FY 2019 Alzheimer's Disease and Related Dementias Bypass Budget Milestones

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Molecular Pathogenesis and Physiology 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 AD-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, and 3J]	Launch at least six 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 AD-related dementias. [2015 AD Summit: 1D, 2A, 3E, 3F, 3I, 3H, and 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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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, and 3J]	Launch at least 6 new projects exploring epigenetic mechanisms that underlie the heterogeneity of AD and AD-related dementias.
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 AD-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 nonpharmacological 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 nonpharmacological 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 AD-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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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 AD-related dementias, using genome editing and other cutting-edge technologies (optogenetics/deep brain stimulation/transmagnetic 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	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).

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Drug Development - Novel Targets	Establish a consortium of genetics and genomics experts to develop and execute a large-scale sequencing project to analyze the genomes of a large number of well-characterized individuals, including multiethnic subjects, using next-generation sequencing approaches; identify a broad range of AD and ADRD risk and protective gene variants in subjects with age-related dementias. These efforts should incorporate diverse sample sets (including racial/ethnic groups, the oldest old, and other well-characterized individuals from epidemiological/observational studies) and include replication studies and data harmonization. [2012 AD Summit]	Identification of new risk and protective alleles for late-onset AD and AD-related dementias that lead to the identification of at least one novel therapeutic approach, drug target, or pathway for prevention.
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.
Nonpharmacologic 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 nonpharmacological interventions impact brain health and the course of AD and AD-related dementias. [2012 AD Summit: 5B, 5C, 5D, and 5F]	Identification of at least 3 new therapeutic targets for neuroprotection based on knowledge of mechanisms mediating the impact of nonpharmacological interventions of brain health in aging, AD, and AD-related dementias. Preclinical proof-of-concept for at least 3 types of nonpharmacological interventions that can inform clinical trial design.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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, and 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 AD-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 and ADRD Research Implementation Area	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 AD-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 AD-related dementias. [2012 AD Summit: 3D]	Development of at least 1 sensitive neuropsychological assessment measure that has been validated for the detection or tracking of the earliest clinical manifestations of AD and AD-related dementias.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Biomarkers	Develop and test methods for the standardization of immunoassays and mass-spectrometry/single reaction monitoring assay or other methodologies for CSF abeta and tau and other biomarkers as they become clinically applicable. Develop and test methods for standardization of collection and analysis of MRI and PET neuroimaging data. [2012 AD Summit: 3E]	CLIA laboratory qualification in US & the equivalent certification in the EU for at least one CSF biomarker of disease pathology. For neuroimaging data, qualification of at least one biomarker for use in clinical trials by the FDA and/or the EMA.
Trial Design	Convene a meeting that brings together epidemiologists, clinical trialists, clinical practitioners, representatives from industry, and patient advocates from diverse communities to formulate guidelines for defining clinically significant outcomes and methods for comprehensive analysis and interpretation of trial data. [2015 AD Summit: 3K]	Develop guidelines for defining clinically significant outcomes and methods for comprehensive analysis and interpretation of trial data.
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 1 large multisite 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).

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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, and 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.
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.
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, and 5E]	Completion of 12 Phase I drug trials for agents against 6 existing therapeutic targets.

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AD and ADRD Research Implementation Area	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, and 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 in 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 biosamples for interrogation of responsiveness. [2012 AD Summit: 3A, 3B, 3F, and 5E]	Comprehensive success/failure analysis of data from at least 3 phase III trials.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Drug Development - Novel Targets	Identify, characterize, and complete early validation for at least 6 novel therapeutic targets for AD and AD-related dementias (a minimum of 3 targets for presymptomatic 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, and 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.
Drug Development - Novel Targets	Initiate drug discovery efforts to develop novel therapeutic agents against at least 6 novel therapeutic targets (a minimum of 3 targets for presymptomatic and early-stage disease and a minimum of 3 for advanced disease). [2012 AD Summit: 1A, 1B, 1D, and 5A]	Complete preclinical development, through IND filing, of at least 12 therapeutics agents against at least 3 novel targets (at least 1 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, these trials will provide evidence of target engagement. [2012 Summit: 3A, 3B, 3F, and 5E]	Completion of 12 phase I drug trials for agents against 6 novel targets, providing conclusive evidence of safety and target engagement.
Drug Development - Novel Targets	Initiate phase ll (proof of concept) drug trials for agents against 3-6 novel therapeutic targets. These trials will provide proof of mechanism and/or evidence of target engagement of the target being tested. [2012 AD Summit: 3A, 3B, 3F, and 5E]	Completion of at least 6 phase II drug trials for agents against novel targets, providing conclusive evidence of therapeutic mechanism/target engagement. Of these, at least 3 trials should be in asymptomatic, at-risk individuals (e.g. FAD or ApoE4 carriers, Down syndrome, amyloid positive, type II diabetes etc.)

