Alzheimer's Disease-Related Dementias (ADRD) Summit 2016

Prioritized Research Milestones

National Institute of
Neurological Disorders
and Stroke

Topic 1: Multiple Etiology Dementias (MED)		
Focus Area 1: Improved Diagnostic Skills in the Community		
Milestone	**Success Criteria**	**Timeline (Timeframe)[1]**
1. Detect cognitive impairment when patient or relative voices a concern to health care providers.	• Initiate at least 2 research programs to develop and validate assessment paradigms that meet the unmet need to detect cognitive impairment and dementia in large and diverse populations seen in primary care practice. Investigators may use existing tools (algorithms, or protocols), may improve upon existing tools, or develop new tools; however, they should be simple to utilize, standardized, reimbursable, and quick. Administration can be by physicians, by non-physician medical personnel, or, alternatively, via non-traditional methods such as telemedicine, mobile devices or computers. The outcome of the cognitive assessment should yield appropriate follow-up, including referral guidance. • Assessment paradigms should come with training materials suitable for both physicians and non-physician medical personnel that will administrate the tools, and be appropriate for primary care and other everyday clinical settings.	3-7 years (2017)
2. Improving differential diagnosis of symptomatic cognitive impairment.	• Initiate one or more research programs to achieve improved and increased differential diagnoses of cognitive impairment and dementia by medical specialists who are accessible to the general public (e.g., but not limited to, neurologists, geriatricians, neuropsychologists and geriatric psychiatrists), including in more remote and less populated areas of the country. Integrate and leverage biomarkers when possible across all of cognitive impairment and dementia (i.e. not limited to AD, FTD, VCID, LBD). • These research programs should also focus on differential diagnosis of rapidly progressive dementias, and potentially treatable cognitive impairment and dementia, followed by appropriate recommendations for medical follow-up.	3-7 years (2017)

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3. Increase training of health professionals to meet the expanding demand for cognitive impairment and dementia diagnosis and care, as well as the critical challenges of and need for human-based research.	• Establish training programs with equal missions of research and training (MD, PhD, and other professionals) of individuals who are trained in the full spectrum of basic through clinical research in AD/ADRD, including in health disparities of AD/ADRD, and who in the future plan to be: (i) basic, basic disease-related, or clinical researchers; (ii) clinicians who lead clinical research, clinicians who support clinical research (e.g. by supporting enrollment in clinical trials); (iii) and clinicians may or may not be directly involved in research, but who seek AD/ADRD training in order to be effective for their constituents. For these training programs it will be important to include trainees from diverse research backgrounds; quantitative research is strongly encouraged, and should be reflected in the training and the background of many trainees (e.g., statistics, bioinformatics, physics, etc.). • Establish a scholarship program that will support later stage in training health professionals (MD, PhD, and other relevant health professionals) to attend the AD/ADRD Summits.	7-10 years (2017)
4. Develop diagnostics/biomarkers in asymptomatic individuals.	• Develop at least one improved imaging or fluid biomarker for AD, cerebrovascular disease (including the health of the neurovascular unit), and each of the ADRDs, to estimate future risk for cognitive impairment in asymptomatic individuals. • Conduct one or more studies that validate diagnostic and theragnostic utility of new biomarkers in asymptomatic populations, especially in minority groups and in middle age using population-based studies. Include evaluation of the relative clinical importance of different etiologies when more than one etiology is present.	3-7 years (2017)
Focus Area 2: Basic and Clinical Research in Interactions between Dementia Pathophysiologies		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
5. Promote basic and clinical research in multi-etiology dementia.	• Initiate at least one funding opportunity announcement that is focused on identifying molecular pathways that accelerate cognitive dysfunction or protect cognition that are agnostic to specific pathologies, i.e. that might act on mechanisms that are common to more than one neurodegenerative process. • Initiate at least one funding opportunity announcement that promotes	3-7 years (2017)

