FY 2020 Alzheimer's Disease and Related Dementias Bypass Budget Milestones

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Population Studies and Precision Medicine Research	1.A: Enable precision medicine research by supporting deep and longitudinal molecular endophenotyping of existing and new at-risk cohorts as well as cohorts and/or individuals who resist disease despite high genetic risk (e.g., Down syndrome, ApoE 4 homozygous, FAD mutation carriers). Ensure that these efforts include and prioritize molecular profiling in cohorts from special populations and patients with atypical AD and ADRD (e.g., Down syndrome, early- and late-onset familial AD, early-onset non-autosomal dominant AD), ethnic minorities, and other under-represented groups. [2015 AD Summit: 1A, 2A, 2B, and 3A; 2018 AD Summit: 2C and 3B].	Initiate at least six research programs to support: • longitudinal and postmortem collection and rapid distribution of biosamples from brain and peripheral tissues in existing and newly launched cohorts across diverse population groups. • generation of high-quality, multiomic data (e.g., genomic, epigenomic, proteomic, metabolomics, microbiome) as a public/community resource to maximize data accessibility and usability for downstream analyses. • collection of nontraditional data modalities to complement the rich phenotypic clinical and molecular data, using wearable sensors and mobile health technologies. • high-quality data curation, annotation, and data storage/big-data infrastructure to ensure that the data are made broadly and rapidly available as a public resource according to FAIR data standards.
Population Studies and Precision Medicine Research	1.B: Quantify the exposome in existing and new AD cohorts to gain a more precise measure of environmental exposure factors and their relationship to AD risk and individual trajectories of disease progression. These studies should employ a life-course approach across diverse populations (e.g., race, ethnicity, immigration status, geographical region, education, age, gender) and incorporate methods aimed at understanding how ancestry, race/ethnicity, and socioeconomic disparities interact with exposome factors to modulate AD risk. [2015 AD Summit: 3B and 3D; 2018 AD Summit: 5A and 5B; 2017 Dementia Care Summit: 1.1, 1.2, and 1.3]	Provide supplemental funding to at least six clinical research studies to explore the impact of environmental exposure on the pathogenesis of AD and AD-related dementias and on responsiveness to treatment. Launch at least three clinical research studies that incorporate deep molecular phenotyping, new environmental and behavioral sensors, and cognitive assessment technologies to detect the impact of the exposome on AD risk and resilience. Provide funding to enhance existing data resources with information on early-life exposures/events. Provide funding to enhance administrative data linkages.
Population Studies and Precision Medicine Research	1.C: Continue to establish new cohorts that include participants across diverse racial, ethnic, and socioeconomic backgrounds and incorporate the collection of multiomic and clinical data (e.g., imaging, personal wearables, sensors for in-home monitoring) to accelerate the identification of genomic variants and other risk and protective factors contributing to the heterogeneity and multifactorial etiology of dementia and to enable the development of predictive models of disease and wellness. Ensure that these cohorts represent the current and future projected population trends. [2015 AD Summit: 1B and 3C; 2018 AD Summit 2A and 2B; 2017 Dementia Care Summit: 1.1, 1.2, and 1.3].	Establish at least three new cohorts that incorporate deep molecular endophenotyping with participants of African, Native American, Asian, mixed ancestry (e.g. Latinos), as well as younger cohorts (midlife and younger). 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 collection, storage, and rapid distribution of biosamples, including brain tissue.

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Population Studies and Precision Medicine Research	1.D: Develop a state-of-the-art protocol for assessing dementia on large, nationally representative samples that includes racial/ethnic subsamples large enough to support disparities research and is adaptable for use in comparable studies around the world. [2015 AD Summit: 1B, 1D, 3C, 3D, and 4B; 2017 Dementia Care Summit: 1.1, 1.2, and 1.3].	Archive and share data for use by the research community. Update national estimates of the prevalence and incidence of dementia and cognitive impairment, and address important questions about the epidemiology and population impact of dementia. Repeat national estimates in 2021 to measure trends in dementia prevalence. Support research projects comparing international differences, to identify potential risk and protective factors. Support research on health disparities by racial and ethnic groups. Use existing cohort studies to investigate critical periods for intervention success; include cohort well before midlife.
Population Studies and Precision Medicine Research	1.E: Expand existing large-scale, open-science molecular profiling efforts by: • increasing the bandwidth for the generation and analysis of high-quality molecular data (e.g., genetics and epigenetics, transcriptomics, proteomics, metabolomics, lipidomics, glycomics, exposome) from human tissues and cell lines. • investing in the development of methods for multiscale modeling across omics data types. • ensuring that diverse cohorts and special populations are included and prioritized in these efforts. [2018 AD Summit: 3B]	Provide supplemental funding to at least six existing projects or programs that are generating high-dimensional on human aging cohorts to close key molecular data gaps, including molecular profiling for posttranslational modification, methods development for multiscale modeling, and inclusion of samples from diverse cohorts and special populations. Ensure that existing and newly funded projects continue to operate under open-science principles.
Population Studies and Precision Medicine Research	1.F: Support the inclusion of measures of AD-related phenotypes and environmental exposures in non-AD cohorts to enable new discovery research and to accelerate cross-validation of discoveries made in AD cohorts. [2018 AD Summit: 5C]	Provide supplemental funding to at least six clinical research studies on well-phenotyped, diverse, midlife cohorts, to explore the impact of environmental exposures on the pathogenesis of AD and AD-related dementias. These efforts should include support for the development of novel, open-source computational methods for data mining and data integration.
Population Studies and Precision Medicine Research	1.G: Augment current and future human cohorts with more advanced, longitudinal immunological profiling (e.g., Cytof) to enable precision medicine research and to better understand the roles of the different arms of the central nervous system and peripheral immunity in brain aging and AD. [2018 AD Summit: 1H and 2E]	Provide supplemental funding to support longitudinal immunologic profiling to existing and newly launched midlife and aging cohorts with rich phenotypic data on brain health.
Population Studies and Precision Medicine Research	1.H: Enable access to electronic health records data and provide support for their integration with clinical and molecular data to build person-specific predictive models of disease and wellness and to enable disease subclassification. These efforts should include better electronic phenotyping of AD through the application of machine learning methods. [2018 AD Summit: 2G, 2H, and 4K]	Hold an advisory meeting focused on understanding and overcoming barriers to sharing and the usability of electronic health records in the U.S. and globally. Initiate a research program focused on electronic phenotyping of AD through the application of machine-learning methods and integration of EHR data with genomic, molecular, clinical, and other patient-relevant data to build person-specific models of disease, to identify disease subtypes, and to identify biomarkers and molecular signatures for these subtypes.

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Research on Disease Mechanisms	2.A: 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 neurodegeneration, AD, and AD-related dementias to better understand the mechanism(s) of vulnerability and resilience in AD across all levels of biologic complexity (from cellular to population level) and 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; 2018 AD Summit: 1A and 1H]	Launch at least six new research programs that use data-driven, systems-based approaches to integrate AD and ADRD research with the study of the fundamental biology of aging and the neurobiology of aging. These programs should support epidemiologic, genomic, and basic research to understand: • the dynamic interaction between aging and neurodegeneration. • mechanisms underlying individual differences in trajectories of brain aging, disease risk, age of onset, progression, and clinical presentation. Ensure that these integrative research studies include underrepresented minority populations and patients with extreme phenotypes, atypical presentations of AD.
Research on Disease Mechanisms	2.B: Establish new research programs that employ data-driven, systems-based approaches to understand the interaction between peripheral systems (in particular: immune, metabolic, and microbiome) and the brain and the impact of this interaction on brain aging and neurodegeneration. These efforts should integrate human and animal model research and characterize the extent to which molecular (e.g., epigenomic, transcriptomic, metabolomic) variation identified in peripheral tissues can be used as a proxy for interindividual variation in the trajectories of brain aging, AD, and AD-related dementias. [2015 AD Summit: 1D, 2A, 3E, 3F, 3I, 3H, and 3J; 2018 AD Summit: 1H and 2N]	Launch at least six new research programs 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. Provide support for studies that align blood and brain omics from longitudinal mouse and other preclinical models with human blood and brain omics to enable cross-species dynamic modeling of the trajectory of brain aging and disease progression.
Research on Disease Mechanisms	2.C: 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; 2018 AD Summit: 5G]	Launch at least six new projects focused on exploring epigenetic mechanisms that underlie the heterogeneity of AD and AD-related dementias and the causal role of the exposome in brain aging and AD/ADRD.
Research on Disease Mechanisms	2.E: 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 three projects should focus on understanding the mechanisms of risk reduction by APOE2.
Research on Disease Mechanisms	2.F: 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 at multiple levels (e.g., epigenetic, gene expression, proteomic, neuronal, network, systems) to identify new targets and approaches for AD prevention. [2015 AD Summit: 3J; 2018 AD Summit: 5E]	Launch at least 12 new projects focused on understanding the short-term and long-term consequences of disrupted/optimized circadian rhythms and sleep on brain aging and dementia and the mechanistic links between sleep/circadian disruption and AD and related dementias, to identify new targets and approaches for AD prevention.

