Alzheimer's Disease-Related Dementias (ADRD) Summit 2022

Prioritized Research Milestones and Success Criteria

National Institute of
Neurological Disorders
and Stroke

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Background

On March 22-23, 2022, the National Institute of Neurological Disorders and Stroke (NINDS) hosted the 4th Alzheimer's Disease-Related Dementias (ADRD) Research Summit. The summit is one of a series of triennial conferences (also including the Alzheimer's Disease Research Summit and the Dementia Care Summit) designed to respond to the National Plan to Address Alzheimer's Disease. Committees of research experts and ADRD stakeholders developed the focus areas for the Summit, organized around five broad topics, including multiple etiology dementias (MED), health equity in AD/ADRD, Lewy body dementias (LBD), frontotemporal dementia (FTD), vascular contributions to cognitive impairment and dementia (VCID), and three MED special topics, post-TBI AD/ADRD, LATE (TDP-43 in common late-onset dementias) and the impact of COVID-19 on AD/ADRD risk and outcomes. Informed by pre-Summit review of the research landscape, iterative Committee discussions over the six months leading up to the Summit, a public request for information (RFI) with 11 responses, and direct public input at the Summit itself, the eight Committees developed milestones that represent national ADRD research priorities. These milestones will be integrated with the existing NIH AD/ADRD Research Implementation Milestones (also see Appendix 1). Collectively, these inform future NIH AD/ADRD bypass budgets and, as Congressionally appropriated funds become available, corresponding research activities. In addition, the milestones guide the AD/ADRD research community generally, and as such, broad milestone implementation and execution by federal, national, and international stakeholders will be vital to their impact.

All milestones in this report represent important research goals and are among the top priorities in their respective fields. Each session committee proposed up to eight recommendations, with priority levels ranked from 1 to 4 (1 being the highest priority) and estimated a timeline (number of years) needed to complete or fully implement the milestone once initiated. Neither timelines nor order of sessions during the summit or in the table below reflect prioritization.

The tables below include NINDS AD/ADRD staff developed success criteria for milestones resulting from the ADRD Research Summit 2022. The success criteria are responsive to the milestones and serve to indicate when a milestone is accomplished. Success criteria are brief, quantifiable to the degree possible, and intended to be accessible to a broad audience.

Research Milestone Key:

Summit Session Name		
Milestone #(Priority Level) Milestone Text	**Success Criteria**	**Timeline**
1(1) Milestone text **Read "Milestone #1, Level 1 Priority"** *Corresponding existing AD+ADRD Research Implementation Milestone Number (Research Area) or NEW (Research Area)*	• Steps to be taken to achieve the milestone	*Number of years projected to complete or fully implement the milestone once initiated.*

Health Equity (HE) in AD/ADRD		
Milestone #(Priority Level) Milestone Text	**Success Criteria**	**Timeline**
1(1) Advance equity in AD/ADRD research via inclusion science to improve representative sampling and retention of diverse communities. *NEW (Translational Research and Clinical Interventions)*	• Conduct at least one new project to develop new community-based strategies to recruit, retain, and engage study participants from diverse populations. • Continue to develop, update disseminate, and implement 'best practice' resources for AD/ADRD clinical research to increase engagement and retention of diverse patients and caregivers. • Develop a resource that tracks subject recruitment in clinical trials by gender, race/ethnicity, socioeconomic status, geographic region, and other key features.	*5-7 years*
2(1) Increase training support and capacity of an AD/ADRD scientific workforce of persons historically under-represented in biomedical, behavioral, and social sciences. *AD+ADRD Research Implementation Milestone 4.S (Research Resources)* *See* https://www.nia.nih.gov/research/milestones/research-resources/milestone-4-s	• Support at least two initiatives that prioritize robust mentorship and sponsorship to train under-represented AD/ADRD scholars and trainees at any career stage (undergraduate through senior levels); track and monitor trajectory and impact. • At least one initiative to train AD/ADRD scientists in health equity research. • Develop and disseminate training and education in health equity principles for dementia researchers and dementia care professionals at all career stages.	*1-3 years*
3(2) Promote career development of biomedical, behavioral, and social scientists conducting AD/ADRD health equity research. *NEW (Research Resources)*	• Support at least two initiatives to promote career development and retention of AD/ADRD scientists from diverse backgrounds, including midcareer through senior levels. • At least one initiative to expand AD/ADRD career development resources and opportunities, including by promoting equity in representation of diverse scholars at all levels.	*1-3 years*
4(2) Assess the social, economic and structural impediments to equity in AD/ADRD assessment, diagnosis, and referrals, and impacts on health and economic outcomes. *NEW (Epidemiology/Population Studies)*	• At least two research studies to determine and propose solutions for systemic sociocultural, economic, and health care system factors that are barriers to health equity outcomes in AD/ADRD.	*3-5 years*

