utilize and validate simple assessment tools applicable for a surveillance setting. 2. Initiate a national surveillance plan to monitor differences in AD and ADRD incidence, prevalence, and long term outcomes among racial/ethnic, socioeconomic, geographic and other population differences relevant to disparities. Develop and release a consensus report on risk factors, predictors, consequences, and levels of under-diagnosis of ADRD among disparities populations.	5-7 years
Focus Area 2: Advancing Treatment and Prevention Strategies		
Milestone Recommendation	Success Criteria	Timeline
1. Enhance the design of all trials of vascular health interventions to improve their application to diverse populations.	1. Develop and make widely available guidelines for brain health assessments in clinical trials of vascular interventions in diversity populations. These guidelines will include standardized outcome measures relevant to cognitive outcomes in diverse populations (e.g. clinical, imaging, neurological, cognitive, and vascular) that will facilitate meta-analyses of intervention studies of vascular health in diverse populations, and will draw from expertise in related fields, e.g. stroke, lipid metabolism, cardiovascular intervention, and immune function. The guidelines should provide tiers of vascular, cognitive, and other relevant assessments that are optimized for resources, such as caregiver time, and technology available at sites relevant for cognitive impairment and dementia research in diversity populations. Guidance should also include best practices for recruitment in diverse populations 2. Implement and validate, in vascular health intervention studies that include diverse populations, assessments of standardized outcome measures relevant to AD and ADRD.	5-7 years

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2. Assess lifecourse risk factors for cognitive decline and ADRDs among disparities populations.	1. Determine whether changes in risk factors for dementia, both traditional and novel, occur over the lifecourse in diversity populations in at least one study. Identify critical periods of life and critical lifestyle and other parameters with respect to dementia prevention.	1-3 years
3. Estimate disparities in health burden of ADRDs and risk factors among disparities populations.	1. Determine whether the prevalence of AD and ADRD risk factors (e.g., vascular, behavioral, environmental, or social risks), and their causal impact on outcomes, differs across disparities populations. Use this information to estimate the highest impact intervention targets (i.e., population burden associated with each risk factor) in disparities populations.	1-3 years
4. Identify environmental and genetic factors that modify incidence, presentation, and long-term outcomes of ADRDs in disparities populations.	1. Establish guidelines for best research practices for understanding gene-environment Interactions as contributors to AD and ADRD disparities; these guidelines should address a full range of considerations, including statistical, theoretical, and practical 2. Complete at least one study in diverse populations that integrates genetic and environmental risk factors, and assesses their interactions. This study should be powered to evaluate whether genetic predictors of risk for dementia are similar or different across diverse populations, incorporating measures of environmental risk factors. Facilitate data availability for future research (e.g., via dbGaP). 3. Complete at least one study that assesses in disparities populations the co-occurrence and joint effects of social, environmental and biological (including genetic) risks for cognitive impairment and dementia. Assess such risk interactions for similarities and differences across diverse populations (considering dimensions of race/ethnicity, SES, and geography).	7-10 years

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Topic 3: Lewy Body Dementias (LBD): Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD)		
Focus Area 1: Establish Longitudinal Cohorts with Common Measures, Culminating in Autopsy Studies		
Milestone Recommendation	Success Criteria	Timeline
1. Initiate clinical trials for DLB and PDD using existing and newly developed symptomatic therapies that address key symptoms that impact patient function and the burden put on caregivers.	1. Initiate at least 1 new clinical trial that leverages an existing clinical network infrastructure and one or more FDA-approved drugs for symptomatic improvement of one or more of the core clinical features of DLB and PDD.	1-3 years
2. Create longitudinal clinical, biological, and imaging resources for DLB and PDD from the earliest stages to autopsy studies to improve the accuracy of detection and diagnosis of DLB at the predementia or prodromal stage and to detect PD patients with a high risk of cognitive decline leading to PDD.	1. At least one new study that leverages one or more existing neurodegeneration and/or dementia cohorts to develop and establish research tools to study DLB and PDD. 2. Create or leverage existing resource(s) to collect and share for research standardized clinical and neuropsychological data from individuals with potential early manifestations of DLB, including dream enactment behavior (also known as rapid eye movement sleep behavior disorder), hyposmia, autonomic dysfunction and non-amnestic mild cognitive impairment.	1-3 years
Focus Area 2: Discover Disease Mechanisms through Brain Mapping and Genetics		
Milestone Recommendation	Success Criteria	Timeline
3. Using well defined cohorts with DLB or PDD who have come to autopsy, systematically map disease-specific changes in the brain, spinal cord and peripheral autonomic nervous system with state-of-the-art methods, including genomics, expression arrays, metabolomics and proteomics to identify underlying disease mechanisms that will guide future biomarker and therapeutic approaches.	1. Inventory and report on existing autopsy samples with clinically well-characterized brains with antemortem diagnoses of DLB or PDD that meet high likelihood DLB neuropathological criteria. This report, the "PDD and DLB Sample and Clinical Data Report", will also comment on quality and availability of all these samples and clinical data. 2. Hold a planning workshop, informed by the "PDD and DLB Sample and Clinical Data Report", to determine and propose an optimized implementation plan for mapping brain changes in LBD using the samples, data, and other resources available to best effect .	1-3 years