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Research on Disease Mechanisms	2.G: Maximize the translational potential of genetics research by ensuring rapid and broad sharing of large-scale genetic/genomic data, similar to the open-science, data-sharing model of the AMP-AD program and by supporting programs focused on: • understanding the mechanisms by which genetic variants (including ApoE), discovered through GWAS and sequencing studies, influence AD risk • integrating genomic data with other multiomics data from brain, peripheral tissues, and iPSC cellular models from well-phenotyped cohorts • establishing the gene basis and directionality for genetic variant association so gene networks can be annotated with causality as tools for drug discovery. [2018 AD Summit: 1B, 1C, and 3A]	Launch an open-science research program focused on generating knowledge on the mechanisms by which genetic variants influence AD risk and the directionality for genetic variation association. Develop gene networks that are annotated with causality as open source, analytical tools for drug discovery.
Research on Disease Mechanisms	2.H: Continue to support cross-disciplinary research to discover and understand disease mechanisms that are common between AD and other neurodegenerative disorders, including rare disorders, and leverage these for therapy development. These efforts should include discovering new pathways leading to synaptic and neural damage and understanding the structural variations of pathogenic peptides collected from well-phenotyped, diverse cohorts, to inform the design of structure-specific imaging agents and inhibitors with therapeutic potential. [2018 AD Summit 1H, 4M, and 7H]	Identify and preclinically validate at least three novel therapeutic targets that are common to AD and at least two other neurodegenerative disorders. Launch a minimum of three drug discovery projects targeting pathways common across AD and at least two other neurodegenerative disorders.
Research on Disease Mechanisms	2.I: Enable a systems biology approach to decipher the complex role of the microbiome in brain aging and AD/ADRD and as a modifier of responsiveness to treatment, both pharmacologic and nonpharmacologic. Robust and rigorous study of the microbiome will require that relevant biosamples, high-quality molecular data, and analytical tools are made available as a community resource. [2018 AD Summit: 2J and 5D]	Support microbiome molecular profiling (e.g., metagenome, metatranscriptome, metaproteome, metabolome) across diverse cohorts and in clinical trials to enable systems-based, data-driven approaches aimed at understanding the role of the microbiome in disease heterogeneity, gene-environment interactions, health disparities, and differential responsiveness to treatment. Ensure that these efforts mandate rapid and broad sharing of data, analytical tools, and biosamples, and that they leverage the resources and knowledge generated by the NIH Common Fund Human Microbiome Program.
Research on Disease Mechanisms	2.J: Expand research on the role of social and psychosocial factors, on AD risk and resilience to risk in ethnically and socioeconomically diverse populations to interrogate mechanisms of disparities in health burden of AD and inform intervention strategies and public health policy. These efforts should utilize a life-course approach. [2018 AD Summit: 5F; 2017 Dementia Care Summit: 1.1, 1.2, and 1.3]	Initiate at least six research projects focused on understanding heterogeneous mechanistic pathways of disparities in health burden of AD, testing whether causal pathways to AD differ across disparities populations and identifying critical windows of vulnerability to AD risk.

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Data Sharing and Reproducibility	3.A: Provide resources to make datasets from high-value, publicly funded clinical research/cohort studies widely accessible, usable, reusable, and interoperable. Ensure that studies generating rich molecular and digital datasets on well-phenotyped cohorts make all traditional, derived, and raw data and all data-coding files associated with any published studies available for secondary use in discovery and replication research. [2015 AD Summit: 3A; 2018 AD Summit: 6H and 6I]	Provide funding to make datasets from high-value, publicly funded clinical research/cohort studies annotated, curated, and widely available via web-based resources. Provide support to modernize the data management, data governance, and data infrastructure of high-value existing and legacy cohorts to maximize data accessibility, usability, and interoperability. Ensure adequate support for storage, curation, and annotation of data from clinical research/cohort studies, and make rapid and broad sharing of data a condition for new and continued funding across federal and nonfederal/philanthropic funding organizations.
Data Sharing and Reproducibility	3.B: Provide support to establish and improve interoperability among relevant biomedical data repositories. Democratize the use of large-scale molecular and clinical data by building computational infrastructure for sustainable data storage and processing that will be accessible to researchers worldwide. This should include support for web-based tools and interfaces to allow data mining and analyses of summary results. [2015 AD Summit 4C; 2018 AD Summit 2Q and 6H]	Provide supplemental funding to establish and improve the interoperability among relevant biomedical data repositories funded by NIH or other funding agencies. Expand existing and build new computational infrastructure for sustainable data storage, data curation, and data management, to enable rapid and broad high-fidelity data sharing accessible to researchers worldwide. Support the development of web-based tools and interfaces to allow data mining and analyses of summary results by data scientists, biologists, clinicians, and citizen scientists.
Data Sharing and Reproducibility	3.C: Increase transparency in reporting and reproducibility of research findings by incentivizing and enforcing rapid sharing of raw and processed data, analytical methods, and details of experimental design and by promoting early sharing of research observations through preprint servers. [2018 AD Summit: 1I, 1J, 7G, and 7I]	Develop a partnership across federal and nonfederal AD funding agencies to align incentives and policies for data sharing, independent replication of research findings, and unrestricted access to reagents and research tools.
Data Sharing and Reproducibility	3.D: Enable access to data and associated biosamples and biomarkers from completed, ongoing, and future federally and privately funded clinical trials, to clarify the biomarkers' predictive and theragnostic value, to identify surrogate endpoints and to advance the understanding of heterogeneity of disease and treatment response. [2018 AD Summit: 2P, 4J, 7B, and 7C]	Provide supplemental funding to enhance completed and ongoing clinical trials with molecular profiling of minimally invasive specimens (e.g., serum, peripheral monocytes, microbiome) and use these molecular signatures as indicators of responsiveness and for disease subclassification. Develop standard consenting language and simplified data and material transfer agreements and support big-data infrastructure to ensure the rapid, widespread, and appropriate use and reuse of data and biosamples. Align funding incentives across federal and nonfederal/private trial sponsors to ensure rapid and broad access to data and associated biosamples and biomarkers from legacy, ongoing, and future clinical trials.