	understanding interactions among different neurodegenerative pathologies of dementia, e.g. beta-amyloid, tau, TDP43, Lewy bodies, vascular, etc. Research may focus on synergy, additive interactions, rank order of impact of different pathologies, as well as pleitrophic effects of multiple pathologies in non-cognitive but related symptoms such as those of gait impairment or physical frailty.	
Focus Area 3: Determining the Role for Screening for Cognitive Dysfunction		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
6. Determining the value of screening for clinically relevant cognitive impairment in the absence of a cognitive complaint.	• Complete at least one practical trial of iterative (over time) cognitive impairment screening that determines the value of performing an initial cognitive assessment in middle adulthood that can serve as a baseline for future determination of meaningful change in cognitive function (a sort of "Brain Health Check" and baseline). Measure the effects that positive screenings have on the individual, family, health care system, and health care provider decision making. • Complete at least one practical trial of iterative (over time) cognitive impairment screening on health disparities populations, starting during midlife, to determine the value of cognitive screening in underserved communities.	7-10 years (2017)

Topic 2: Non-Governmental Organizations (NGOs)		
Focus Area 1: Catalyzing Research through Unique Programs and Partnerships		
Milestone	**Success Criteria**	**Timeline (Timeframe)[1]**
1. Establish more effective communication between NIH and NGOs on activities and progress toward ADRD goals in the off-years between triennial ADRD Research Summits.	• Post all ADRD Summit 2016 milestones and success criteria publicly on the National Plan to Address Alzheimer's Disease (NAPA) website at the time of the 2017 annual update of the plan. • In alignment with the leadership roles of the NIA (NIH lead for NAPA response and AD Summits) and the NINDS (NIH lead for ADRD Summits), going forward both NIA and NINDS to participate in the NAPA Council meetings. • NINDS to present annually to NAPA Council on progress toward the ADRD goals/milestones from 2017 onwards. • Convene annual meetings during which NINDS, NIA and NGOs share activities, funding-related information, and progress relevant to the ADRD recommendations.	Ongoing activity (2016)

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Special Joint NGO & MED Topic: Addressing Nomenclature for Discussing Cognitive Impairment and Dementia		
NGO Focus Area 2: Nomenclature Standards when Discussing Dementia **MED Focus Area 4: Revisiting the Nosology of Cognitive Impairment in Late Life**		
Milestone	**Success Criteria**	**Timeline (Timeframe)[1]**
2. (NGO) Organize a working group of dementia stakeholders, including founding partnerships with health disparities communities, to review the current nomenclature used in public awareness, clinical care services and research and to propose strategies to help advance early differential diagnosis and the understanding of dementia and its underlying causes. 7. (MED) Developing a consistent nomenclature in Dementia Research and Care.	• Establish a working group of stakeholders to begin discussions that will develop draft recommendations for integrating nomenclature for all cognitive impairment and dementia such that different stakeholders can utilize unambiguous terms. This will require a universal lexicon for characterizing acquired cognitive impairment that spans the needs of therapeutic endeavors (regulatory requirements), clinical research, clinical practice, advocacy and the lay public. An important part of the goal is to increase the lay public's understanding of dementia diagnoses by using plain and clear language when discussing dementia, without sacrificing accuracy of terminology. • Convene the first in person meeting of the working group within a year of its establishment to present and finalize draft nomenclature recommendations for inclusion in the National Plan.	Ongoing activity (2017)