5(3) Improve AD/ADRD assessment tools (cognitive, biomarkers, -omics) and analytic methods to enhance generalizability and equity of scientific research. *AD+ADRD Research Implementation Milestone 11.H (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-11-h	• At least two research programs to develop and validate culturally informed assessment tools to detect early cognitive changes including non-English-speaking people and people with varying levels of education. • At least one new study that that determines relationships among genes, environmental, and other biological factors that impact AD/ADRD risk and outcomes in diverse populations.	*3-5 years*
6(3) Apply existing and novel surveillance methods to assess inequities, including trends in inequities, in AD/ADRD prevalence, incidence, diagnosis, treatment and care. *AD+ADRD Research Implementation Milestone 1.J (Epidemiology/Population Studies)* *See* https://www.nia.nih.gov/research/milestones/population-studies-precision-medicine-health-disparities/milestone-1-j	• At least one study that applies existing and novel surveillance methods to assess long-term trends in AD/ADRD prevalence, incidence, diagnosis, treatment, and outcomes in diverse populations.	*3-5 years*
7(4) Identify life course and multi-level mechanisms of and pathways to AD/ADRD inequities and use the discoveries to reduce these inequities. *AD+ADRD Research Implementation Milestone 1.I (Epidemiology/Population Studies)* *See* https://www.nia.nih.gov/research/milestones/epidemiology-population-studies/milestone-1-i	• One longitudinal community-based cohort study of incident cognitive impairment and dementia in populations that experience heath disparities. • Two studies on how the impact of multi-level AD/ADRD risk factors differs across diverse populations. • At least one clinical trial to develop and implement real-world approaches, in primary care to decrease known multi-level risk factors for cognitive impairment and dementia over the life course in diverse populations.	*5-7 years*
8(4) Prioritize infrastructure and policy research to understand individual, community, and societal drivers of inequities in cost of and access to treatments and care, and the impact on AD/ADRD outcomes. *AD+ADRD Research Implementation Milestone 13.M (Dementia Care and Impact of Disease)* *See* https://www.nia.nih.gov/research/milestones/care-caregiver-support/milestone-13-m	• Establish a national database for health equity in dementia research focused on the impact of social determinants of health, outcomes, treatment, and provision of quality care • At least two new research studies in health disparity populations on policy factors that impact access to AD/ADRD care. • At least one national study modeling and assessing the economic impact of improving access and/or cost of care in populations experiencing AD/ADRD health disparities.	*5-7 years*