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Data Sharing and Reproducibility	3.E: Accelerate independent evaluation of research findings by mandating the open distribution of publicly and privately or philanthropically funded computational and experimental research tools for their use and reuse across the research community. Establish mechanisms to harmonize methods and outcomes across all research domains including SOPs and best practices for all stages of analysis so that they can be reused, evaluated, and expanded. [2018 AD Summit: 7D and 7F]	Align funding requirements and policies across federal and nonprofit funding agencies supporting AD research to ensure open distribution of computational and experimental research tools and to support harmonization of methods and outcomes across all research domains, including SOPs and best practices for all stages of analysis.
Data Sharing and Reproducibility	3.F: Democratize the use of large-scale molecular and clinical data by building computational infrastructure for sustainable data storage and processing that will be accessible to researchers worldwide. This should include support for web-based tools and interfaces to allow data mining and analyses of summary results. [2018 AD Summit: 2Q, 3I, and 7E]	Establish and maintain cloud-based resources for data storage, sharing, and compute; enable reproducible computational analysis and support cloud-based compute costs such that researchers are not limited by their access to local compute services.
Translational Tools, Infrastructure, and Capabilities	4.B: Create infrastructure and 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; 2018 AD Summit: 2O and 3F]	Create at least one translational center for animal model resources. Support the generation of large longitudinal, multiomic data on existing and newly developed transgenic mouse models necessary to build molecular network maps that connect molecular attributes of AD across mouse models and humans. Enable comprehensive analyses of clinical and deep omics profiles in panels of genetically diverse mice, which better model human genomes.
Translational Tools, Infrastructure, and Capabilities	4.C: Continue to develop animal models with higher predictive validity for use in preclinical drug development and to accelerate the discovery of translationally relevant disease mechanisms and treatment strategies. [2018 AD Summit: 2O, 2N, 3F, and 3G]	Expand the existing open-source/open-science translational infrastructure for next-generation AD animal models by developing: • new transgenic mouse models with humanized immune systems expressing AD risk-related human genes for use in preclinical drug development and to gain a better understanding of the role of the immune system in risk and progression of AD/ADRD. • nonmurine models, including nonhuman primates, for use in comparative aging biology and integrative physiology studies of AD pathophysiology. • animal models for the neuropsychiatric symptoms of AD.
Translational Tools, Infrastructure, and Capabilities	4.D: Expand biorepository infrastructure to enable storage and rapid distribution of clinical data and biosamples collected from diverse populations for deep molecular phenotyping. These resources should include biorepositories for samples and clinical data from ongoing clinical trials to support multiomic data generation. [2015 AD Summit: 2K and 6A; 2018 AD Summit: 2I, 2P, 4J, 7B, and 7C].	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. Develop standard consenting language and simplified data and material transfer agreements. Support data and sample sharing platforms to ensure the rapid, widespread, appropriate, and productive use of data and samples.

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Translational Tools, Infrastructure, and Capabilities	4.E: 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; 2018 AD Summit: 3D]	Create a repository of fully characterized, quality controlled, and fully sequenced reference iPSC lines accessible to the wide research community that can serve as: • a standard control for healthy genotypes and for generating edited-isogenic lines carrying specific AD risk variants. • a source of cell lines from individuals from diverse cohorts with AD-related phenotypes and specific naturally occurring mutations/risk alleles. • a resource to test and provide reference data on protocols to generate all CNS cell types.
Translational Tools, Infrastructure, and Capabilities	4.F: Develop improved iPSC protocols for all relevant cell types and human-based organoid model systems. Support the development of co-culture systems utilizing 3D organoid-like spheres to recapitulate complex interactions in a dish and develop novel ex-vivo models of "cognition in a dish" and "ancestry in a dish" for precision medicine research. Invest in the development of high-throughput systems of AD-relevant cells and organoids driven by robotics with digital readouts (such as high content imaging) to leverage reinforcement learning techniques for more data-driven target discovery and screening. [2015 AD Summit: 2H; 2018 AD Summit: 1G, 2N, and 3E]	Establish infrastructure to develop standardized and deeply phenotyped in vitro model resources, including iPSC-based and primary cells, brain slice, and organoid models. Establish the translational validity of these in vitro models to recapitulate the molecular/network perturbations identified in the individual (human or animal) from which the in vitro model was generated. Ensure rapid and broad distribution of the cell-based and organoid research models, data, and analytical methods for use in basic research and therapy development, similar to the open-science/open source principles of the MODEL-AD Consortium.
Translational Tools, Infrastructure, and Capabilities	4.G: Support quantitative systems pharmacology approaches that couple biological network and pathway analyses with mechanistic systems models and integrate data from disparate sources (e.g., preclinical, clinical, in vitro, ex vivo, in vivo, acute, chronic intervention) to enable predictive drug development. These efforts should: • encourage precompetitive academic–industry collaborations • ensure full-transparency of data and analytical methods development • support cross-disciplinary training in all aspects of quantitative systems pharmacology, spanning experimental and clinical work to various types of modeling and simulation. [2012 AD Summit: 2A and 2B; 2018 AD Summit: 3J, 3K, and 4F]	Create a network of translational centers that will develop and apply the principles of quantitative and systems pharmacology to AD and ADRD drug development. These centers will bring together expertise and technology needed for integration of multimodal 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; rigorous preclinical efficacy testing and development of translatable, preclinical biomarkers; comprehensive success and failure analyses; and implementation of precision medicine principles in clinical trial design. The centers will also provide training in all aspects of quantitative systems pharmacology, spanning experimental and clinical work to various types of modeling and simulation for the next generation of translational scientists.

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Translational Tools, Infrastructure, and Capabilities	4.J: Expand existing and create new integrative training programs for junior neuroscience, behavioral, and social science researchers (predoc, postdoc, and junior faculty) that include training in aging biology, systems biology, geriatrics, all aspects of data science, and traditional and emerging drug discovery disciplines. These efforts should include cross-disciplinary training programs in AD, aging, epidemiology, neuropsychology, environmental health, genomics, and data science, to enhance the workforce needed for research on gene–environment interactions in AD and AD health disparities. Establish new training programs and fellowship and career development programs to develop a new translational and data science workforce. [2015 AD Summit: 1J, 4D, and 4E; 2018 AD Summit: 4N, 5M, and 6J; 2017 Dementia Care Summit: 5.4]	Establish new training programs as well as fellowship and career development programs to develop a new translational and data science workforce. Provide support for digital health workshops and training programs for researchers from academia and industry.
Translational Tools, Infrastructure, and Capabilities	4.K: Leverage the power of human genetics to enable precision medicine research for AD by: • improving the accessibility of large-scale AD genetics data • expanding genetics efforts across AD and ADRD cohorts as open science programs, similar to the Psychiatric Genetics Consortium and AMP-T2D consortia, • encouraging commercial entities to share genetic data. [2018 AD Summit: 2R and 3A]	Support a large-scale, coordinated, genotyping/sequencing effort across AD and ADRD cohorts. Develop an open-access, aggregated genetics data search engine/portal for Alzheimer's and related disorders (akin to the AMP-T2D portal) to facilitate access to genetic data and analyses by the wide research community and to enable commercial entities to share genetic data.
Translational Tools, Infrastructure, and Capabilities	4.L: Support standardized, single-cell molecular profiling (e.g., genomic, proteomic, metabolomic) and open-access data infrastructure to develop a single-cell atlas for the aging brain, AD, and ADRD that can be queried by data scientists and basic and clinical researchers. The selection of samples for single-cell profiling needs to be optimized to allow integration of molecular profiles with existing clinical and whole-tissue molecular data (from brain and peripheral tissues) generated on the same individuals, to aid novel target and biomarker discovery for precision medicine. Support the development of integrative, computational models of cellular interactions in the CNS underlying brain aging and transition to AD and ensure their rapid and wide dissemination to the research community. These efforts should include research on: • understanding cell-specific vulnerability to beta-amyloid, tau, and other pathogenic insults. • neuron-glia, glia-glia, and other intercellular interactions in the context of brain aging and AD/neurodegeneration. [2018 AD Summit: 1D, 1E, 1F, 2K and 3C]	Launch a program to support deep, single-cell molecular profiling using cells from participants from at least six diverse cohorts to complement whole brain and peripheral tissue molecular profiling conducted in the same participants. Provide support for adequate hosting, curation, analyses, and mining of the datasets and network models via existing and/or new data-sharing platforms.