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Topic 3: Health Disparities (HD)		
Focus Area 1: Treatment and Prevention Strategies		
Milestone	**Success Criteria**	**Timeline (Timeframe)[1]**
1. Assess epidemiology and mechanistic pathways of disparities in health burden of AD/ADRD.	• Initiate and/or leverage at least two longitudinal community-based cohort studies of incident cognitive impairment and dementia in diverse populations that are designed to assess epidemiologic and mechanistic pathways. Embed biospecimen and clinical data collection to facilitate wide sharing for research. Studies should incorporate cutting-edge imaging, fluid-based and other biomarkers, autopsy (when possible), and other biospecimens for mechanism-oriented research. • Complete at least two studies investigating whether changes in risk factors for cognitive impairment and dementia occur over the lifecourse in diversity populations. Identify critical periods of life and critical lifestyle and other parameters with respect to cognitive impairment and dementia prevention. • Complete at least two studies investigating whether the prevalence and interaction of AD/ADRD risk factors (e.g., genetic, vascular, behavioral, environmental, or social risks), and their 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. Facilitate data availability for future research (e.g., via dbGaP and other sharing resources).	3-7 years (2016)
2. Enrich the design of trials of vascular health interventions to improve their application to AD/ADRD among aging diverse populations.	• Develop and make widely available guidelines for brain health assessments in clinical trials of vascular interventions in aging diversity populations. These guidelines will include standardized outcome measures (e.g., clinical, imaging, neurological, cognitive, and vascular) in diverse populations that will facilitate meta-analyses of vascular health intervention trials, and will draw from expertise in cognitive and impairment and dementia and related fields such as stroke, lipid metabolism, cardiovascular intervention, and immune function. The guidelines should provide tiers of assessments that are optimized for resources in different care settings, such	3-7 years (2017)

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	as caregiver time and technology available and should provide best practices for recruitment in diverse populations. • Implement and validate these guidelines, including standardized outcome measures relevant to AD/ADRD in vascular health intervention studies that include diverse populations.	
Focus Area 2: Monitoring Changes in AD/ADRD Disparities		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
3. Develop a system to monitor the magnitude and trends in health disparities in incidence of AD/ADRD.	• Complete at least one study that covers dementia, including the spectrum of AD/ADRD 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. • Enhance national programs to monitor differences in AD/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 AD/ADRD among disparities populations.	3-7 years (2017)
Focus Area 3: Assessment		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
4. Improve tools for assessment of disparities in risks, preclinical disease characteristics, and costs of AD/ADRD among health disparities populations by leveraging existing data and cohorts, designing targeted studies, and using advanced psychometric analyses for	• Develop best practices and tools for assessing cognitive function, cognitive impairment, and dementia in diverse populations by using 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). These best practices will include a series of validated tools for assessing AD/ADRD and tracking disease progression over time, and methodology for documenting salient symptoms and for understanding disease burden to individuals and family members/caregivers. Tools should operate the same across time and populations, and facilitate harmonized comparison of assessment data among diverse populations, and, optimally, between existing and	1-3 years (2016)

improving tools for assessment of disparities in risks, preclinical disease characteristics, and costs of AD/ADRD among health disparities populations.	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. • Develop normative references that would facilitate harmonized comparisons among assessments of cognitive function, cognitive impairment, and dementia in diverse populations.	
5. Increase utilization of culturally- and linguistically-appropriate assessment tools within ongoing and newly generated studies of AD/ADRD and vascular health intervention trials.	• Implement use of a practical and minimal core of culturally- and linguistically-appropriate best practices, paradigms, and tools for assessing cognitive impairment and dementia in newly initiated studies of AD/ADRD and vascular health intervention trials.	1-3 years (2016)
Focus Area 4: Community Partnerships, Recruitment, and Retention		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
6. Generate an AD/ADRD Health Disparities Task Force that is specifically designed to provide guidance and expertise for community engagement, study design, recruitment and retention into sites to ensure recruitment of diverse populations into newly generated epidemiological studies and clinical trials.	• Establish an AD/ADRD Health Disparities Task Force that consists of various stakeholders and experts with a specific focus on community engagement, recruitment and retention of diverse populations in epidemiological studies and clinical trials. • The purpose of the AD/ADRD Health Disparities Task Force is to refine and disseminate guidelines for increasing diverse participation in AD/ADRD clinical research and best practices for community partnership and outreach among specific disparities populations. Such guidelines should address logistical barriers (e.g., transportation, and cultural issues), and should suggest how to identify and leverage local initiatives, institutions, agencies, and other organizations focused on health outcomes in disparities populations.	1-3 years (2016)
7. Develop novel community engagement and outreach methods and identify existing methods to facilitate	• Complete at least two studies on mixed methods research to develop new 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/ADRD.	1-3 years (2016)