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Drug Repurposing and Combination Therapy Development	Convene an advisory meeting of experts from the pharmaceutical industry, government, academia, FDA, and the nonprofit sector to advance rational drug repositioning and combination therapy based on translational bioinformatics and network pharmacology approaches and to explore opportunities for new public-private partnerships to facilitate drug rescue/repurposing and combination therapy. [2012 AD Summit: 4A, 4B, 4C, and 4D]	Development of recommendations for rational repositioning and combination therapy development. Development, negotiation, and implementation of appropriate agreements among the stakeholders involved in repositioning and combination therapy of drugs for AD and related dementias. These agreements should address legal issues, intellectual property rights, and liability to expedite rigorous clinical testing of repurposed drugs.
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/subnetworks 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, and 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/nonpharmacologic 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 and ADRD Research Implementation Area	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, and 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 AD-related dementias. [2012 AD Summit: 4A, 4B, 4C, and 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: advancing nonpharmacological interventions for the cognitive and behavioral symptoms of AD and AD-related dementias by nonpharmacological treatments, informing the design of therapeutic approaches combining pharmacological and nonpharmacological treatments and identification of best practices for implementation of nonpharmacological interventions. [2012 AD Summit: 5B, 5C, 5D, and 5F]	Recommendations developed for advancing nonpharmacological interventions for AD and ADRD treatment and prevention to enable successful implementation of effective nonpharmacological interventions.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Nonpharmacologic Interventions	Initiate clinical trials for at least 3 nonpharmacological 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, and 5F]	Completion of at least 2 phase II trials for nonpharmacological 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.
Nonpharmacologic Interventions	Initiate clinical trials for at least 3 interventions combining pharmacological and nonpharmacological interventions for AD and ADRD treatment or prevention. Of these, at least 1 trial will be a pivotal phase III trial. [2012 AD Summit: 5B, 5C, 5D, and 5F]	At least 2 phase II trials completed for interventions combining pharmacological and nonpharmacological interventions for AD and ADRD treatment or prevention with conclusive evidence of therapeutic mechanism. Comprehensive success/failure analysis of data from at least 1 phase III trial.
Nonpharmacologic Interventions	Initiate at least 1 clinical trial for primary prevention of AD and AD-related dementias among high risk individuals in midlife, including a nonpharmacological treatment arm. [2015 AD Summit: 3B, and 3D; 2012 AD Summit: 5.E]	Completion of at least 1 Phase II primary prevention trial for nonpharmacological interventions in midlife. Successful trials will provide evidence for potential therapeutic mechanisms and include the collection of biomarker data for future validation and longitudinal follow-up within the trial cohort.
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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Trial Design	Support research on the effectiveness of dissemination methodologies to facilitate the implementation of effective prevention strategies. [2015 AD Summit: 3L]	Launch at least 3 research projects evaluating the effectiveness of dissemination methodologies.
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, and 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 AD-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 that provides participants an option for broad sharing of deidentified data in various types of clinical research on AD and AD-related dementias. [2015 AD Summit: 1C, 5H]	Launch at least 3 clinical research studies with electronic consenting methods that give participants the option for broad sharing of deidentified data.
Public-Private Partnerships	Convene an advisory meeting focused on facilitating public-private partnerships aimed at accelerating the development of effective therapies for AD and ADRD treatment and prevention. [2012 AD Summit: 1H, 1I, 1K, and 6C]	Established working groups on: Rapid Data Sharing and Analysis, Enabling Bidirectional Translation in AD Drug Development, Eliminating IP Barriers for Target Validation Through Clinical Proof of Concept.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Public-Private Partnerships	Convene meetings of the working groups for Rapid Data Sharing and Analysis, Enabling Bidirectional Translation in AD and ADRD Drug Development, 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, and 6C]	Recommendations developed on 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); creation of computational tools for development of biological network models of AD, AD-related dementias and normal aging; creation of tools that will foster development of bio network models that provide a predictive framework for using drugs in combination or singly removing legal and IP barriers surrounding data sharing. One or more partnerships established to accelerate key steps in AD drug development.
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).
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 1 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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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 multistakeholder partnership aimed at enabling the sharing of all data and biosamples from preclinical and clinical studies
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, and 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 nontraditional 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.
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 of environmental exposure on the pathogenesis of AD and AD-related dementias and/or on responsiveness to treatment.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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 and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Population Studies	Develop state-of-the-art protocol for assessing dementia on large, nationally representative samples that include racial/ethnic subsamples large enough to support disparities research and are adaptable for use in comparable studies around the world. [2015 AD Summit: 1B, 1.D, 3C, 3D, and 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 AD-related dementias, and responsiveness to treatment.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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 3 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.
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.
Care and Caregiver Support		
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, and 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 1 sensitive and robust measure for the detection of the earliest manifestations of caregiving burden and for monitoring its long-term consequences.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Research on Care and Caregiver Support	Establish data infrastructure for the study of dementia caregiving. [2015 AD Summit: 4.B, 4.E, and 4.F]	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.
Research on Care and Caregiver Support	13.D: 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, and 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 1 novel association, target, pathway, or intervention target or approach through use of the database.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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, and 5F]	Support research projects that will inform the design of cost-effective, community-based, informal caregiving intervention tools that address unmet psychological and physical health needs of caregivers and that ensure a safe home environment, to enable individuals with AD and AD-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 and ADRD Research Implementation Area	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, and 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, and 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 and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Research Resources		
Data Sharing and Reproducibility	Provide resources to make datasets from existing and legacy clinical research studies on AD and AD-related dementias widely accessible 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 AD-related dementias annotated, curated, and 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, and 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 datasets 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 datasets. - 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 and ADRD Research Implementation Area	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	Provide support for storage and rapid distribution 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 AD-related dementias.
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 1 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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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: therapeutic target selection and initial target validation, predictive toxicology, and 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 1 multicenter clinical trial that utilizes a national IRB.
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, and all aspects of data science, as well as traditional and emerging drug discovery disciplines. [2015 AD Summit: 1J, 4D, and 4E]	Establish new training programs, as well as fellowship and career development programs to develop a new translational and data science workforce.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
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, and 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	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 eliminate the stigma of aging and dementia; provide accurate, evidence-based information on environmental and lifestyle factors associated with the development and maintenance of a healthy brain and cognition; and encourage participation in clinical trials. [2012 AD Summit 6A]	Launch national public education campaign to eliminate the stigma of aging and dementia; provide accurate, evidence-based information on environmental and lifestyle factors associated with the development and maintenance of a healthy brain and cognition; and 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 education 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 and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Recruitment and Citizen Engagement	Establish a working group including clinical trial recruitment experts to dynamically evaluate and update the materials and information provided in the central resource.	Recommendations for successful recruitment methods.
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.
Alzheimer's Disease-Related Dementias		
ADRD 6: Vascular Contributions to Cognitive Impairment and Dementia (VCID), Including Vascular Cognitive Impairment and Vascular Dementia Focus Area 2: Human-Based Studies	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 2 human SVD cohorts. Identify a neuroimaging marker for the vascular pathology of arteriolosclerosis. <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 2 SVD cohorts.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 4: Lewy Body Dementias (LBD) Focus Area 3: Develop and Validate Biological and Imaging Biomarkers	Develop imaging approaches to enhance the differential diagnostic accuracy of LBD compared to other dementing illnesses, detect latent and prodromal LBD, and 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 1 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 a-synuclein or other relevant radiopharmaceuticals) with an emphasis on multimodal studies.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 3: Health Disparities (HD) Focus Area 1: Treatment and Prevention Strategies	Assess epidemiology and mechanistic pathways of disparities in health burden of AD/ADRD.	Initiate and/or leverage at least 2 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 2 studies investigating whether changes in risk factors for cognitive impairment and dementia occur over the life course in diverse populations. Identify critical periods of life and critical lifestyle and other parameters with respect to cognitive impairment and dementia prevention. Complete at least 2 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).