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Translational Tools, Infrastructure, and Capabilities	4.M: Support the development of genome-scale metabolic models to capture the heterogeneity of metabolic transitions from healthy to pathologic brain aging and use the metabolome as a functional readout for other omics data to delineate pathways implicated in disease initiation and progression and to identify disease subtypes. [2018 AD Summit: 3H and 2H]	Provide support for: • generation of high-quality targeted and nontargeted metabolomic profiling data across diverse, human cohorts (spanning midlife through extreme old age) for which genetic and rich clinical data are available. • development of analytical methods needed to integrate metabolomic data with genetic, molecular imaging, and other clinical data. • development of open-source, genome-scale, metabolic models for use in target validation and disease subclassification.
Translational Tools, Infrastructure, and Capabilities	4.N: Provide support for high-cost capital equipment/core facilities and staff training to make available for wide use high-throughput technologies such as molecular profiling, cryo-EM, advanced human brain imaging, and other emerging technological capabilities. [2018 AD Summit: 3L]	Launch a research resource initiative to support high-cost capital equipment.
Translational Tools, Infrastructure, and Capabilities	4.O: De-risk novel candidate targets by supporting the development of high-quality, open-source, target-enabling tools that can serve as starting points for drug discovery campaigns or as research tools to understand the biology of “dark targets." [2018 AD Summit: 3M]	Enable the development of target-enabling packages (TEPs) for up to 100 novel, disease-relevant, candidate targets derived via unbiased, data-driven approaches. These tools should include: purified target proteins/crystal structures, biochemical assays suitable for functional characterization and for compound screens; validated antibodies; cell-based assays for target modulation; potent and specific small molecules or biologics. Ensure that all data and reagents are made available to the wide community of researchers with no restriction on use.
Drug Development—Existing Targets	5.A: 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 AD Summit: 3A, 3B, 3F, and 5E]	Complete 12 Phase I drug trials for agents against six existing therapeutic targets.
Drug Development—Existing Targets	5.B: 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]	Complete three to six Phase II drug trials for agents against currently known targets, providing conclusive evidence of therapeutic mechanism/target engagement.
Drug Development—Existing Targets	5.C: Initiate Phase III drug trials for agents against at least three currently known therapeutic targets. Of these, at least one trial will be asymptomatic at-risk populations. These trials will incorporate a combination of biomarkers (e.g., fluid, 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]	Perform comprehensive success/failure analysis of data from at least three Phase III trials.