engagement, understanding and partnership with health disparities populations.	• The AD/ADRD Health Disparities Task Force will develop and disseminate guidelines, incorporating existing or new methods, for increasing diverse participation in AD/ADRD clinical research, as well as best practices for community partnership and outreach among specific disparities populations. Such guidelines should address logistical barriers (e.g., transportation, and cultural issues), and should suggest how to identify and leverage local initiatives, institutions, agencies, and other organizations focused on health outcomes in disparities populations.	

Topic 4: Lewy Body Dementias (LBD)		
Focus Area 1: Establish Longitudinal Diverse Cohorts with Common Measures, Culminating in Autopsy		
Milestone	**Success Criteria**	**Timeline (Timeframe)[1]**
1. Initiate clinical trials for motor and non-motor manifestations of Lewy Body dementias (LBD), which is meant to include both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), in diverse populations using existing and newly developed therapies that address symptoms that have the greatest impact on patient function and caregiver burden.	• Initiate at least 1 new clinical trial that leverages an existing clinical network infrastructure and one or more FDA-approved drugs or nonpharmacologic treatments for the symptomatic improvement of one or more of the main disabling clinical features of LBD.	1-3 years (2016)
2. Create longitudinal clinical, biological, and imaging resources for LBD from the earliest stages to autopsy to improve accuracy of detection and diagnosis of DLB at the pre-dementia or prodromal stage and to detect PD patients with a high risk of cognitive decline	• Complete at least one new study that leverages one or more existing neurodegeneration or dementia cohorts to develop and establish research tools to study DLB and PDD. Studies should collect and share standardized clinical and neuropsychological data from individuals with potential early manifestations of DLB and PDD, as above.	7-10 years (2016)

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leading to PDD.		
Focus Area 2: Discover Disease Mechanisms Through Brain Mapping and Genetics		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
3. Using well defined cohorts of LBD who have come to autopsy, systemically characterize disease-specific changes in the brain, spinal cord, and peripheral autonomic nervous system with state-of-the-art methods, including genomics, expression arrays, metabolomics, and proteomics to identify underlying disease mechanisms that will guide future biomarker and therapeutic approaches. Data generated in this initiative should be incorporated into an open-access, centralized data management system that links clinical, biological, and autopsy data.	• Establish an inventory and report on existing autopsy samples with well-characterized brain and other tissue samples with antemortem clinical syndrome and postmortem neuropathology consistent with LBD. Consensus clinical and pathological criteria for DLB and PDD should be used when feasible. This "LBD Pathologic, Biological, and Clinical Data Inventory" will contain metadata and annotation on the quality of the pathologic data and quality and availability of all biological samples and clinical data. • Determine and propose an optimized implementation plan for characterizing brain changes in LBD using the samples, data, and other resources available to best effect, potentially by holding a planning workshop, informed by the LBD Pathologic, Biological, and Clinical Data Inventory.	3-7 years (2018)
4. Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that impact the risk for and clinical features of LBD.	• Identify families with multiple affected members of PDD or DLB and perform genomic analyses. • Conduct a definitive assessment of genetic risk architecture in clinically well-characterized patients with LBD and in autopsy cases meeting consensus criteria for LBD. • Convene a workshop to address the methodological challenges in exploring gene-	3-7 years (2016)