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Frontotemporal Dementia (FTD)		
Milestone #(Priority Level) Milestone Text	**Success Criteria**	**Timeline**
1(1) Understand FTD epidemiology and genetics in diverse populations, including how socioeconomic and ethnocultural status affects disease risk and manifestations. *NEW (Epidemiology/Population Studies)*	• At least one initiative that supports development of new clinical assessment tools to identify and characterize FTD in diverse populations. • At least one natural history study of FTD, including genetic risks and genetic causes for FTD, that is powered to determine whether there are differences in the prevalence, incidence, risk, and resilience factors for FTD in diverse populations.	*1-5 years*
2(2) Develop an array of FTD biomarkers for diagnosis, prediction, disease monitoring, target engagement, and patient stratification for clinical trials. *AD+ADRD Research Implementation Milestone 9.Q (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/diagnosis-assessment-and-disease-monitoring/milestone-9-q	• At least two new FTD biomarkers that are validated for clinical trials, including in at least two populations that experience health disparities.	*2-7 years*
3(3) Accelerate the evaluation of novel FTD treatments by developing new clinical trial resources and FTD-specific designs, and by conducting new prevention and treatment trials. *AD+ADRD Research Implementation Milestone 9.S (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-s	• Initiate at least one sporadic FTD clinical trial in a real-world clinical setting. • Develop or leverage an existing research registry for FTD clinical studies that includes underserved and minority group representation reflecting population demographics. • Develop standardized protocols for prevention studies of familial FTD syndromes or clinical trials in symptomatic, sporadic, and familial FTD. • Initiate at least one clinical trial of novel FTD therapeutics.	*1-5 years*
4(4) Identify overlapping pathogenic mechanisms between FTD and other neurodegenerative disorders and syndromes. *NEW (Disease Mechanisms)*	• At least three studies to identify and compare overlapping molecular, genetic, clinical, and pathologic drivers and risk factors for FTD clinical outcomes with other AD/ADRD diagnoses.	*2-7 years*

5(1) Advance understanding of FTD and identify therapeutic targets through the creation, validation, and use of pre-clinical and translational tools and resources. *AD+ADRD Research Implementation Milestone 4.Q (Research Resources)* *See* https://www.nia.nih.gov/research/milestones/enabling-infrastructure/milestone-4-q	• At least three new animal and/or cell-based models that replicate key aspects human FTD. • Develop and/or validate at least two in vivo functional assays for FTD translational research, including with endpoints in animal models that are relevant for FTD biology and/or clinical outcomes. • One new resource that harmonizes critical FTD datasets across disease stages for data sharing to enable translational research.	*7-10 years*
6(2) Accelerate pre-clinical disease-modifying and symptomatic therapeutic development in FTD. *NEW (Translational Research and Clinical Interventions)*	• At least three studies to identify and/or validate drivers of FTD that are potential targets for intervention. • At least one new FTD intervention with FDA approval to proceed with clinical trials.	*2-7 years*
7(3) Elucidate the mechanisms of cell type vulnerability and cell-intrinsic and –extrinsic effects on FTD pathogenesis, with the goal of accelerating development of therapeutic targets. *NEW (Disease Mechanisms)*	• At least three new studies focused on cell-intrinsic and cell-environment mechanisms that result in susceptibly to or resilience against clinically relevant FTD disease mechanisms, and that are potential targets for intervention. • Develop at least 2 human or humanized cell-based models that recapitulate cell-specific vulnerability or resilience to FTD disease mechanisms.	*3-10 years*
8(4) Define genetic and molecular modifiers of FTD (including in diverse populations). *AD+ADRD Research Implementation Milestone 6.I (Translational Research And Clinical Interventions)* *See* https://www.nia.nih.gov/research/milestones/translational-clinical-research-pharmacological/milestone-6-i	• At least two studies to genotype and perform genomic analysis on patients, including in diverse populations, across the full spectrum of FTD diagnoses; at least one study must include a sporadic FTD cohort. • At least one study on how genetic background and environment are linked to patient clinico-pathological syndrome and disease progression.	*3-10 years*

Vascular Contributions to Cognitive Impairment and Dementia (VCID)