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 3: Health Disparities (HD) Focus Area 2: Monitoring Changes in AD/ADRD Disparities	Develop a system to monitor the magnitude and trends in health disparities in incidence of AD/ADRD.	Complete at least 1 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.
ADRD 4: Lewy Body Dementias (LBD) Focus Area 1: Establish Longitudinal Diverse Cohorts with Common Measures, Culminating in Autopsy	Initiate clinical trials for motor and nonmotor manifestations of 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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 5: Frontotemporal Lobar Degeneration (FTD) Focus Area 2: Clinical Science	Develop FTD biomarkers for diagnosis and disease progression.	Development, testing, and pathological confirmation of at least 1 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 populations in biomarker development and testing studies described above.
ADRD 1: Multiple Etiology Dementias (MED) Focus Area 1: Improved Diagnostic Skills in the Community	Develop diagnostics/biomarkers in asymptomatic individuals.	Develop at least 1 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 1 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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 1: Multiple Etiology Dementias (MED) Focus Area 1: Improved Diagnostic Skills in the Community	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: basic, basic disease-related, or clinical researchers; clinicians who lead clinical research or clinicians who support clinical research (e.g. by supporting enrollment in clinical trials); and clinicians who 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 the later stage in training health professionals (MD, PhD, and other relevant health professionals) to attend the AD/ADRD Summits.
ADRD 4: Lewy Body Dementias (LBD) Focus Area 1: Establish Longitudinal Diverse Cohorts with Common Measures, Culminating in Autopsy	Create longitudinal clinical, biological, and imaging resources for LBD from the earliest stages to autopsy to improve accuracy of detection and diagnosis of dementia with Lewy bodies (DLB) at the predementia or prodromal stage and to detect Parkinson's disease patients with a high risk of cognitive decline leading to Parkinson's disease dementia (PDD).	Complete at least 1 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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 4: Lewy Body Dementias (LBD) Focus Area 2: Discover Disease Mechanisms Through Brain Mapping and Genetics	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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 1: Multiple Etiology Dementias (MED) Focus Area 2: Basic and Clinical Research in Interactions Between Dementia Pathophysiologies	Promote basic and clinical research in multi-etiology dementia.	Initiate at least 1 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 1 funding opportunity announcement that promotes understanding interactions among different neurodegenerative pathologies of dementia, e.g. beta-amyloid, tau, TDP-43, 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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 3: Health Disparities (HD) Focus Area 3: Assessment	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.	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 a 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 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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 1: Multiple Etiology Dementias (MED) Focus Area 3: Improved Diagnostic Skills in the Community	Determining the value of screening for clinically relevant cognitive impairment in the absence of a cognitive complaint.	Complete at least 1 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 1 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.
ADRD 4: Lewy Body Dementias (LBD) Focus Area 4: Model Disease Processes to Develop Potential Symptomatic and Disease-Modifying Therapies	Recognizing the importance of alpha-synuclein and AD pathophysiologic processes in LBD, new animal, cellular, and in vitro models are needed to 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 alpha-synuclein biology and how it is related to LBD, as well as alpha-synuclein interactions with beta-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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 4: Lewy Body Dementias (LBD) Focus Area 4: Model Disease Processes to Develop Potential Symptomatic and Disease-Modifying Therapies	Develop disease-modifying interventions for LBD based on discovering biomarkers, molecular targets, and genetic and environmental modifiers that enhance, delay or prevent the onset of disease.	Initiate 1 or more clinical trials that test prospective therapies based on pharmaceutical approaches, gene therapy, regenerative medicine, surgical interventions, or nonpharmacological approaches to prevent or alter disease processes.
ADRD 5: Frontotemporal Lobar Degeneration (FTD) Focus Area 1: Basic Science: Pathogenesis and Toxicity	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).

