FY 2018 Alzheimer's Disease and Related Dementias Bypass Budget Milestones

AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Category A. Molecular Pathogenesis and Pathophysiology of Alzheimer's Disease		
Research on Disease Mechanisms	Create new research programs that use data-driven, systems-based approaches to integrate the study of fundamental biology of aging with neurobiology of aging and research on AD and related dementias to gain a deeper understanding of the complex biology and integrative physiology of healthy and pathologic brain aging. [2015 AD Summit: 1D, 2A, 3E, 3F, 3I, 3H, 3J]	Launch at least 6 cross-disciplinary projects that use data-driven, systems-based approaches to integrate AD and ADRD research with the study of the fundamental biology of aging/neurobiology of aging.
Research on Disease Mechanisms	Establish new research programs that employ data-driven, systems-based approaches to understand the interaction between peripheral systems (in particular: immune, metabolic, microbiome) and the brain and the impact of this interaction on brain aging and neurodegeneration. These efforts should include characterizing the extent to which molecular (epigenomic, transcriptomic and metabolomic) variation identified in peripheral tissues can be used as a proxy for inter-individual variation in the trajectories of brain aging, AD and related dementias. [2015 AD Summit: 1D, 2A, 3E, 3F, 3I, 3H, 3J]	Launch at least 6 cross-disciplinary projects that use data-driven, systems-based approaches aimed at understanding the interaction between peripheral organ systems and the brain and the impact of this interaction on brain aging and neurodegeneration.
Research on Disease Mechanisms	Create research programs on epigenetics to understand how genetic and environmental factors interact across the lifespan to influence brain aging and risk for disease and to identify potential targets for treatment and prevention. [2015 AD Summit: 1D, 2A, 3E, 3F, 3I, 3H, 3J]	Launch at least 6 new projects exploring epigenetic mechanisms that underlie the heterogeneity of AD and related dementias.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Research on Disease Mechanisms	Create research programs in basic, translational and clinical research aimed at comprehensive understanding of the impact of sex differences on the trajectories of brain aging and disease, phenotypes of AD and ADRD risk and responsiveness to treatment. [2015 AD Summit: 1A]	Launch at least 12 new projects exploring the impact of sex differences on the trajectories of brain aging and disease, phenotypes of risk for AD and related dementias and responsiveness to treatment.
Research on Disease Mechanisms	Create cross-disciplinary research programs aimed at understanding the integrative physiology of APOE and its pharmacogenetic effects on various pharmacological and non-pharmacological interventions. [2015 AD Summit: 3H]	Launch at least 10 cross disciplinary projects aimed at developing a deeper understanding of the protective and risk factor properties of APOE and its pharmacogenetic effects on various pharmacological and non-pharmacological interventions. Of these at least 3 projects should be focused on understanding the mechanisms of risk reduction by APOE2.
Research on Disease Mechanisms	Create new research programs aimed at understanding the integrative physiology of circadian rhythms and sleep and its impact on brain aging and the risk of AD and related dementias. [2015 AD Summit: 3J]	Launch at least 6 new projects focused on understanding the short-term and long term consequences of disrupted/optimized circadian rhythms and sleep on brain aging and dementia, across all levels of biological complexity.
Drug Development - Novel Targets	Establish a searchable, open access research database that contains all clinical, biomarker, and epidemiological data, and related genotypes and phenotypes from existing genetic studies; analyze these data to identify regions of the genome that are targets for AD and ADRD therapeutics. [2012 AD Summit: 1C]	At least one novel target, pathway or therapeutic approach identified through use of the database.
Drug Development - Novel Targets	Create new research programs that use data-driven, network biology approaches aimed at understanding the (epi)genetics and complex biology of cognitive resilience in individuals with high genetic risk for dementia and in individuals with exceptional longevity. [2015 AD Summit: 2B and 3G]	Launch at least 6 research projects aimed at identifying molecular networks causally linked to cognitive resilience as potential therapeutic targets for disease prevention- these efforts should support the preclinical validation of the identified targets.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Non-Pharmacologic Interventions	Initiate interdisciplinary research programs that integrate epidemiological and mechanistic research including cutting edge systems biology approaches to gain an in depth understanding of the mechanisms by which various non-pharmacological interventions impact brain health and the course of AD and related dementias. [2012 AD Summit: 5B, 5C, 5D, 5F]	Identification of at least 3 new therapeutic targets for neuroprotection based on knowledge of mechanisms mediating the impact of non-pharmacological interventions of brain health in aging, AD and related dementias. Preclinical proof-of-concept for at least 3 types of non-pharmacological interventions that can inform clinical trial design.