Milestone #(Priority Level) Milestone Text	Success Criteria	Timeline
1(1) Establish and refine experimental models and technologies to identify disease-relevant mechanisms underlying VCID. *AD+ADRD Research Implementation Milestone 4.R (Research Resources)* *See* https://www.nia.nih.gov/research/milestones/enabling-infrastructure/milestone-4-r	• Establish at least 2 new small vessel VCID animal models suited for VCID and mixed dementias of aging research that reproduce small vessel disease and other key pathogenic processes thought to result in human VCID. • At least two new in vitro models to study specific molecular mechanisms of VCID that are not feasible in animal models. • At least one new project to develop new imaging and other tools that can be used to better understand mechanisms of VCID etiology.	*5-8 years*
2(3) Study the neurovascular unit structure and function to establish how it is impacted by VCID. *AD+ADRD Research Implementation Milestone 2.Q (Disease Mechanisms)* *See* https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-q	• At least two new projects to understand the role of perivascular and paravascular clearance pathways that may protect the brain from VCID. • At least three new projects to determine how normal neurovascular unit function and blood brain barrier function are impacted by VCID risk factors.	*4-6 years*
3(4) Use experimental models to investigate how aging, cerebrovascular and cardiovascular disease impact myelin, white matter degeneration and neurodegeneration. *AD+ADRD Research Implementation Milestone 2.R (Disease Mechanisms)* *See* https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-r	• A national consortium to advance new basic research that provides rigorous and novel insight into how cerebrovascular disease, cardiovascular disease, and risk factors in different brain vascular zones , including in both gray matter and white matter, lead to VCID.	*5-8 years*
4(1) Develop and validate markers of VCID in diverse populations using 1) cognitive, physical, or other functional assessments, and 2) biomarkers of key vascular processes, including in the most common scenario where VCID is accompanied by AD in human studies. *AD+ADRD Research Implementation Milestone 9.R (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-r	• Complete at least one human-based project to validate for clinical trials imaging and fluid-based biomarkers of small vessel VCID in that include general and diverse populations in the United States (at a minimum Black/African American, Hispanic/Latino, and White populations). • At least one clinically validated VCID biomarker that is clinical trial ready with a defined biomarker category and context of use.	*3-5 years*

5(2) Identify and apply 1) interventions (medication, lifestyle, or a combination of these) that reduce cardiovascular and cerebrovascular risk and 2) care models to test their efficacy for prevention and treatment of VCID across the spectrum of severity and in diverse populations. *AD+ADRD Research Implementation Milestone 8.E (Translational Research And Clinical Interventions)* *See* https://www.nia.nih.gov/research/milestones/translational-clinical-research/non-pharmacological/milestone-8-e	• Initiate at least one VCID clinical trial to test whether intervention(s) known to reduce cardiovascular and cerebrovascular risk also decrease VCID burden, and that is sufficiently powered to answer key questions in at least two populations that experience health disparities. • At least one new project to determine whether the best existing models for delivering care to persons with AD/ADRD overall, and supporting their caregivers, are effective in persons affected by VCID including in populations affected by health disparities.	*7-10 years*
6(4) Understand the impact on VCID of other known dementia risk factors (e.g., aging, genetics) and co-morbid neurodegeneration along the life-course in diverse populations to establish VCID interactions with other dementia disease processes. *AD+ADRD Research Implementation Milestone 2.S (Disease Mechanisms)* *See* https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-s	• One or more studies to understand independent associations between biomarkers of VCID and biomarkers of other dementia-associated brain pathologies and comorbidities in a human cohort sufficiently powered to answer key questions in at least two populations that experience health disparities.	*7-10 years*
7(2) Incorporate VCID mechanisms derived from basic science animal/human studies into the design of human trials targeting prevention or treatment of dementia/mild cognitive impairment. *AD+ADRD Research Implementation Milestone 4.U (Research Resources)* *See* https://www.nia.nih.gov/research/milestones/research-resources/milestone-4-u	• At least one new VCID clinical project or trial informed by basic VCID science research outcomes (e.g. biomarkers that emerge from basic studies) and basic mechanisms.	*5-7 years*
8(3) Validate hypothesized mechanisms of VCID in large-scale, including community-based diverse, human studies leveraging existing and in-process biospecimens, genomics, and imaging data. AD+ADRD Research Implementation Milestone 4.T *(Research Resources)* *See* https://www.nia.nih.gov/research/milestones/research-resources/milestone-4-t	• At least one new VCID human data science model systems platform that leverages data, resources, and results from human VCID clinical research and clinical trials. • At least one new VCID study using human data science/systems approach that leverages data, resources, and results from, and also test hypotheses from, human VCID clinical research and clinical trials.	*4-6 years*