	environment interactions for LBD. • Implement methods for assessing environmental determinants by working with basic scientists and epidemiologists to identify a prioritized list of exposures. Take into account known associations in related disorders such as PD as well as the cellular biology underlying LBD. Genotype cohorts with well characterized environmental exposures and collect environmental exposures in genetically well characterized cohorts. Take advantage of other databases to apply methods such as geocoding to infer exposures (e.g., particulate matter in air, pesticide use in certain states).	
Focus Area 3: Develop and Validate Biological and Imaging Biomarkers		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
5. Develop imaging approaches to 1) enhance the differential diagnostic accuracy of LBD compared to other dementing illnesses, 2) detect latent and prodromal LBD, and 3) monitor disease progression in natural history and treatment studies by integrating established and new imaging tools. Validate these tools against postmortem neuropathology.	• Standardize analytical approaches and neuroimaging methods to facilitate multicenter studies possibly through a workshop that brings together experts in dementia, movement disorders, and related disciplines. • Begin and complete at least one new study to validate available and proposed imaging tools for the differential diagnoses of LBD compared to other dementing illnesses in longitudinally followed cohorts ultimately confirmed by autopsy. Include in this study emerging technologies (e.g. functional MRI and molecular imaging of α-synuclein or other relevant radiopharmaceuticals) with an emphasis on multimodal studies.	3-7 years (2016)
6. Use new (see 4.1.2.) or existing longitudinal case-control studies of individuals with LBD, longitudinal cohort studies tracking cognitive decline, or studies capturing incident cases of LBD, to	• Identify collections of tissue and biofluid samples, as well as other samples (e.g., studies of microbiome) from existing or newly developed longitudinal case-control or cohort studies in which samples are collected using standardized protocols and in which the samples are linked to clinical data that includes DLB and PDD cases. Follow “best practice” procedures for collection, use, and storage of samples. • Develop and validate at least one novel biomarker using well-characterized LBD	3-7 years (2017)

develop biomarkers for LBD-related pathologic changes, diagnosis, differential diagnosis, disease progression, and the relative amount of Alzheimer's and other pathologies. As new markers of molecular disease mechanisms are discovered, incorporate them into biomarker studies for diagnosis of latent or prodromal disease and for monitoring molecular processes and their response to therapies.	samples in existing LBD clinical trials or a new large study.	
Focus Area 4: Model Disease Processes to Develop Potential Symptomatic and Disease Modifying Therapies		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
7. Recognizing the importance of alpha-synuclein and AD pathophysiologic processes in LBD, new animal, cellular, and *in vitro* models are needed that recapitulate key features, including clinical heterogeneity, of these disorders with the ultimate goal of identifying strategies that can be carried forward into clinical trials.	• Establish research focused on developing a better understanding of the basic science of LBD. This should include, but not be limited to better understanding of α-synuclein biology and how it is related to LBD, as well as α-synuclein interactions with β-amyloid, tau, TDP-43 and other proteins informed from systematic mapping, profiling, and epidemiological studies proposed in Focus Area 2. • Develop one or more new in vitro and in vivo models that fit known molecular pathology of LBD. Optimally, new animal models will be informed by human based systematic mapping, profiling and epidemiological studies of LBD.	7-10 years (2017)
8. Develop disease-modifying interventions for LBD based on discovering biomarkers,	• Initiate one or more clinical trials that test prospective therapies based on pharmaceutical approaches, gene therapy, regenerative medicine, surgical interventions, or non-pharmacological approaches to prevent or alter disease	7-10 years (2018)

molecular targets, and genetic and environmental modifiers that enhance, delay or prevent the onset of disease.	processes.	