Category B. Diagnosis, Assessment, and Disease Monitoring		
Biomarkers	Develop and validate translatable biomarkers for their use in preclinical and clinical drug development. These efforts should include the development of pharmacodynamic biomarkers of target engagement, biomarkers of incipient disease (ocular, olfactory) and biomarkers for detection and tracking of synaptic dysfunction. [2015 AD Summit: 1I and 2I]	Develop and validate at least 12 translatable biomarkers for use in preclinical and clinical drug development.
Biomarkers	Initiate synthesis and testing of novel PET ligands and develop and test novel CSF/blood biomarkers for assessment of disease related pathological burdens such as tau, inflammation, synaptic dysfunction. [2012 AD Summit: 1E]	Development and testing of 3-5 novel PET ligands and/or CSF/blood biomarkers for assessment of AD and ADRD pathology.
Biomarkers	Initiate development of imaging and/or fluid biomarkers to demonstrate target engagement for 5 novel therapeutic targets for AD and related dementias. [2012 AD Summit: 1E]	Identification of 3 imaging and/or fluid biomarkers for which there is proof of engagement of novel therapeutic targets.
Biomarkers	Incorporate imaging and/or fluid biomarkers into Phase II (proof of concept) drug trials to provide proof of mechanism and/or evidence of target engagement as trials for 3-6 existing and 3-6 novel therapeutic targets are initiated. [2012 AD Summit: 1E]	Initiation and completion of 5 Phase II (proof of concept) drug trials using imaging and/or fluid biomarkers for proof of target engagement.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Biomarkers	Incorporate imaging and/or fluid biomarkers into Phase III (pivotal) drug trials to select subjects and/or provide evidence of target engagement as trials for 3-6 existing and 3-6 novel therapeutic targets are initiated. [2012 AD Summit: 1E]	Initiation of 3 Phase III (pivotal) drug trials using imaging and/or fluid biomarkers to select at risk subjects and/or for proof of target engagement.
Biomarkers	Initiate studies to develop minimally invasive biomarkers for detection of cerebral amyloidosis, AD and related dementias pathophysiology. [2012 AD Summit: 1F and 1G]	Development and testing of 5 biomarkers that utilize biofluids or other minimally invasive imaging, electrophysiological recording, or other methodologies to assess the burden of AD and ADRD pathophysiology that could be used in community based and epidemiological studies of AD and related dementias.
Biomarkers	Initiate studies to link peripheral blood-based biomarkers and central imaging and CSF biomarkers. [2012 AD Summit: 1F and 1G]	Identification of 3 peripheral blood-based biomarkers that have a high correlation with central imaging and/or CSF biomarkers.
Biomarkers	Launch research programs to develop and validate sensitive neuropsychological and behavioral assessment measures to detect and track the earliest clinical manifestations of AD and related dementias. [2012 AD Summit: 3D]	Development of at least one sensitive neuropsychological assessment measure that has been validated for the detection or tracking of the earliest clinical manifestations of AD and related dementias.
Enabling Technologies and Disease Monitoring	Develop research programs aimed at evaluating a variety of technologies for in-place monitoring of individuals at all stages of disease to capture various types of patient relevant data and caregiver related outcomes (i.e. daily physical function, home safety, quality of life). [2015 AD Summit: 4A]	Launch at least one large multi-site research platform for evaluating in-place monitoring technology and utilize the platform to evaluate at least 6 innovative new technologies focused on dementia assessment and care in various dwelling environments (e.g., rural, urban, assisted living, apartment dwelling, single family, etc).
Enabling Technologies and Disease Monitoring	Embed wearable technologies as well as pervasive computing approaches in existing large community based longitudinal cohort studies as well as clinical trials to enable continuous capture of various types of participant relevant data. [2015 AD Summit: 4C, 4F, 4G, 4I]	Introduce the use of mobile/pervasive computing technologies in at least 3 existing longitudinal cohort studies – each study should be conducted in a different at risk population. The studies should be designed to allow the collection of raw sensor data to enable pooling of data across studies. The sensor collection apps and data collection server infrastructure used in these studies should be built and released as open source tools.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Enabling Technologies and Disease Monitoring	Build cross disciplinary teams that bring together clinical researchers with experts in mathematics, human factors design, software engineering to develop innovative monitoring technologies for diverse aging populations. [2015 AD Summit: 4D]	Initiate at least 10 research projects focused on developing new disease monitoring technologies.
Public Private Partnerships	Convene meetings of the working groups for (i) Rapid Data Sharing and Analysis, (ii) Enabling Bidirectional Translation in AD and ADRD drug development, (iii) Eliminating IP barriers for Target Validation through clinical proof of concept. Each working group will formulate concrete steps needed to accelerate the timeframe of AD and ADRD drug development. [2012 AD Summit: 1H, 1I, 1K, 6C]	Recommendations developed on (i) the creation of an open access, web-based resource that integrates complete, diverse multidimensional biological and chemical data that will be useful in advancing information on drug targets, including mechanistic information that will aid in the development of measures of target engagement (PD readouts); (ii) creation of computational tools for development of biological network models of AD, related dementias and normal aging; (iii) creation of tools that will foster development of bio network models that provide a predictive framework for using drugs in combination or singly (iv) removing legal and IP barriers surrounding data sharing. One or more partnerships established to accelerate key steps in AD drug development.