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Drug Development—Novel Targets	6.D: 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 three for advanced disease). [2012 AD Summit: 1A, 1B, 1D, and 5A; 2018 AD Summit: 4E]	Complete preclinical development, through IND filing, of at least 12 therapeutic agents against at least three novel targets (at least one novel target should be for presymptomatic disease). Invest in the expansion of therapeutic modalities, including natural products, gene therapy, antisense oligonucleotides, and cell therapy.
Drug Development—Novel Targets	6.E: Initiate first-in-human, Phase I drug trials for therapeutic agents against at least six novel therapeutic targets. These trials will provide evidence of safety and target engagement. [2012 AD Summit: 3A, 3B, 3F, and 5E]	Complete 12 Phase I drug trials for agents against six novel targets, providing conclusive evidence of safety and target engagement.
Drug Development—Novel Targets	6.F: 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]	Complete at least six Phase II drug trials for agents against novel targets, providing conclusive evidence of therapeutic mechanism/target engagement. Of these, at least three trials should be in asymptomatic, at-risk individuals (e.g., FAD or ApoE4 carriers, Down syndrome, amyloid positive, type II diabetes).
Drug Development—Novel Targets	6.H: Initiate interdisciplinary research programs that integrate clinical, genomic, 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; 2018 AD Summit: 1A]	Identify at least three 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. Perform preclinical proof-of-concept studies for at least three types of nonpharmacological interventions that can inform clinical trial design.
Drug Repurposing and Combination Therapy Development	7.C: Continue to develop resources, capabilities, and partnerships to advance data-driven drug repositioning and combination therapy. [2018 AD Summit: 4B, 4C, and 4D]	Support the development of an AD connectivity map, whereby genes, drugs, and disease states are connected by common gene and other omics expression signatures in disease-relevant cell types (iPSC neurons, microglia, astrocytes, mixed cell cultures, organoids). Establish an academic/industry partnership where industry partners can submit failed Phase II/III compounds for molecular profiling that would enable computational drug repositioning analysis for AD. Improve the regulatory environment for repurposing of drugs and combination therapies to obtain longer periods of exclusivity, similar to those for orphan indications.
Drug Repurposing and Combination Therapy Development	7.D: Initiate early clinical development for at least six existing drugs or drug combinations for the treatment or prevention of AD and AD-related dementias. [2012 AD Summit: 4A, 4B, 4C, and 4D]	Complete at least four Phase II trials with repurposed drugs and/or drug combinations. Successful trials will provide conclusive evidence of therapeutic mechanism/target engagement.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Nonpharmacologic Interventions	8.A: 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. • identification of best practices for implementation of non-pharmacological interventions. Develop culturally sensitive guidelines for social and behavioral interventions for AD and ADRD prevention to inform study design, cohort selection, intervention delivery and dosing, and outcomes assessments. Incentivize efforts to increase harmonization of protocols across studies to enhance research rigor and reproducibility. [2012 AD Summit: 5B, 5C, 5D, and 5F; 2018 AD Summit: 5L; 2017 Dementia Care Summit: 4.1 and 4.2]	Convene an advisory meeting that brings together social/behavioral research scientists with clinical trial and data science experts and patient advocates from diverse communities to formulate culturally sensitive guidelines for social and behavioral interventions for AD /ADRD prevention needed for study design, cohort selection, intervention delivery and dosing, and establishing meaningful outcomes. Develop recommendations for advancing nonpharmacological interventions for AD and ADRD treatment and prevention to enable successful implementation of effective nonpharmacological interventions. Provide support for the harmonization of protocols across social and behavioral intervention trials.
Nonpharmacologic Interventions	8.B: Increase investment in clinical trials that robustly test a variety of lifestyle interventions. Employ precision medicine research principles in nonpharmacologic interventions by incorporating deep molecular profiling and digital/wearable technologies for tracking responsiveness. [2012 AD Summit: 5B, 5C, 5D, and 5F; 2018 AD Summit: 4L and 5H; 2017 Dementia Care Summit: 4.1, 5.1, 5.4, and 12.3]	Initiate clinical trials for at least three nonpharmacological interventions aimed at AD and ADRD treatment and/or prevention. Ensure that the trials are designed to robustly test the therapeutic mechanism and to enable comprehensive success/failure analysis upon trial completion. Provide supplemental funding for at least six nonpharmacologic interventions to incorporate: • digital health devices to track adherence to treatment and treatment response. • deep, longitudinal multiomics profiling to understand mechanisms of action and person-specific trajectories of response. Employ engaged research models for stakeholder involvement as research partners, including centers and other research networks.
Nonpharmacologic Interventions	8.C: Support studies that employ data-driven approaches to robustly test the efficacy of multimodal interventions that combine pharmacological and lifestyle interventions. [2012 AD Summit: 5B, 5C, 5D, and 5F; 2018 AD Summit: 5H and 5I; 2017 Dementia Care Summit: 4.2]	Initiate clinical trials for at least three interventions combining pharmacological and nonpharmacological interventions for AD and ADRD treatment or prevention. These trials should incorporate digital health devices and deep, longitudinal molecular phenotyping to: • track person-specific trajectories of treatment response. • understand the therapeutic mechanism of action. • enable comprehensive success/failure analysis. Ensure inclusion of diverse populations in studies.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Biomarkers	9.A: 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 (e.g., ocular, olfactory), and biomarkers for detection and tracking of synaptic dysfunction. [2015 AD Summit: 1I and 2I; 2018 AD Summit: 3O]	Develop and validate at least 12 translatable biomarkers for use in preclinical and clinical drug development.
Biomarkers	9.B. Accelerate the development of the next-generation CNS imaging ligands and biofluid molecular signatures targeting a variety of disease processes (e.g., neuroinflammation, bioenergetic/metabolic compromise, oxidative stress, synaptic pathology) that can be used as research tools or developed into diagnostic, prognostic, theragnostic, or target engagement biomarkers. [2012 AD Summit: 1E; 2018 AD Summit: 3O]	Initiate synthesis and testing of CNS imaging ligands (PET/SPECT) for at least 12 novel, prioritized candidate targets. Ensure that these reagents are made available as open-source tools for target validation and predictive drug development. Identify at least six multiomic biomarker signatures (e.g., metabolomic, proteomic, cell-free RNAseq) that can be quantitatively measured in peripheral fluids and have been validated across at least three diverse cohorts.
Biomarkers	9.D: 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; 2018 AD Summit: 4F]	Enrich three to six Phase II (proof of concept) drug trials with imaging and/or fluid biomarkers for proof of target engagement and proof of clinical mechanisms.
Biomarkers	9.E: 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 three to six existing and three to six novel therapeutic targets are initiated. [2012 AD Summit: 1E]	Initiate at least three Phase III (pivotal) drug trials with imaging and/or fluid biomarkers to select at-risk subjects and/or for proof of target engagement.
Biomarkers	9.F: Initiate studies to develop minimally invasive biomarkers for detection of cerebral amyloidosis, AD, and AD-related dementias pathophysiology. [2012 AD Summit: 1F and 1G]	Develop and test at least three 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	9.H: 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; 2017 Dementia Care Summit: 2.3 and 2.5]	Develop at least one sensitive neuropsychological assessment measure that has been validated for the detection or tracking of the earliest clinical manifestations of AD and AD-related dementias. Extend ongoing research on social and emotional functioning and decision-making in MCI/AD to identify early behavioral markers of disease. Support research to develop clinical tools for assessment of early deficits in decision making, motivation, and social and emotional functioning in AD.
Trial Design	10.A: 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; 2017 Dementia Care Summit: 2.4 and 4.4]	Develop guidelines for defining clinically significant outcomes and methods for comprehensive analysis and interpretation of trial data. Fund research to advance methods for measuring person-centered outcomes, to include outcomes that matter to people with dementia and caregivers, including through self-report measures across the disease severity spectrum and care settings.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Trial Design	10.D: Create new research programs to implement innovative trial designs with a precision medicine research paradigm. These efforts should support the development of novel statistical approaches (e.g., Bayesian methods, modeling, simulations) for more efficient trial design and resources, to evaluate the utility of intermediate, prognostic endpoints and platform trials (e.g., umbrella, basket). [2015 AD Summit: 3K; 2018 AD Summit: 4F, 4G, and 4H; 2017 Dementia Care Summit: 2.1 and 2.2]	Launch at least six 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. Stratify participant risk groups in at least three clinical trials using dense omics and gene-environment interaction profiling. Support administrative data linkages with EHR and private payer claims data.
Enabling Technologies and Disease Monitoring	11.B: 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; 2018 AD Summit: 6M; 2017 Dementia Care Summit: 2.5]	Develop criteria and methods for screening, testing, and validating new technologies for disease monitoring. 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.
Enabling Technologies and Disease Monitoring	11.C: Embed wearable technologies and pervasive computing approaches in existing and new clinical research, longitudinal cohort studies, and clinical trials to enable continuous capture of various types of participant relevant data. Support development of wearable/sensor data standards and automated scripts that convert incoming data into a standardized format to enable their integration with other types of patient level data (e.g., clinical, molecular, digital). [2015 AD Summit: 4C, 4F, 4G, and 4I; 2018 AD Summit: 6G and 6D; 2017 Dementia Care Summit: 12.1, 12.2, 12.3, 12.4]	Introduce the use of mobile/pervasive computing technologies in at least three existing and three new clinical research studies conducted across diverse populations. 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. Include the development of wearable/sensor data standards and support for the development of automated scripts that convert incoming data into a standardized format to enable their integration with other types of patient level data (clinical, molecular, digital).
Enabling Technologies and Disease Monitoring	11.D: Support the development and commercialization of wearables that can increase rigor in measuring environmental exposures and intervention dosing for various nonpharmacological modalities (e.g., light, sound, sleep, physical activity). [2015 AD Summit: 4D; 2018 AD Summit: 5K; 2017 Dementia Care Summit 12.2, 12.3, and 12.4]	Launch at least 10 projects conducting research and commercialization efforts toward the development of wearable sensors that can be used to quantify: • disease monitoring. • environmental exposures. • intervention dosing for nonpharmacological modalities.
Enabling Technologies and Disease Monitoring	11.E: Build end-to-end secure, high-frequency data capture platforms to enable continuous monitoring of research participants across the disease trajectory; these capabilities should include remote methods for consenting and collection and validation of multiple health indices as digital biomarkers for health and disease. [2018 AD Summit: 6A; 2017 Dementia Care Summit: 12.1]	Provide support to develop at least one high-frequency data capture platform to enable: • secure, high-frequency monitoring of research participants across the disease trajectory. • remote methods for consenting and collection. • validation of multiple health indices as digital biomarkers for health and disease.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Recruitment and Citizen Engagement	12.F: Develop and deploy citizen-science methods to engage diverse and underrepresented populations including the full spectrum of age, race, ethnicity, and technological sophistication and access in optimizing approaches to disease monitoring and data sharing. Support projects that use citizen science to accelerate collection of various types of quantitative and qualitative patient-relevant data and data analyses. [2015 AD Summit: 5G; 2018 AD Summit: 6B; 2017 Dementia Care Summit: 5.4]	Launch at least three citizen science projects that use existing platforms or develop new, crowd-powered medical research platforms for collection and/or analysis of patient-relevant data. These projects should engage study participants across diverse and underrepresented populations in developing and optimizing the study design.
Recruitment and Citizen Engagement	12.G: 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 educate patients, caregivers, physicians, and other stakeholders on the importance of patient enrollment into clinical trials and natural history and noninterventional studies that could yield biomarkers for precision medicine research. [2012 AD Summit: 6A; 2018 AD Summit: 4Q; 2017 Dementia Care Summit: 6.1 and 6.4]	Launch 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 educate patients, caregivers, physicians, and other stakeholders on the importance of enrollment in clinical trials as well as natural history and noninterventional studies that could yield biomarkers for precision medicine research. Encourage recruitment of diverse populations. Launch a national campaign targeting primary care physicians to inform their assessments of patients for cognitive impairment and encourage referrals to clinical research. Disseminate the ROAR toolkit, develop additional training materials, and work with state and local aging services and public health providers to provide education and training for their clients.
Research on Care and Caregiver Support	13.A: 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, e.g., primary care, home health care, adult day care, nursing home, assisted living, hospice) on individuals, families, and society, and to inform design of new care delivery systems for individuals with dementia. [2015 AD Summit: 4K, 4B, 4J, and 5D; 2017 Dementia Care Summit: 3.1, 3.3, 3.4, 7.1, 7.3, 7.4, 7.5, and 7.6]	Define and characterize informal and formal caregiving, the domains of needs of caregivers and care recipients across the care continuum, the key social structural variables that contribute to variance in caregiving burden, and factors that characterize care delivery and care coordination models that reduce burden on caregivers and care recipients. Recommend research priorities on the impact of caregiving on caregivers' psychological and physical health, workforce participation, and financial security. Recommend research programs that can inform the development of new care models, including for those living alone.
Research on Care and Caregiver Support	13.B: 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; 2017 Dementia Care Summit: 3.2 and 3.3]	Identify and validate assessments suitable for use in a range of research contexts, including observational and interventional studies and large population-based surveys. Identify and validate at least one sensitive and robust measure for the detection of the earliest manifestations of caregiving burden and for monitoring its long-term consequences. Identify and validate at least one improved and cost-effective model of care that includes research on caregiver outcomes following the cessation of caregiving.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Research on Care and Caregiver Support	13.C: Establish data infrastructure for the study of dementia caregiving. [2015 AD Summit: 4B, 4E, and 4F; 2017 Dementia Care Summit: 3.1, 3.3, and 3.4]	Identify existing cohorts of nationally representative and cross-national samples and determine the need for data collection in new cohorts. Establish 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; 2017 AD Care Summit: 3.3]	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, intervention target, or approach through use of the database. Support research that addresses population disparities in impacts of caregiving.
Research on Care and Caregiver Support	13.E: 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; 2017 Dementia Care Summit: 3.4]	Support research projects that will inform the design of cost-effective, community-based, informal caregiving interventions and 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.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Research on Care and Caregiver Support	13.F: 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 nonresearch settings across the full care continuum, including patients in a variety of settings (e.g., home, nursing home, assisted living, hospice). [2015 AD Summit: 5B, 5C, 5D, and 5F; 2017 Dementia Care Summit: 9.4]	Conduct cluster randomized trials comparing interventions stemming from 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. This will allow researchers to follow longer-range health effects of caregiving and identify effective interventions. Identify programs that work best for different stages of the care continuum. Launch a research program to identify interventions with demonstrated reduction in harm to people with dementia due to elder mistreatment. Identify which programs work best with different population subgroups (e.g., racial, ethnic, geographic, socioeconomic). Develop new models of care that can be adopted by insurers. Collaborate with other federal agencies to disseminate caregiver training materials and interventions based on research.
Research on Care and Caregiver Support	13.H: Create research programs to evaluate novel and innovative dissemination and implementation methods to scale up promising practices in dementia care across settings and across the disease severity spectrum. [2017 Dementia Care Summit: 7.6]	Initiate at least three implementation research studies testing dementia care interventions in new settings or with new dementia populations (e.g., long-term care interventions applied to home-based care).
Research on Care and Caregiver Support	13.I: Support research on technology-based dementia assessment, care, and management. [2017 Dementia Care Summit: 12.1, 12.2, 12.3, and 12.4]	Launch programs to increase the evidence base on effectiveness of technology-based solutions across categories of use (e.g., assessment/monitoring, provision of services, outreach). Expand evidence to include new technology applications such as sensing and monitoring systems, technology-enhanced assessment programs, EMRs, and robotic applications. Address cost-effectiveness, usability, challenges, and unintended consequences for populations of various levels of education, health, and computer/technology literacy.
Research on Care and Caregiver Support	13.J: Expand research on the care workforce and supply of skilled labor. Identify the barriers to entry, challenges of retention, and causes and effects of turnover. [2017 Dementia Care Summit: 11.1, 11.3, and 11.4]	Quantify the economic impact on people with dementia and their families and on health systems, attributable to current and projected future dementia and aging workforce limitations. Identify features of effective programs for workforce management and enhancement. Develop strategies to support existing caregivers in the workforce to address issues such as skills training and precarious employment.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
Research on Care and Caregiver Support	13.K: Expand research leading to understanding of effectiveness and impacts of nonresidential and residential care of people with dementia. Support research projects that identify community programs that can improve the lives of persons with dementia and their families, including home modifications and the support of Dementia Friendly Communities. [2017 Dementia Care Summit: 7.1, 7.2, 7.3, 7.4, 7.5, 9.1, and 9.4]	Identify new effective models of dementia care for residential and nonresidential settings, appropriate for widespread adoption. Identify care models that are effective in diverse populations, including those who live alone and those diverse in socioeconomic status, racial and ethnic composition, and rural/urban settings. Support research projects that identify community programs (e.g., home- and community-based services) that can improve the lives of people with dementia and their families, including home modifications and the support of Dementia Friendly Communities.
Public-Private Partnerships	14.C: 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	14.D: 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	14.E: 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; 2018 AD Summit: 6N]	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
Public-Private Partnerships	14.G: 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; 2018 AD Summit: 6N]	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 among 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.
Public-Private Partnerships	14.I: Develop and disseminate best practices for the collection, processing, and multiomics molecular profiling of human and animal model biosamples. [2018 AD Summit: 2F]	Ensure adoption of best practices across different research groups and institutions to enable harmonized analyses of data collected at the national and international level.