Topic 5: Frontotemporal Lobar Degeneration (FTD)		
Focus Area 1: Basic Science: Pathogenesis and Toxicity		
Milestone	**Success Criteria**	**Timeline (Timeframe)[1]**
1. Clarify the mechanism of tau pathogenesis and associated neurodegeneration.	• Improve understanding of or determine the roles of the key pathophysiological events (post- translational tau modifications, aggregation, microtubule dysfunction, interneuronal spread, or other tau (dys)functions that contribute to neurodegeneration in human tauopathy. • Develop one or more model systems that reproduce one or more of the aforementioned processes accurately to enable the testing of new therapeutic targets and approaches. • Determine the mechanism of aggregated tau pathology spreading, including how tau seed species get out of neurons and transmit pathology to other cells and what role of different tau conformer strains play in determining the pattern of tau inclusions. Determine the relationship of tau aggregation and spreading to neurodegeneration.	3-7 years (2016/2017)
2. Determine the molecular basis for *C9ORF72* expansion- and *GRN* mutation-related neurodegeneration.	• Identification of predominant mechanism(s) of C9ORF72 and GRN mutation-related FTD/ALS pathogenesis, with convergent findings in human tissues and model systems. • Prioritization of targets to move forward into therapy development after testing therapeutic hypotheses in model systems.	7-10 years (2016/2017)
3. Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity.	• Identification of the predominant mechanism(s) of TDP-43 and FUS-related pathogenesis and neurodegeneration. • Acquisition of new evidence regarding whether TDP-43 aggregation spreads via interneuronal transmission and clarification of the normal functions of TDP-43 and FUS.	7-10 years (2016/2017)

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	• Prioritization of targets for therapy development by testing therapeutic hypotheses in relevant model systems.	
4. Develop better FTLD *in vivo* and cell-based model systems.	• Generation of one or more in vivo and cell-based models of TDP-43, FUS, GRN haploinsufficiency, and C9ORF72 expansion disease, which faithfully recapitulate key biochemical, anatomical, neuropathological and functional aspects of FTLD and can contribute to therapeutic development. In particular, emphasis should be placed on the development of models of C9ORF72 expansion that recapitulate RNA foci, RAN dipeptide repeat protein inclusions, and TDP-43 aggregation. • Improve current transgenic and other models of tauopathy such that pathological changes recapitulate the anatomical sequence observed in forms of FTD. Develop and validate in vivo functional assays and neuropathological endpoints for mammalian models that are aligned with the anatomical sites targeted in FTD. Identify mild model phenotypes associated with GRN haploinsufficiency (for example using sensitive emerging gene and protein expression profiling approaches).	1-3 years (2016/2017)
Focus Area 2: Clinical science		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
1. Expand efforts to genotype patients with FTD and identify new genes and their functional relationship to FTLD pathogenesis.	• Identification of at least one novel drug target or pathway or prevention, supported by the functional analysis of the new genes and risk alleles identified based on GWAS, whole exome and whole genome and targeted sequencing. These efforts should include kindreds with combined FTD and ALS phenotypes in gene discovery studies and should include underserved and minority populations.	3-5 years (2017/2018)
2. Develop FTD biomarkers for diagnosis and disease progression.	• Development, testing, and pathological confirmation of at least one novel PET ligand and/or CSF/blood biomarker for the molecular diagnosis of diverse forms of FTLD-tau, -TDP and –FUS. • Development and testing of 2-3 sensitive, systems-level outcome biomarkers (MRI/fMRI/PET/EEG/clinical/digital-wearable) for monitoring progression during early stage disease, seeking to inform early clinical proof- of-concept studies, complement clinical outcome measures in Phase III and ultimately provide endpoints on which drug registration can be based. Inclusion of underserved and minority	3-7 years (2017/2018)

	populations in biomarker development and testing studies described above.	
3. Create an international FTD clinical trial network.	• Development of 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. Focused FTD clinical trial platforms should be established. Underserved and minority group representation within the clinical trial registry should reflect population demographics. Coordinate with related existing national and international efforts.	1-3 years (2017/2018)
4. Understand phenotypic heterogeneity and natural history.	• Completion of 1-2 natural history studies 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. • Completion of 1-2 natural history studies of patients with sporadic FTD, starting from early symptomatic FTD. Data will enable identification of novel genetic and environmental disease modifiers that influence clinical presentation and biomarkers for diagnosis and disease progression.	>10 years; in progress