Category C. Translational Research and Clinical Interventions		
Drug Development - Existing Targets	Initiate first in human, phase I drug trials for therapeutic agents against at least 6 existing therapeutic targets. In addition to testing for safety, these trials will include assessment of target engagement. [2012 Summit: 3A, 3B, 3F, 5E]	Completion of 12, Phase I drug trials for agents against 6 existing therapeutic targets.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Drug Development - Existing Targets	Initiate phase II (proof of concept) drug trials for agents against 3-6 currently known therapeutic targets. Of these at least 2 will be for targets involved in at-risk asymptomatic individuals (e.g. FAD or ApoE4 carriers, Down syndrome, amyloid positive, type II diabetes etc.) These trials will be designed to provide or confirm proof of mechanism and/or evidence of target engagement for the therapeutic agent being tested. [2012 AD Summit: 3A, 3B, 3F, 5E]	Completion of 3-6 phase II drug trials for agents against currently known targets, providing conclusive evidence of therapeutic mechanism/target engagement.
Drug Development - Existing Targets	Initiate phase III drug trials for agents against at least 3 currently known therapeutic targets. Of these at least one trial will be asymptomatic, at risk populations. These trials will incorporate a combination of biomarkers (fluid and imaging) and cognitive measures as outcomes and include collection of DNA and other bio-samples for interrogation of responsiveness. [2012 AD Summit: 3A, 3B, 3F, 5E]	Comprehensive success/failure analysis of data from at least 3 phase III trials.
Drug Development - Novel Targets	Identify, characterize, and complete early validation for at least 6 novel therapeutic targets for AD and related dementias (a minimum of 3 targets for pre-symptomatic and early stage disease and a minimum of 3 for advanced disease). These efforts should include therapeutic targets for the neuropsychiatric and behavioral disturbances in AD and ADRDs. [2012 AD Summit: 1A, 1B, 1D, 5A]	Validation based on availability of the following for each novel target: a systems-level understanding of the gene, protein and metabolic networks within which they operate, one or more cell based/animal models that are freely available to the research community, a quantitative assessment of the integrative response to the modulation of the target in one or more model organisms, and identification of pharmacodynamic biomarker(s) for target engagement.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Drug Development - Novel Targets	Initiate drug discovery efforts to develop novel therapeutic agents against at least 6 novel therapeutic targets (a minimum of three targets for presymptomatic and early stage disease and a minimum of three for advanced disease). [2012 AD Summit: 1A, 1B, 1D, 5A]	Complete preclinical development, through IND filing, of at least 12 therapeutics agents against at least 3 novel targets (at least one novel target should be for presymptomatic disease).
Drug Development - Novel Targets	Initiate first in human, phase I drug trials for therapeutic agents against at least 6 novel therapeutic targets. In addition to sufficient these trials will provide evidence of target engagement. [2012 Summit: 3A, 3B, 3F, 5E]	Completion of 12 phase I drug trials for agents against 6 novel targets, providing conclusive evidence of safety and target engagement.
Drug Repurposing and Combination Therapy Development	Expand existing and develop new systems biology and systems pharmacology research programs to build multiscale models of disease that will lead to the identification of networks/sub-networks as drug targets and readouts of therapeutic activity and advance the validation of existing and novel targets, rational drug repositioning and rational development of combination therapy. [2015 AD Summit: 1E, 2D, 2E, 2F, 2G.]	Launch at least 6 cross-disciplinary research programs that bring together experts in translational bioinformatics, computational biology, genetics, epidemiology, drug discovery and clinical research to develop a predictive model of the disease. Efforts should support: -development of computational tools and infrastructure to allow basic and clinical researchers to query model in silico and validate it by using it for patient stratification, predictions of efficacy, on- and off-target adverse effects. -identification of quantitative methods to access synergy between (1) multiple therapeutic agents and (2) pharmacologic/non-pharmacologic perturbations. -development of phenotypic screens (in cell based and/or animal models) to advance rational drug repositioning and data-driven development of combination therapy based on the ability of individual or combinations of therapeutic agents to shift the network state away from disease.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Drug Repurposing and Combination Therapy Development	Initiate research programs for translational bioinformatics and network pharmacology to support rational drug repositioning and combination therapy from discovery through clinical development. [2012 AD Summit: 4A, 4B, 4C, 4D]	Identification of at least 6 existing drugs suitable for repurposing and/or combination therapy for AD and ADRD prevention or treatment. The drugs selected for repurposing or combination therapy will be prioritized based on: - Evidence that they modulate disease relevant pathways/networks gained from computational and empirical approaches. - Preclinical proof-of-efficacy in a relevant model system. - Availability of biomarkers to monitor target engagement in humans. - Sufficient evidence of safety for the intended target population.