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 5: Frontotemporal Lobar Degeneration (FTD) Focus Area 2: Clinical Science	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.
ADRD 5: Frontotemporal Lobar Degeneration (FTD) Focus Area 2: Clinical Science	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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 6: Vascular Contributions to Cognitive Impairment and Dementia (VCID), Including Vascular Cognitive Impairment and Vascular Dementia Focus Area 1: Basic Mechanisms and Experimental Models	Develop next-generation experimental models and translational imaging methods for VCID. Establish new animal models that: reproduce small vessel disease and other key pathogenic processes thought to result in cognitive impairment; are easily applicable to both VCID and AD research for advances in mixed etiology dementias; address vascular contributions to dementia via both white matter and grey matter; or include genetic and acquired conditions that are associated with VCID.	Develop at least 1 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 1 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 1 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).

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 6: Vascular Contributions to Cognitive Impairment and Dementia (VCID), Including Vascular Cognitive Impairment and Vascular Dementia Focus Area 2: Human-Based Studies	Identify lifestyle and vascular interventions to treat, prevent, or postpone VCID.	Identify at least 1 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.
ADRD 1: Multiple Etiology Dementias (MED) Focus Area 1: Improved Diagnostic Skills in the Community	Improving differential diagnosis of symptomatic cognitive impairment.	Initiate 1 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, and 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.

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AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 4: Lewy Body Dementias (LBD) Focus Area 3: Develop and Validate Biological and Imaging Biomarkers	Use new or existing longitudinal case-control studies of individuals with LBD, longitudinal cohort studies tracking cognitive decline, or studies capturing incident cases of LBD to develop biomarkers for LBD-related pathologic changes, diagnosis, differential diagnosis, disease progression, and the relative 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.	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 1 novel biomarker using well-characterized LBD samples in existing LBD clinical trials or a new large study.