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4. Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that influence the risk and clinical features of DLB and PDD.	1. Identify families with multiple affected members of PDD and/or DLB for genomic analyses. 2. Definitive assessment of genetic risk architecture in clinically well-characterized patients with PDD or DLB and/or autopsy confirmed high likelihood DLB. 3. Convene a workshop of interested parties to address methodological issues needed to explore gene-environment interactions for DLB and PDD.	5-7 years
Focus Area 3: Develop and Validate Biological and Imaging Biomarkers		
Milestone Recommendation	Success Criteria	Timeline
5. Develop imaging approaches to enhance the diagnostic accuracy of DLB and PDD, detect latent and prodromal DLB and PDD, and monitor disease progression in natural history and treatment studies by integrating established and new imaging tools.	1. At least one new study to validate available and proposed imaging tools for the diagnosis and classification of DLB and PDD against longitudinally followed cohorts or autopsy confirmed cases. Include in this study emerging technologies, e.g. fMRI and molecular imaging of α-synuclein. 2. Convene a workshop in which analytical approaches and standardization of neuroimaging methods can be addressed to facilitate multicenter studies.	5-7 years
6. Use existing or new longitudinal case-control studies of individuals with DLB and PDD to develop biomarkers for Lewy-related pathologic changes, disease progression, and the relative amount of concurrent AD. As new markers of molecular disease mechanisms are discovered, incorporate them into biomarker studies for diagnosis of latent or prodromal disease and for monitoring molecular processes and their response to therapies.	1. Identify collections of tissue and biofluid samples from existing longitudinal case-control cohorts in which samples were collected in standardized protocols and in which the samples are linked to clinical data that includes DLB and PDD cases. 2. Initiate at least one large study to develop and validate novel biomarkers using well characterized DLB or PDD samples.	5-7 years

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Focus area 4: Model Disease Processes to Develop Potential Symptomatic and Disease Modifying Therapies		
Milestone Recommendation	Success Criteria	Timeline
7. Recognizing the importance of α-synuclein and AD pathophysiologic processes in DLB and PDD, new animal, cellular, and in vitro models are needed that recapitulate key features of these disorders with the ultimate goal of identifying strategies that can be carried forward into clinical trials.	1. Establish basic research studies focused on developing a better understanding of the basic science of LBD, e.g., but not limited to, alpha synuclein biology and how it is related to LBD, and beta-amyloid and alpha synuclein interactions. 2. Develop one or more new animal models that fit known molecular pathology of DLB and PDD. Optimally, new animal model/s will be informed by human based systematic mapping of DLB and PDD, and by results of biomarker studies.	3-7 years
8. Develop disease-modifying interventions based upon research discoveries.	1. Initiate one or more disease modifying clinical trials that prevent or alter disease processes using prospective therapies based on pharmaceutical approaches, gene therapy, regenerative medicine, surgical interventions, or other novel approaches.	7-10 years

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Topic 4: FTD and Related Tauopathies		
Focus Area 1: Basic Science: Pathogenesis and Toxicity		
Milestone Recommendation	Success Criteria	Timeline
1. Clarify the mechanism of tau pathogenesis and associated neurodegeneration.	1. Identify specific tau-related pathophysiological events, and corresponding targets, that contribute to neurodegeneration in humans with tauopathy. 2. Develop model systems that verify and enable testing of interventions for new therapeutic targets in tauopathy. 3. Determine the relationship between tau misfolding and assembly to spread of tau aggregation and neurodegeneration.	3-7 years
2. Develop better FTD in vivo and cell-based model systems.	1. Generate *in vivo* and cell-based models of TDP-43/FUS, GRN haploinsufficiency, and C9ORF72 expansion models that recapitulate key biochemical, neuropathological and functional aspects of FTD and can contribute to therapeutic development. 2. Develop and validate *in vivo* functional assays and neuropathological endpoints for mammalian models that are aligned with FTD anatomy.	1-3 years
3. Determine the molecular basis for C9ORF72 expansion- and GRN-related neurodegeneration.	1. Identify key mechanism(s) of *C9ORF72* FTD/ALS and *GRN*-related pathogenesis that can be targeted for intervention.	3-7 years
4. Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity.	1. Identify key mechanism(s) of TDP-43 and FUS-related pathogenesis that can be targeted for intervention.	3-7 years
Focus Area 2: Clinical Science: FTD Clinical Discovery, Tools, and Cohorts		
Milestone Recommendation	Success Criteria	Timeline
1. Expand efforts to genotype patients with FTD and identify new genes.	1. Initiate at least one new large study to discover new genes and risk alleles for FTD. Where appropriate and synergistic, these efforts should include amyotrophic lateral sclerosis (ALS) kindreds in gene discovery studies.	1-3 years