Drug Repurposing and Combination Therapy Development	Initiate early clinical development for at least 6 existing drugs or drug combinations for the treatment or prevention of AD and related dementias. [2012 AD Summit: 4A, 4B, 4C, 4D]	Completion of at least 4 phase II trials with repurposed drugs and/or drug combinations. Successful trials will provide conclusive evidence of therapeutic mechanism/target engagement.
Non-Pharmacologic Interventions	Convene an advisory meeting to delineate an interdisciplinary research agenda focused on: (i) advancing non-pharmacological interventions for the cognitive and behavioral symptoms of AD and related dementias by non- pharmacological treatments, (ii) informing the design of therapeutic approaches combining pharmacological and non-pharmacological treatments and (iii) identification of best practices for implementation of non-pharmacological interventions. [2012 AD Summit: 5B, 5C, 5D, 5F]	Recommendations developed for advancing non-pharmacological interventions for AD and ADRD treatment and prevention to enable successful implementation of effective non-pharmacological interventions.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Non-Pharmacologic Interventions	Initiate clinical trials for at least 3 non-pharmacological interventions aimed at AD and ADRD treatment and/or prevention. Of these at least one trial will be a pivotal, phase III trial. [2012 AD Summit: 5B, 5C, 5D, 5F]	Completion of at least 2 phase II trials for non-pharmacological interventions aimed at AD and ADRD treatment and/or prevention. Successful trials will provide conclusive evidence of therapeutic mechanism. Comprehensive success/failure analysis of data from at least one phase III trial.
Trial Design	Create new research programs to implement innovative trial designs. [2015 AD Summit: 3K]	Launch at least 6 clinical trials using innovative trial designs such as adaptive trial design, functional challenge studies, pragmatic clinical trials, population-based cohort designs, and clinical trial/population-based cohort hybrid designs. At least 3 of these should stratify participant risk groups using dense "omics" and gene-environment interaction profiles.
Recruitment and Citizen Engagement	Provide supplemental funding for clinical research studies to build diverse community partnerships needed to increase research participation. [2015 AD Summit: 5A, 5B, 5C, 5D]	Provide supplemental funding for at least 20 clinical research studies aimed at building partnerships with diverse communities.
Recruitment and Citizen Engagement	Provide supplemental support for clinical research on AD and related dementias to overcome the major logistical barriers to participation including bringing clinical trials to the participants' living environments. [2015 AD Summit: 5B]	Provide supplemental funding for at least 20 clinical research studies aimed at overcoming the major logistical barriers to participation.
Recruitment and Citizen Engagement	Pilot the use of electronic consent which provides participants an option for broad sharing of de-identified data in various types of clinical research on AD and related dementias. [2015 AD Summit: 1C and 5H]	Launch at least 3 clinical research studies with electronic consenting methods that give participants the option for broad sharing of de-identified data.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Public Private Partnerships	Develop partnerships that expand the precompetitive space through clinical proof of mechanism to accelerate translational learning and to fill critical knowledge gaps in understanding the network biology of drug targets and drug-target interactions. [2015 AD Summit: 6E and 6F]	Establish at least one precompetitive partnership to validate the therapeutic targets that will be delivered by the Accelerating Medicines Partnership for AD (AMP-AD), as well as other pioneer targets, through clinical proof of mechanism/proof of concept.
Public Private Partnerships	Develop a partnership among key stakeholders to implement the sharing of all data and biosamples from preclinical and clinical studies to enable the adoption of formal failure analysis across the drug development continuum. The partnership should provide resources for data hosting and curation. [2015 AD Summit: 2K]	Convene a meeting that brings together experts from industry and academia, regulatory and funding agencies, bioethics experts, patients and patient advocates to establish the framework for a multi-stakeholder partnership aimed at enabling the sharing of all data and biosamples from preclinical and clinical studies
Category D. Epidemiology		
Population Studies	Create research programs aimed at extensive molecular endophenotyping of existing, at-risk cohorts from longitudinal studies that are genetically, epigenetically, or otherwise at risk (e.g. due to cerebrovascular, metabolic, or neuroinflammatory compromise), as well cohorts and/or individuals who resist disease despite high genetic risk (e.g. Down Syndrome, ApoE 4 homozygous, FAD mutation carriers). [2015 AD Summit: 1A, 2A, 2B, 3A]. This is consistent with the longer term goals of the Precision Medicine Initiative.	Initiate at least 3 programs which include dense molecular phenotyping (genomic, epigenomic, proteomic, metabolomics, microbiome) and incorporate the collection of non-traditional data modalities using wearable sensors and mobile health technologies as dimensions of health and disease. These programs should include big-data infrastructure resources to ensure that the data are made available as a public resource and support for collection, storage and rapid distribution of biosamples including brain tissue.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Population Studies	Incorporate environmental context in human studies (e.g., epidemiological cohorts) and in clinical trials, such as biomarkers of environmental exposure and geocodes to assess personal and shared environmental contribution to AD and ADRD pathogenesis and response to therapy. [2015 AD Summit: 3B and 3D]	Provide supplemental funding to at least 6 clinical research studies to explore the impact environmental exposure on the pathogenesis of AD and related dementias and/or on responsiveness to treatment.