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**	16.A.1: Detect cognitive impairment when patient or relative voices a concern to health care providers.	Initiate at least two research programs to develop and validate assessment paradigms that meet the unmet need to detect cognitive impairment and dementia in large and diverse populations seen in primary care practice. Investigators may use existing tools (algorithms or protocols), may improve existing tools, or develop new tools; however, they should be simple to utilize, standardized, reimbursable, and quick. Administration can be by physicians or other medical personnel or via nontraditional methods such as telemedicine, mobile devices, or computers. The outcome of the cognitive assessment should yield appropriate followup, including referral guidance. Assessment paradigms should come with training materials suitable for both physicians and nonphysician medical personnel who will administer the tools and be appropriate for primary care and other everyday clinical settings.
ADRD 1: Multiple Etiology Dementias (MED) **Focus Area 1: Improved Diagnostic Skills in the Community**	16.A.2: Improve differential diagnosis of symptomatic cognitive impairment.	Initiate one or more research programs to achieve improved and increased differential diagnoses of cognitive impairment and dementia by medical specialists who are accessible to the general public (including but not limited to neurologists, geriatricians, neuropsychologists, and geriatric psychiatrists), including those living in more remote and less populated areas of the country. Integrate and leverage biomarkers when possible across all levels of cognitive impairment and dementia (including but not limited to AD, frontotemporal dementia, vascular contributions to cognitive impairment/dementia, and Lewy body dementia). Focus on differential diagnosis of rapidly progressive dementias and potentially treatable cognitive impairment/dementia, followed by appropriate recommendations for medical followup.
ADRD 1: Multiple Etiology Dementias (MED) **Focus Area 1: Improved Diagnostic Skills in the Community**	16.A.3: Increase training of health professionals to meet the expanding demand for cognitive impairment and dementia diagnosis and care, as well as the critical challenges of and need for human-based research.	Establish training programs with equal missions of research and training (MD, PhD, and other professionals) of individuals who are trained in the full spectrum of basic through clinical research in AD/ADRD, including in health disparities of AD/ADRD, who plan to be: basic, basic disease-related, or clinical researchers; clinicians who lead clinical research or 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 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 background of many trainees (e.g., statistics, bioinformatics, physics). Establish a scholarship program that will support later-stage-in-training health professionals (MD, PhD, and other relevant health professionals) to attend the AD/ADRD Summits.