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2. Develop FTD biomarkers for diagnosis and disease progression.	1. Initiate at least one new large study focused on development, testing, and pathological confirmation of novel PET ligands and/or CSF/blood biomarkers for the molecular diagnosis of FTLD-tau, -TDP and –FUS. 2. Development and testing of sensitive, systems-level surrogate biomarkers (e.g. MRI/fMRI/PET/EEG/clinical) to detect and monitor prodromal FTD and progression during early stage disease; the goal is to inform early in disease clinical proof- of-concept studies, complement clinical outcome measures in Phase III clinical trials, and ultimately the foundation for endpoints on which drug registration can be based.	3-7 years
3. Create an international FTD clinical trial network.	1. Develop a patient registry for FTD clinical studies and a centralized database for de-identified clinical, genetic and biomarker data that can be shared with the broader research community to refine disease models, clinical endpoints and trial design.	1-3 years
4. Understand phenotypic heterogeneity and natural history.	1. Completion of at least 1 natural history study of preclinical inherited FTD (especially *MAPT, GRN* and *C9ORF72*-related FTD) by following individuals from health to disease. Data enable identification of novel genetic and environmental disease modifiers that influence clinical presentation and biomarkers for diagnosis and disease progression. 2. Completion of at least 1 natural history studies of patients with sporadic FTLD, starting from early symptomatic FTD and prioritizing clinical syndromes for which the clinico-pathological correlation is high (*e.g.,* progressive supranuclear palsy and tau, semantic variant primary progressive aphasia and TDP-43 Type C, FTD with MND and TDP-43 Type B). Data will enable identification of novel genetic and environmental disease modifiers that influence clinical presentation and biomarkers for diagnosis and disease progression.	> 10 years

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Topic 5: Vascular Contributions to ADRD: Focus on Small Vessel Disease and AD/Vascular Interactions		
Focus Area 1: Basic Mechanisms and Experimental Models		
Milestone Recommendation	Success Criteria	Timeline
1. Develop next-generation experimental models of VCID.	1. Establish new animal models that: (i) reproduce small vessel disease and other key pathogenic processes thought to result in cognitive impairment; or (ii) are easily applicable to both VCID and AD research for advances in mixed dementias; or (ii) address vascular contributions to dementia via both white matter and grey matter; 2. Develop tools for cell- (endothelial, smooth muscle, pericyte, etc.) and region- (gray vs. white matter, cortex vs. striatum, etc.) specific characterization of the effects of altered cerebrovascular and neurovascular unit (glia, immune cells, etc.) function.	3-7 years
2. Encourage basic science research that investigates the impact of AD risk factors on cerebrovascular function.	1. Initiate new basic research that provides rigorous and novel insight into how factors involved in AD pathogenesis (Aß, tau, apoE, other AD-associated gene products, etc.) affect cerebrovascular function or vascular-related brain injury.	3-7 years
3. Encourage basic science research that investigates the impact of cerebrovascular risk factors on AD-related neurodegeneration.	1. Initiate at least one new basic research project that provides rigorous and novel insight into how cerebrovascular disease (small vessel) or cerebrovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, etc.) impact the development or progression of AD-related neurdegeneration.	3-7 years

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Focus Area 2: Human-Based Studies		
Milestone Recommendation	Success Criteria	Timeline
1. Develop and validate noninvasive markers of key vascular processes related to cognitive and neurologic impairment.	Development: 1. Identify neuroimaging or biochemical biomarker(s) that *independently* correlate with the presence and severity of advanced small vessel disease (SVD) in at least two human SVD cohorts. 2. Identify a neuroimaging marker for the vascular pathology of arteriolosclerosis. Validation: 1. Establish a direct link from in vivo imaging to ex vivo imaging to histopathology for biomarker(s) identified in the Development phase. 2. Establish a link between the presence or progression of the biomarker(s) identified in the development phase and cognitive/neurologic impairment or decline in at least two SVD cohorts.	Development: 1-3 years Validation: 3-7 years
2. Determine interrelationships among cerebrovascular disease and risk factors, Aβ, and neurodegeneration.	1. Perform comprehensive studies of the independent associations between biomarkers of cerebrovascular disease and biomarkers of Aß- and tau-related pathology/neurodegeneration in a human cohort. 2. Initiate at least one intervention study to identify the effects of modifying vascular risk factors on biomarkers of Aß- and tau-related pathology/neurodegeneration.	3-7 years
3. Identify next generation vascular interventions to treat or prevent VCID.	1. Use leading edge biomarkers of small vessel disease and of cognitive/neurologic function in human trials of interventions aimed at decreasing the burden of VCID by modifying vascular risk factors or processes. 2. Initiate a human clinical trial of an intervention derived from SVD-related biological pathways identified in animal or human studies, using leading edge biomarkers.	7-10 years

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