Population Studies	Create new cohorts to accelerate the identification of genomic variants and other risk and protective factors contributing to the heterogeneity and multifactorial etiology of dementia. [2015 AD Summit: 1B and 3C]. This is consistent with the longer term goals of the Precision Medicine Initiative.	Establish at least 3 new cohorts for extensive endophenotyping with participants of African, Native American, Asian, and mixed ancestry, e.g. Latinos as well as younger cohorts (midlife and younger participants). The phenotyping should include cognitive, behavioral, imaging, exposome measurements, multidimensional "omics" data and multiple types of physiologic measurements that can be used for systems biology and gene-environment interaction studies. These programs should include big-data infrastructure resources to ensure that the data are made available as a public resource and support for collection, storage and rapid distribution of biosamples including brain tissue. Proposed U24 to harmonize cognitive measures across NIA, NHLBI, NINDS, and NIDDK major cohort studies results in readily comparable cognitive measures sensitive to change

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Population Studies	Develop state-of-the-art protocol for assessing dementia on large nationally representative samples that (a) includes racial/ethnic subsamples large enough to support disparities research and (b) is adaptable for use in comparable studies around the world [2015 AD Summit: 1B, 1D, 3C, 3D, 4B].	Archive and share data for use by the research community. Update national estimates of the prevalence and incidence of dementia and cognitive impairment as well as address important questions about the epidemiology and population impact of dementia. Repeat national estimates in 2021 to measure trend in dementia prevalence Support research projects comparing international differences to identify potential risk and protective factors. Support research on health disparities by racial/ethnic groups. 3 years (2016-2018) for protocol development, implementation and archiving; 4 years (2016 - 2019) for research.
Research on Disease Mechanisms	Create research programs in basic, translational and clinical research aimed at comprehensive understanding of the impact of sex differences on the trajectories of brain aging and disease, phenotypes of AD and ADRD risk and responsiveness to treatment. [2015 AD Summit: 1A]	Launch at least 12 new projects exploring the impact of sex differences on the trajectories of brain aging and disease, phenotypes of risk for AD and related dementias and responsiveness to treatment.
Enabling Technologies and Disease Monitoring	Continue to develop standard outcome measures to enable data comparisons across studies, including but not limited to cognitive functioning and physical function and ensure that these measures are validated across a variety of educational, linguistic, and cultural groups. [2015 AD Summit: 4B]	Launch at least one large longitudinal study evaluating the validity of standard outcome measures across three or more diverse groups. The study should be sufficiently powered to enable the validation of each of the outcome measures within each of the diverse groups.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Recruitment and Citizen Engagement	Collaborate with external organizations to increase awareness of large-scale registries that encompass the spectrum of the disease from healthy and at-risk asymptomatic to symptomatic individuals from early midlife to late life willing to participate in clinical research aimed at AD and ADRD prevention and treatment.	A central repository of AD and ADRD related registries and cohorts created and publicized. Demonstrate increased participation in registries.
Category E. Care and Caregiver Support		
Trial Design	Convene an advisory meeting to evaluate how assays and best practices developed in the context of the NIH Common Fund Science of Behavior Change and other related NIH activities could be incorporated into the design of primary prevention trials or for clinical trials targeting risk factors associated with increased risk of AD and related dementias. [2012 AD Summit: 5E]	Meeting report recommendations that would guide the inclusion of behavioral target engagement assays and best practices in NIH-supported prevention and treatment trials for AD and related dementias.
Research on Care and Caregiver Support	Convene an exploratory expert meeting to delineate and prioritize an interdisciplinary research agenda focused on assessing the impact of informal and formal caregiving across the full care continuum (to include primary care, home health care, adult day care, nursing home, assisted living, hospice, etc.) on individuals, families, and society, and to inform design of new care delivery systems for individuals with dementia. [2015 AD Summit: 4K,4B, 4J, 5D]	Definition and characterization of informal and formal caregiving, the domains of needs of caregivers and care recipients across the care continuum, the key social structural variables which contribute to variance in caregiving burden, and factors that characterize care delivery and care coordination models that reduce burden on caregivers and care recipients. Recommendations developed for research priorities on the impact of caregiving on caregivers' psychological and physical health, workforce participation and financial security. Recommendations developed for research programs that can inform development of new care models.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Research on Care and Caregiver Support	Launch research programs to develop and validate assessments of the psychological, financial, and physical health impact of caregiving. [2015 AD Summit: 4B, 4D, 4H]	Identification and validation of assessments suitable for use in a range of research contexts including observational and interventional studies and large population-based surveys. Identification and validation of at least one sensitive and robust measure for the detection of the earliest manifestations of caregiving burden and for monitoring its long-term consequences.