Topic 6: Vascular Contributions to Cognitive Impairment and Dementia (VCID), Including Vascular Cognitive Impairment and Vascular Dementia		
Focus Area 1: Basic Mechanisms and Experimental Models		
Milestone	**Success Criteria**	**Timeline (Timeframe)[1]**
1. Develop next-generation experimental models and translational imaging methods for VCID. Establish new animal models that: (i) reproduce small vessel disease and other key pathogenic processes thought to result in cognitive impairment; (ii) are easily applicable to both VCID and AD research for advances in mixed etiology dementias; (iii) address vascular contributions to dementia via both white matter and grey matter or (iv) include genetic and acquired conditions that are associated with VCID.	• Develop at least one combinatorial animal model that reproduces key aspects of human VCID pathophysiology with respect to acquired or environmental risk factors (aging, hypertension, obesity, metabolic syndrome). Encourage animal models that can establish the relationship between aging, vascular risk factors, and disease progression. • Develop at least one animal model that incorporates monogenic causes of AD and VCID to produce pathophysiology similar to human VCID that is present in typical mixed dementia with pathological AD plus VCID. • Establish at least one new tool to determine cellular variation in the vascular tree within different regions of the brain that can be used to test how aging and vascular risk factors impact brain function at the synaptic, neuronal, network, systems, and behavioral level. • Identify imaging approaches for use in animal models that can synergize with those being used as biomarkers in human VCID. • Specifically support basic science projects that directly address or measure the effects of age on the vascular tree, the interaction of age with vascular risk factors, and tissue pathologies that lead to VCID (e.g. chronic blood brain barrier breakdown, hypoperfusion, chronic inflammation, and the effects of neurovascular unit damage on neuronal network structure and activity).	3-7 years (2016)

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2. Encourage basic science research that investigates the impact of aging, AD pathology, and genes on peri- and para-vascular clearance mechanisms, the NVU, and cerebrovascular function.	• Develop at least two new basic science research projects that can provide direct insight into how aging and AD pathology impact vascular clearance of amyloid and other metabolites. • Develop at least one new basic science research project that will determine how aging and AD pathology progressively modulate cerebrovascular function, preferably at the level of the neurovascular unit.	3-7 years (2018)
3. Encourage basic science research that investigates the impact of cerebrovascular risk factors/genes and atherosclerosis on AD-related neurodegeneration.	• 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/metabolic syndrome, dyslipidemia, etc.) or stroke impact the development or progression of AD-related neurodegeneration. • Encourage behavioral studies on the impact of cerebrovascular disease alone or as a comorbidity that incorporate functional testing of both hippocampal/memory and frontal/executive functioning to mimic the brain regions and functional systems impacted by ADRDs.	3-7 years (2018)
Focus Area 2: Human-Based Studies		
Milestone	**Success Criteria**	**Timeline (Timeframe)**
1. Develop and validate longitudinally tracked noninvasive markers of key vascular processes related to cognitive and neurologic impairment.	<u>Development:</u> • 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. • Identify a neuroimaging marker for the vascular pathology of arteriolosclerosis.	1-3 years (2016)
	<u>Validation:</u> • Establish a direct link from in vivo imaging to ex vivo imaging to histopathology for biomarker(s) identified in the Development phase. • 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	3-7 years (2018)

	two SVD cohorts.	
2. Determine interrelationships (cross-sectional and longitudinal) among aging, cerebrovascular disease and risk factors, resilience factors, genetic variants, amyloid, tau, and neurodegeneration.	• Complete one or more comprehensive studies of the independent associations between biomarkers of cerebrovascular disease and biomarkers of Aß- and tau-related pathology/neurodegeneration in a human cohort. • 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 (2018)
3. Identify lifestyle and vascular interventions to treat, prevent, or postpone VCID.	• Identify at least one intervention strategy that decreases the burden of VCID by modifying vascular risk factors/processes in human clinical trials that use leading edge biomarkers of small vessel disease and cognitive/neurologic function • Initiate and complete a human clinical trial or leverage existing trials of an intervention derived from SVD-related biological pathways identified in animal or human studies, using leading edge biomarkers.	7-10 years (2022)