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**	16.A.4: Develop diagnostics/biomarkers in asymptomatic individuals.	Develop at least one improved imaging or fluid biomarker for AD, cerebrovascular disease (including health of the neurovascular unit), and each of the ADRDs to estimate future risk for cognitive impairment in asymptomatic individuals. Conduct one or more studies that validate diagnostic and theragnostic utility of new biomarkers in asymptomatic populations, especially in minority groups and in middle age using population-based studies. Include evaluation of the relative clinical importance of different etiologies when more than one etiology is present.
ADRD 1: Multiple Etiology Dementias (MED) **Focus Area 2: Basic and Clinical Research in Interactions Between Dementia Pathophysiologies**	16.B.5: Promote basic and clinical research in multi-etiology dementia.	Initiate at least one funding opportunity announcement that is focused on identifying molecular pathways that accelerate cognitive dysfunction or protect cognition or that are agnostic to specific pathologies, i.e., that might act on mechanisms common to more than one neurodegenerative process. Initiate at least one funding opportunity announcement that promotes understanding interactions among different neurodegenerative pathologies of dementia (e.g., beta-amyloid, tau, TDP43, Lewy bodies, vascular damage). Research may focus on synergy, additive interactions, rank order of impact of different pathologies, and pleitrophic effects of multiple pathologies in noncognitive, related symptoms such as gait impairment or physical frailty.
ADRD 2: Nongovernmental Organizations (NGOs) **Focus Area 2: Catalyzing Research Through Unique Programs and Partnerships**	17.A.1: Establish more effective communication between NIH and NGOs on activities and progress toward ADRD goals in the off-years between triennial ADRD Research Summits.	Post all ADRD Summit 2016 milestones and success criteria publicly on the National Plan to Address Alzheimer's Disease (NAPA) website at the time of the 2017 annual update of the plan. In alignment with the leadership roles of NIA (NIH lead for NAPA response and AD Summits) and NINDS (NIH lead for ADRD Summits), going forward both NIA and NINDS will participate in NAPA Council meetings. NINDS will present annually to the NAPA Council on progress toward ADRD goals/milestones from 2017 onward. Convene annual meetings during which NINDS, NIA, and NGOs share activities, funding-related information, and progress relevant to the ADRD recommendations.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 3: Health Disparities (HD) Focus Area 1: Treatment and Prevention Strategies	19.A.1: Assess epidemiology and mechanistic pathways of disparities in health burden of AD/ADRD.	Initiate and/or leverage at least two longitudinal community-based cohort studies of incident cognitive impairment and dementia in diverse populations that are designed to assess epidemiological 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, and autopsy (when possible) and other biospecimens for mechanism-oriented research. Complete at least two studies investigating whether changes in risk factors for cognitive impairment and dementia occur over the 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 two studies investigating whether the prevalence and interaction of AD/ADRD risk factors (e.g., genetic, vascular, behavioral, environmental, or social risks), and their impact on outcomes, differs across disparities populations. Use this information to estimate the highest impact intervention targets (i.e., population burden associated with each risk factor) in disparities populations. Facilitate data availability for future research (e.g., via dbGaP and other sharing resources).
ADRD 3: Health Disparities (HD) Focus Area 1: Treatment and Prevention Strategies	19.A.2: Enrich the design of trials of vascular health interventions to improve their application to AD/ADRD among aging diverse populations.	Develop and make widely available guidelines for brain health assessments in clinical trials of vascular interventions in aging diversity populations. These guidelines will include standardized outcome measures (e.g., clinical, imaging, neurological, cognitive, vascular) in diverse populations that will facilitate meta-analyses of vascular health intervention trials and will draw from expertise in cognitive impairment, dementia and related fields such as stroke, lipid metabolism, cardiovascular intervention, and immune function. The guidelines should provide tiers of assessments that are optimized for resources in different care settings, such as caregiver time and technology available and should provide best practices for recruitment in diverse populations. Implement and validate these guidelines, including standardized outcome measures relevant to AD/ADRD in vascular health intervention studies that include diverse populations.
ADRD 3: Health Disparities (HD) Focus Area 2: Monitoring Changes in AD/ADRD Disparities	19.B.3: Develop a system to monitor the magnitude of and trends in health disparities in incidence of AD/ADRD.	Complete at least one study that covers dementia, including the spectrum of AD/ADRD embedded within large-scale community-based health surveillance systems, including potentially primary care, designed to utilize and validate simple assessment tools applicable for a surveillance setting. Enhance national programs to monitor differences in AD/ADRD incidence, prevalence, and long-term outcomes among racial/ethnic, socioeconomic, geographic, and other population differences relevant to disparities. Develop and release a consensus report on risk factors, predictors, consequences, and levels of underdiagnosis of AD/ADRD among disparities populations.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 3: Health Disparities (HD) **Focus Area 3: Assessment**	19.C.4: Improve tools for assessment of disparities in risks, preclinical disease characteristics, and costs of AD/ADRD among health disparities populations by leveraging existing data and cohorts, designing targeted studies, and using advanced psychometric analyses for improving tools for assessment of disparities in risks, preclinical disease characteristics, and costs of AD/ADRD among health disparities populations.	Develop best practices and tools for assessing cognitive function, cognitive impairment, and dementia in diverse populations by using diverse, community-based research cohorts and mixed methodology (e.g., including but not limited to clinical assessment, questionnaires, neuropsychiatric instruments, informant-based surveys, and adaptive psychometric tests). These best practices will include a series of validated tools for assessing AD/ADRD and tracking disease progression over time, and methodology for documenting salient symptoms and 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 surveillance. Develop normative references that would facilitate harmonized comparisons among assessments of cognitive function, cognitive impairment, and dementia in diverse populations.
ADRD 4: Lewy Body Dementias (LBD) **Focus Area 1: Establish Longitudinal Diverse Cohorts with Common Measures, Culminating in Autopsy**	20.A.1: 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 one 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.
ADRD 4: Lewy Body Dementias (LBD) **Focus Area 1: Establish Longitudinal Diverse Cohorts with Common Measures, Culminating in Autopsy**	20.A.2: Create longitudinal clinical, biological, and imaging resources for LBD from the earliest stages to autopsy to improve accuracy of detection and diagnosis of DLB at the pre-dementia or prodromal stage and to detect PD patients with a high risk of cognitive decline leading to PDD.	Complete at least one new study that leverages one or more existing neurodegeneration or dementia cohorts to develop and establish research tools to study DLB and PDD. Studies should collect and share standardized clinical and neuropsychological data from individuals with potential early manifestations of DLB and PDD, as above.
ADRD 4: Lewy Body Dementias (LBD) **Focus Area 2: Discover Disease Mechanisms Through Brain Mapping and Genetics**	20.B.3: Using well-defined cohorts of LBD who have come to autopsy, systemically characterize disease-specific changes in the brain, spinal cord, and peripheral autonomic nervous system with state-of-the-art methods, including genomics, expression arrays, metabolomics, and proteomics to identify underlying disease mechanisms that will guide future biomarker and therapeutic approaches. Data generated in this initiative should be incorporated into an open-access, centralized data management system that links clinical, biological, and autopsy data.	Establish an inventory and report on existing autopsy samples with well-characterized brain and other tissue samples with antemortem clinical syndrome and postmortem neuropathology consistent with LBD. Consensus clinical and pathological criteria for DLB and PDD should be used when feasible. This "LBD Pathological, Biological, and Clinical Data Inventory" will contain metadata and annotation on the quality of the pathological 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 Pathological, Biological, and Clinical Data Inventory.

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**	20.B.4: Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that impact the risk for and clinical features of LBD.	Identify families with multiple members affected by PDD or DLB and perform genomic analyses. Conduct definitive assessment of genetic risk architecture in clinically well-characterized patients with LBD and in autopsy cases meeting consensus criteria for LBD. Convene a workshop to address methodological challenges in exploring gene–environment interactions for LBD. Implement methods for assessing environmental determinants by working with basic scientists and epidemiologists to identify a prioritized list of exposures. Take into account known associations in related disorders such as PD and the cellular biology underlying LBD. Genotype cohorts with well-characterized environmental exposures and collect environmental exposures in genetically well-characterized cohorts. Take advantage of other databases to apply methods such as geocoding to infer exposures (e.g., particulate matter in air, pesticide use in certain states).
ADRD 4: Lewy Body Dementias (LBD) **Focus Area 3: Develop and Validate Biological and Imaging Biomarkers**	20.C.5: Develop imaging approaches to enhance the differential diagnostic accuracy of LBD compared with 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 one new study to validate available and proposed imaging tools for the differential diagnoses of LBD compared with 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 alpha-synuclein or other relevant radiopharmaceuticals) with an emphasis on multimodal studies.
ADRD 4: Lewy Body Dementias (LBD) **Focus Area 3: Develop and Validate Biological and Imaging Biomarkers**	20.C.6: 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 pathological 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 one novel biomarker using well-characterized LBD samples in existing LBD clinical trials or a new large study.