Research on Care and Caregiver Support	Establish data infrastructure for the study of dementia caregiving. [2015 AD Summit: 4B, 4E, 4F]	Identification of existing cohorts of nationally representative and cross-national samples and determination of the need for data collection in new cohorts. Establishment of standard protocols for harmonizable survey data collection and data infrastructure. Supplement existing national panel studies to collect data on formal and informal caregiving. Support archiving of data from population-based and intervention studies with appropriate content related to informal and formal caregiving.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Research on Care and Caregiver Support	Support secondary analysis of data from population based and intervention studies with appropriate content related to informal and formal caregiving. [2015 AD Summit: 4E, 4F, 4H]	Identify predictors of high-risk caregivers. Identify economic impact of informal caregiving on families and societies. Conduct cross-national comparative research. Identify potential buffers and predictors of healthy caregivers and positive caregiving outcomes for care recipients. Identify at least one novel association, target, pathway, or intervention target or approach through use of the database.
Research on Care and Caregiver Support	Partner with community organizations to support a research agenda that will lead to the development of a national framework for dementia caregiver support in the community. [2015 AD Summit: 4K, 4I, 5B, 5C, 5D, 5F]	Support research projects that will inform the design of cost-effective, community-based, informal caregiving interventions tools that address unmet psychological and physical health needs of caregivers and which ensure a safe home environment, to enable individuals with AD and related dementias to remain in their homes for as long as possible. Identify or develop effective in-home, in-community, off-the-shelf intervention programs and tools to support caregiver well-being and health that aid in the integration of formal and informal care.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Research on Care and Caregiver Support	Partner with insurers (including CMS) to conduct comparative effectiveness research to determine which existing evidence-based interventions to reduce burden in caregivers are effective if implemented as an adjunct to primary care in non-research settings across the full care continuum, including patients in a variety of settings (home, nursing home, assisted living, hospice). [2015 AD Summit: 5B, 5C, 5D, 5F]	Conduct cluster randomized trials comparing interventions stemming from contact with caregiver dyads in primary care, with insurers supporting intervention costs and enrolled participants agreeing to allow researchers to link the data obtained in the study with billing data, to allow researchers to follow longer range health effects of caregiving and effective interventions. Identification of programs that work best for different stages of the care continuum. Conduct intervention feasibility and intervention efficacy trials to develop strengths-based and skill-building intervention for preventing elder abuse and neglect in at-risk caregiving dyads Identification of which programs work best with different population subgroups (racial, ethnic, geographic, socioeconomic) Development of new models of care that can be adopted by insurers. OCPL - Collaborate with other federal agencies to disseminate caregiver training materials and interventions based on research
Research on Care and Caregiver Support	Leverage existing palliative care research networks to develop and advance interventions for palliative and hospice care of persons with advanced dementia and their families. [2012 AD Summit: 5E, 5G; 2015 AD Summit: 2J, 4B, 4D, 4H, 4K, 4L, 6A]	Launch cross-disciplinary projects to design and test clinical interventions and models of palliative and hospice care for persons with advanced dementia and their families These programs should address needs across diverse cultural subgroups, care settings, and rural/urban locales.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Category F. Research Resources		
Data Sharing and Reproducibility	Provide resources to make datasets from existing and legacy clinical research studies on AD and related dementias widely accessable and ensure their adequate annotation and curation to maximize their usability.	Provide funding to make datasets from publicly funded clinical research studies on AD and related dementias, annotated, curated and made widely available via web-based resources.
Data Sharing and Reproducibility	Provide support to establish/improve the interoperability among relevant biomedical data repositories.	Provide supplemental funding to establish/improve the interoperability among relevant biomedical data repositories funded by NIH or other funding agencies.