Lewy Body Dementias (LBD)		
Milestone #(Priority Level) Milestone Text	**Success Criteria**	**Timeline**
1(1) Prepare for and initiate clinical trials that aim to alleviate or slow the course of LBD symptoms, and delay or prevent the onset of disease. *AD+ADRD Research Implementation Milestone 5.D (Translational Research And Clinical Interventions)* *See* https://www.nia.nih.gov/research/milestones/translational-clinical-research-pharmacological/milestone-5-d	• An LBD clinical trial network with the personnel and infrastructure to conduct clinical trials, including validated clinical tools to track LBD symptoms. • Complete one or more clinical trials that test prospective therapies to prevent or alter LBD processes or symptoms.	*1 -7 years*
2(2) LBD Clinical Characterization and Intervention: Develop and refine neuroimaging biomarkers that track progression, assist in differential diagnosis, provide therapeutic target engagement, and relate to pathology. *AD+ADRD Research Implementation Milestone 9.O (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-o	• At least two new studies that evaluate, improve, develop, validate, and standardize clinical trial ready LBD neuroimaging biomarkers for the diagnosis, diagnosis, and progression of LBD that are sensitive and specific versus similar disorders. • At least one clinically validated LBD neuroimaging biomarker that is clinical trial ready.	*2-7 years*
3(3) Develop and refine biomarkers for diagnosis, prediction, and prognosis utilizing biofluids, tissues, and digital and electrophysiological methods. *AD+ADRD Research Implementation Milestone 9.P (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-p	• At least one clinical trial ready validated LBD biomarker that uses biofluids, tissues, digital or electrophysiological approaches (or a combination of approaches) for LBD diagnosis, prediction, and/or prognosis.	*2-7 years*
4(4) Expand existing and develop new longitudinal LBD study cohorts, including diverse populations, from pre-symptomatic disease to autopsy to support diagnostic, epidemiologic, and therapeutic studies. *AD+ADRD Research Implementation Milestone 9.J (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-j	• Increase the number of people enrolled in research cohorts that investigate LBD from pre-symptomatic LBD through autopsy. This research will be powered to answer key questions in at least 2 populations that experience health disparities. • Create and apply criteria to ensure that longitudinal LBD cohort studies collect and share de-identified, standardized data.	*1-7 years*

5(1) Delineate genetic loci and their functions contributing to the onset and progression of LBDs using genetic, transcriptomic, epigenetic, and environmental characterization analyses. *AD+ADRD Research Implementation Milestone 1.L (Epidemiology/Population Studies)* *See* https://www.nia.nih.gov/research/milestones/epidemiology-population-studies/milestone-1-l	• At least 2 new projects to identify new genomic changes and environmental influences that impact LBD. • Discover a molecular mechanism that links at least one novel genetic locus to the risk for developing LBD.	*1-7 years*
6(2) Enhance and standardize the techniques for neuropathologic characterization of LBD and the use of LBD pathology cohorts including more diverse cohorts. *AD+ADRD Research Implementation Milestone 1.K (Epidemiology/Population Studies)* *See* https://www.nia.nih.gov/research/milestones/population-studies-precision-medicine-health-disparities/milestone-1-k	• Optimize, standardize, and disseminate best practices for clinical data collection, donation, sampling, preparation, storage and distribution of post-mortem LBD tissue, including specific emphasis and guidance for best practices relevant to diverse populations. • At least one project or effort to increase donation and post-mortem clinical data on subjects who are at-risk for LBD and who are from diverse populations.	*2-7 years*
7(3) Develop models to understand the pathophysiology and normal molecular and cellular functions of α-synuclein to support drug discovery. *AD+ADRD Research Implementation Milestone 2.T (Disease Mechanisms)* *See* https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-t	• At least three new projects designed both to understand and to compare normal and LBD-associated alpha synuclein biology. • At least two new models of LBD that reproduce key features of LBD pathology and/or symptoms and are translatable for human LBD drug development.	*5-7 years*
8(4) LBD Pathogenesis and Mechanisms of Toxicity: Identify mechanisms of selective vulnerability, disease heterogeneity, disease spread/propagation, and interaction with other age-related pathologies as therapeutic targets. *AD+ADRD Research Implementation Milestone 2.M (Disease Mechanisms)* *See* https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-m	• At least one new project investigating α-synuclein spreading and α-synuclein interactions with other dementia-associated pathologies and how these interactions increase (or decrease) risk of symptomatic disease. • At least two studies to understand why some brain cells are vulnerable to pathological alpha-synuclein accumulation while others are resistant.	*5-7 years*