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**	20.D.7: Recognize the importance of alpha-synuclein and AD pathophysiologic processes in LBD. New animal, cellular, and in vitro models are needed that recapitulate key features, including clinical heterogeneity, of these disorders, with the ultimate goal of identifying strategies that can be carried forward into clinical trials.	Establish research focused on developing better understanding of the basic science of LBD. This research 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.
ADRD 4: Lewy Body Dementias (LBD) **Focus Area 4: Model Disease Processes to Develop Potential Symptomatic and Disease-Modifying Therapies**	20.D.8: 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 one 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**	21.A.1: Clarify the mechanism of tau pathogenesis and associated neurodegeneration.	Improve understanding of, or determine roles of, key pathophysiological events (post-translational tau modifications, aggregation, microtubule dysfunction, interneuronal spread, or other tau [dys]functions) that contribute to neurodegeneration in human tauopathy. Develop one or more model systems that reproduce one or more of the aforementioned processes accurately to enable the testing of new therapeutic targets and approaches. Determine the mechanism of aggregated tau pathology spreading, including how tau seed species get out of neurons and transmit pathology to other cells, and what role different tau conformer strains play in determining the pattern of tau inclusions. Determine the relationship of tau aggregation and spreading to neurodegeneration.
ADRD 5: Frontotemporal Lobar Degeneration (FTD) **Focus Area 1: Basic Science: Pathogenesis and Toxicity**	21.A.2: Determine the molecular basis for C9ORF72 expansion and GRN mutation-related neurodegeneration.	Identify predominant mechanism(s) of C9ORF72 and GRN mutation-related FTD/ALS pathogenesis, with convergent findings in human tissues and model systems. Prioritize targets to move forward into therapy development after testing therapeutic hypotheses in model systems.
ADRD 5: Frontotemporal Lobar Degeneration (FTD) **Focus Area 1: Basic Science: Pathogenesis and Toxicity**	21.A.3: Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity.	Identify the predominant mechanism(s) of TDP-43 and FUS-related pathogenesis and neurodegeneration. Acquire new evidence regarding whether TDP-43 aggregation spreads via interneuronal transmission, and clarify the normal functions of TDP-43 and FUS. Prioritize targets for therapy development by testing therapeutic hypotheses in relevant model systems.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 5: Frontotemporal Lobar Degeneration (FTD) **Focus Area 1: Basic Science: Pathogenesis and Toxicity**	21.A.4: Develop better FTLD in vivo and in cell-based model systems.	Generate 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 developing 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).
ADRD 5: Frontotemporal Lobar Degeneration (FTD) **Focus Area 2: Clinical Science**	21.B.1: Expand efforts to genotype patients with FTD and identify new genes and their functional relationship to FTLD pathogenesis.	Identify at least one novel drug target or pathway or prevention, supported by the functional analysis of the new genes and risk alleles identified based on GWAS, whole exome and whole genome, and targeted sequencing. These efforts should include kindreds with combined FTD and ALS phenotypes in gene discovery studies and should include underserved and minority populations.
ADRD 5: Frontotemporal Lobar Degeneration (FTD) **Focus Area 2: Clinical Science**	21.B.2: Develop FTD biomarkers for diagnosis and disease progression.	Develop, test, and confirm pathologically at least one novel PET ligand and/or CSF/blood biomarker for the molecular diagnosis of diverse forms of FTLD-tau, -TDP and -FUS. Develop and test two to three 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. Include underserved and minority populations in biomarker development and testing studies described above.
ADRD 5: Frontotemporal Lobar Degeneration (FTD) **Focus Area 2: Clinical Science**	21.B.3: Create an international FTD clinical trial network.	Develop a patient registry for FTD clinical studies and a centralized database for de-identified clinical, genetic, and biomarker data that can be shared with the broader research community to refine disease models, clinical endpoints, and trial design. 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.

AD and ADRD Research Implementation Area	Research Implementation Milestones	Success Criteria
ADRD 5: Frontotemporal Lobar Degeneration (FTD) **Focus Area 2: Clinical Science**	21.B.4: Understand phenotypic heterogeneity and natural history.	Complete one or two natural history studies of preclinical inherited FTD (especially MAPT-, GRN-, and C9ORF72-related FTD) by following individuals from health to disease. Data will enable identification of novel genetic and environmental disease modifiers that influence clinical presentation and biomarkers for diagnosis and disease progression. Complete one or two 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 6: Vascular Contributions to Cognitive Impairment and Dementia (VCID), Including Vascular Cognitive Impairment and Vascular Dementia **Focus Area 1: Basic Mechanisms and Experimental Models**	22.A.1: 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 one combinatorial animal model that reproduces key aspects of human VCID pathophysiology with respect to acquired or environmental risk factors (e.g., aging, hypertension, obesity, metabolic syndrome). Encourage animal models that can establish the relationship among aging, vascular risk factors, and disease progression. Develop at least one animal model that incorporates monogenic causes of AD and VCID to produce pathophysiology similar to human VCID that is present in typical mixed dementia with pathological AD plus VCID. Establish at least one new tool to determine cellular variation in the vascular tree within different regions of the brain that can be used to test how aging and vascular risk factors impact brain function at the synaptic, neuronal, network, systems, and behavioral level. Identify imaging approaches for use in animal models that can synergize with those being used as biomarkers in human VCID. Specifically support basic science projects that directly address or measure the effects of age on the vascular tree, the interaction of age with vascular risk factors, and tissue pathologies that lead to VCID (e.g., chronic blood brain barrier breakdown, hypoperfusion, chronic inflammation, the effects of neurovascular unit damage on neuronal network structure and activity).
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**	22.A.2: Encourage basic science research that investigates the impact of aging, AD pathology, and genes on peri- and para-vascular clearance mechanisms, the NVU, and cerebrovascular function.	Develop at least two new basic science research projects that can provide direct insight into how aging and AD pathology impact vascular clearance of amyloid and other metabolites. Develop at least one new basic science research project that will determine how aging and AD pathology progressively modulate cerebrovascular function, preferably at the level of the neurovascular unit.

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	22.A.3: Encourage basic science research that investigates the impact of cerebrovascular risk factors/genes and atherosclerosis on AD-related neurodegeneration.	Initiate at least one new basic research project that provides rigorous and novel insight into how cerebrovascular disease (small vessel) or cerebrovascular risk factors (e.g., hypertension, diabetes mellitus/metabolic syndrome, dyslipidemia) or stroke impact the development or progression of AD-related neurodegeneration. Encourage behavioral studies on the impact of cerebrovascular disease alone or as a comorbidity that incorporate functional testing of both hippocampal/memory and frontal/executive functioning to mimic the brain regions and functional systems impacted by ADRDs.
ADRD 6: Vascular Contributions to Cognitive Impairment and Dementia (VCID), Including Vascular Cognitive Impairment and Vascular Dementia Focus Area 2: Human-Based Studies	22.B.1: Develop and validate longitudinally tracked noninvasive markers of key vascular processes related to cognitive and neurological impairment.	Identify neuroimaging or biochemical biomarker(s) that independently correlate with the presence and severity of advanced small vessel disease in at least two human small vessel disease cohorts. Identify a neuroimaging marker for the vascular pathology of arteriolosclerosis. 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 two small vessel disease cohorts.
ADRD 6: Vascular Contributions to Cognitive Impairment and Dementia (VCID), Including Vascular Cognitive Impairment and Vascular Dementia Focus Area 2: Human-Based Studies	22.B.2: Determine interrelationships (cross-sectional and longitudinal) among aging, cerebrovascular disease and risk factors, resilience factors, genetic variants, amyloid, tau, and neurodegeneration.	Complete one or more comprehensive studies of the independent associations between biomarkers of cerebrovascular disease and biomarkers of beta-amyloid- and tau-related pathology/neurodegeneration in a human cohort. Initiate at least one intervention study to identify the effects of modifying vascular risk factors on biomarkers of beta-amyloid- and tau-related pathology/neurodegeneration.
ADRD 6: Vascular Contributions to Cognitive Impairment and Dementia (VCID), Including Vascular Cognitive Impairment and Vascular Dementia Focus Area 2: Human-Based Studies	22.B.3: Identify lifestyle and vascular interventions to treat, prevent, or postpone VCID.	Identify at least one intervention strategy that decreases the burden of VCID by modifying vascular risk factors/processes in human clinical trials that use leading-edge biomarkers of small vessel disease and cognitive/neurologic function. Initiate and complete a human clinical trial or leverage existing trials of an intervention derived from SVD-related biological pathways identified in animal or human studies, using leading-edge biomarkers.