Data Sharing and Reproducibility	Convene an advisory meeting of relevant stakeholders to develop a consensus regarding eliminating barriers to sharing, integrating, and reuse of data needed to build predictive models of disease. [2015 AD Summit: 1A, 2C, 3A, 6A]	Develop recommendations for new policies and incentives to enable open, reproducible, and translatable research. These should address: - removing barriers to combining data from multiple sources and sharing processed data with other investigators - generating combined and harmonized data sets that can be shared between investigators - providing genetic and other patient-level data on a common-access cloud site where researchers can perform large-scale computational tasks without the need to download and store large data sets. - providing access to sponsor-level data from clinical trials to revisit those that failed to demonstrate efficacy - supporting electronic consenting and other consenting models that give ownership of health care data to patients and study participants.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Data Sharing and Reproducibility	Convene a meeting with administrators from academic institutions (Deans, Chancellors, Department Chairs), representatives from NIH and other funding agencies, journals and public advocates to develop recommendations for alternative recognition and attribution methods that would foster large-scale team science and increase the transparency and reproducibility of federally-funded research. [2015 AD Summit: 1K and 6B]	Develop recommendations for new metrics for recruitment, career advancement and publication attribution.
Translational Infrastructure and Capabilities	Support the development of the next generation of animal models based on the current understanding of genetic and environmental risk and protective factors for AD and related dementias, using genome editing and other cutting edge technologies (optogenetics/ /deep brain stimulation/trans-magnetic stimulation, and next generation in vivo imaging) to facilitate assessment and validation of findings from human studies. [2015 AD Summit: 1F and 1G]	Develop and characterize at least 12 next generation animal models available to all qualified researchers without IP restrictions for use in basic research and in preclinical drug development.
Translational Infrastructure and Capabilities	Provide support for storage and rapid distributon of biosamples from relevant NIH-funded clinical research studies to ensure that biosamples generated from federally-funded research can be maintained and made available to all qualified researchers after the funding cycle ends.	Establish a contract for storage, maintenance and distribution of biosamples from clinical research studies on AD and related dementias.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Translational Infrastructure and Capabilities	Create infrastructure/resources for extensive characterization of existing and new animal models and development of standardized and rigorous methods for preclinical efficacy testing including web-based resources for transparent reporting of both positive and negative findings. [2012 AD Summit: 2B and 2C; 2015 AD Summit: 1H and 1I]	Create at least one translational center for animal model resources.
Translational Infrastructure and Capabilities	Support the development of standardized, cost-effective, high throughput methods to isolate neural and glial cells for "omics" profiling and drug-screening. [2015 AD Summit: 1G and 2H]	Develop standardized high-throughput methods for isolation and "omic" profiling of relevant neural and glial cell types.
Translational Infrastructure and Capabilities	Develop improved iPSC protocols for all relevant cell types and human-based organoid model systems. [2015 AD Summit: 2H]	Develop and make widely available standardized protocols for the generation of hiPSC for the major cell types (neurons, astrocytes, microglia, oligodendrocytes, pericytes).
Translational Infrastructure and Capabilities	Create a network of translational centers that bring together expertise and technology needed for integration of multi-modal data analysis, mathematical modeling and empirical testing and apply a systems biology/systems pharmacology approach to the most challenging aspects in preclinical therapy development such as: (i) therapeutic target selection and initial target validation, (ii) predictive toxicology, (iii) rigorous preclinical efficacy testing and development of translatable, preclinical biomarkers. The centers will also provide training programs for the new generation of translational scientists. [2012 AD Summit: 2A and 2B]	Creation of at least 3 Translational Centers that will apply the principles of quantitative and systems pharmacology to AD and ADRD drug development.
Translational Infrastructure and Capabilities	Create a National IRB. [2012 AD Summit: 3H]	Initiation of at least one multi-center clinical trial that utilizes a national IRB.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Translational Infrastructure and Capabilities	Create new integrative training programs for junior neuroscience researchers (predoc, postdoc and junior faculty) that include training in aging biology, systems biology, geriatrics, all aspects of data science as well as traditional and emerging drug discovery disciplines. [2015 AD Summit: 1J, 4D, 4E]	Establish new training programs as well as fellowship and career development programs to develop a new translational and data science workforce.
Recruitment and Citizen Engagement	Convene a meeting with key stakeholders and organizations including representatives from the NIH Precision Medicine Initiative to discuss policies for streamlining and innovating patient/participant consent and data sharing. [2015 AD Summit: 5G, 5H, 5I]	Issue guidelines for streamlined electronic consenting and other consenting models that give ownership of health care data to patients and study participants.
Recruitment and Citizen Engagement	12.F: Support projects that use citizen science to accelerate collection of relevant data and data analyses. [2015 AD Summit: 5G]	Launch at least 3 citizen science projects that use existing or develop new crowd-powered medical research platforms for collection and/or analysis of data.
Recruitment and Citizen Engagement	Establish a partnership among NIH and other federal agencies to develop a national public education campaign to (1) eliminate the stigma of aging and dementia, (2) provide accurate evidence-based information on environmental and life-style factors associated with the development and maintenance of a healthy brain and cognition, and (3) encourage participation in clinical trials . [2012 AD Summit: 6A]	Launch national public education campaign to (1) eliminate the stigma of aging and dementia, (2) provide accurate evidence-based information on environmental and life-style factors associated with the development and maintenance of a healthy brain and cognition, and (3) encourage participation in clinical trials. Launch a national campaign targeting primary physicians to inform their assessments of patients for cognitive impairment and encourage referrals to clinical research. Disseminate ROAR toolkit, develop additional training material, and work with state and local aging services and public health providers to provide educational and training for their clients.
Recruitment and Citizen Engagement	Collaborate with research scientists to identify, evaluate and increase knowledge about best practices for recruitment and retention of research participants.	Collect, create and make widely available to researchers central resources for both references and tools, including videos and presentation materials created and available.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
Public Private Partnerships	Develop partnerships to support novel/disruptive science that would incentivize students and early-career investigators to adopt a collaborative approach to research through the use of targeted small funding schemes. [2015 AD Summit: 6D]	Establish at least one partnership to support disruptive team science by young investigators (students and early career investigators).
Portfolio Analysis Tools and Methods	Develop a common AD and ADRD research ontology, as a unified classification system for comparative analysis of research portfolios, and strategic planning, and create a publicly available database that will house the AD and ADRD research portfolios from AD funding agencies in the US and abroad.	Recruitment of all federal and non-federal funding agencies in the US as well as AD and ADRD funding agencies from countries that have an AD National Plan to participate in this database.
Category H. Alzheimer's Disease-Related Dementias		
ADRD 1: Multiple Etiology Dementias Focus Area 1: Differential Diagnosis	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.	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 nonphysicians.
ADRD 1: Multiple Etiology Dementias Focus Area 2: Epidemiology	Conduct population-based studies of dementia prevalence and incidence in diverse ethnic groups and age ranges using imaging and fluid biomarkers.	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.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
ADRD 2: Health Disparities Focus Area 1: Recruitment	Initiate and leverage ongoing longitudinal community-based cohort studies of incident dementia in diverse populations incorporating imaging, fluid biomarkers, and autopsy.	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.
ADRD 2: Health Disparities Focus Area 1: Recruitment	Initiate and leverage ongoing longitudinal community-based cohort studies of incident dementia in diverse populations incorporating imaging, fluid biomarkers, and autopsy.	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.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
ADRD 2: Health Disparities Focus Area 1: Recruitment	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. (2) Facilitate harmonized comparisons among assessments of cognitivefunction, 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.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
ADRD 2: Health Disparities Focus Area 2: Advancing Treatment and Prevention Strategies	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.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
ADRD 2: Health Disparities Focus Area 2: Advancing Treatment and Prevention Strategies	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).
ADRD 3: Lewy Body Dementias Focus Area 1: Establish Longitudinal Cohorts with Common Measures, Culminating in Autopsy Studies	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.	Initiate 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.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
ADRD 3: Lewy Body Dementias Focus Area 2: Discovering Disease Mechanisms Through Brain Mapping and Genetics Focus Area 3: Develop and Validate Imaging Biomarkers	Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that influence the risk and clinical features of DLB and PDD. 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 families with multiple affected members of PDD and/or DLB for genomic analyses. (2) Definitive assessment of genetic risk architecture in clinically wellcharacterized 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. (4) 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. (5) Initiate at least one large study to develop and validate novel biomarkers using well characterized DLB or PDD samples.
ADRD 3: Lewy Body Dementias Focus Area 3: Develop and Validate Biological and Imaging Biomarkers	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.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
ADRD 3: Lewy Body Dementias Focus Area 4: Model Disease Processes to Develop Potential Symptomatic and Disease Modifying Therapies	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 betaamyloid 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.
ADRD 4: FTD and Related Taupathies Focus Area 1: Basic Science	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.
ADRD 4: FTD and Related Taupathies Focus Area 2: Clinical Science	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.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
ADRD 4: FTD and Related Taupathies Focus Area 2: Clinical Science	Expand efforts to genotype patients with FTD and identify new genes.	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.
ADRD 4: FTD and Related Taupathies Focus Area 1: Basic Science Focus Area 2: Clinical Science	Develop better FTD in vivo and cell-based model systems. Develop FTD biomarkers for diagnosis and disease progression.	(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. (3) 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. (4) 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.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
ADRD 5: Vascular Contributions to Cognitive Impairment and Dementia (VCID) Focus Area 1: Basic Mechanisms and Experimental Models	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.
ADRD 5: Vascular Contributions to Cognitive Impairment and Dementia (VCID) Focus Area 1: Basic Mechanisms and Experimental Models	Encourage basic science research that investigates the impact of cerebrovascular risk factors 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, dyslipidemia, etc.) impact the development or progression of AD-related neurdegeneration.

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AD Research Implementation Area	Alzheimer's Disease Research Implementation Milestones	Success Criteria
ADRD 5: Vascular Contributions to Cognitive Impairment and Dementia (VCID) Focus Area 2: Human-based Studies	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.