Multiple Etiology Dementias (MED)		
Milestone #(Priority Level) Milestone Text	**Success Criteria**	**Timeline**
1(1) Evaluate pragmatic approaches to objectively detect cognitive impairment and link to quality care when a patient, care partner, or clinician reports cognitive, behavioral, or functional changes. *AD+ADRD Research Implementation Milestone 9.K (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-k	• Complete at least three clinical trials to validate assessment paradigms to detect cognitive impairment in large and diverse populations in primary care practice and other every day clinical care settings.	*3-5 years*
2(4) Evaluate the benefits, burdens, and harms of screening for cognitive impairment in older adults in the absence of a patient, care partner or clinician report of cognitive, behavioral, or functional changes. *AD+ADRD Research Implementation Milestone 9.N (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-n	• At least one real-world clinical practice study to determine the benefits, burdens, and harms of screening for cognitive impairment including dementia in older adults. This trial is to be powered to answer the question in at least two populations that experience health disparities.	*5-7 years*
3(1) Conduct multimodal clinical and translational research to support the identification of multiple etiologies in diverse populations. *AD+ADRD Research Implementation Milestone 9.L (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-l	• At least one human tissue-, sample-, and data-based translational study, with deep phenotyping of pathologies and co-morbidities, to develop and validate multimodal clinically useful biomarkers, including in diverse populations, to understand AD/ADRD risk and outcomes.	*5-7 years*
4(2) Advance basic research on the common and interacting risk factors and mechanisms of multiple etiology cognitive impairment and dementia in diverse populations. *AD+ADRD Research Implementation Milestone 2.L (Disease Mechanisms)* *See* https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-l	• At least three new mechanistic projects on interacting molecular pathways and risk factors that either accelerate or protect against cognitive decline and dementia in general and diverse US populations.	*3-7 years*

5(1) Conduct clinical studies on approved or promising interventions and treatments to mitigate risk for cognitive decline. *AD+ADRD Research Implementation Milestone 11.I (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/diagnosis-assessment-and-disease-monitoring/milestone-11-I	• Initiate at least one real-world clinical practice setting study on approved or promising interventions and treatments in hospital and community-based settings that targets risk factors for cognitive decline. • Establish a national research consortium to develop, test, refine, implement, and disseminate best practices for determining whether reversible risks and causes of cognitive dysfunction are present in an individual, and how to facilitate successful intervention.	*5-10 years*
6(4) Implement and evaluate outcomes for effective dementia care programs that support persons living with dementia and their caregivers, including those of socially, ethnically, and racially diverse populations. *AD+ADRD Research Implementation Milestone 13.I (Dementia Care and Impact of Disease)* *See* https://www.nia.nih.gov/research/milestones/care-caregiver-support/milestone-13-I	• Hold a workshop and write a report on dementia care programs that effectively support persons with dementia and their caregivers including those of socially, ethnically, and racially diverse populations. This workshop will also address barriers to national implementation. • Establish an AD/ADRD health equity national consortium tasked with applied research to determine how to implement proven care programs, including by identifying barriers and facilitators to widespread diffusion and sustainability of interventions with demonstrated benefit.	*3-7 years*
7(2) Promote education and training on multiple etiology cognitive impairment and dementia to increase the dementia capable workforce, advance researchers including from groups underrepresented in science, and foster inclusive research practices. *AD+ADRD Research Implementation Milestone 11.J (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-11-j	• National AD/ADRD training program for researchers and healthcare professionals that fosters an inclusive workforce and research environment, focuses on multiple etiology cognitive impairment and dementia and its relationship to AD/ADRD diagnoses, and training on rigorous approaches to AD/ADRD research including in groups that experience health disparities.	*5-10 years*
8(3) Conduct research to improve pre- and post-data collection harmonization and sharing practices across multiple etiology cognitive impairment and dementia studies. *NEW (Research Resources)*	• One initiative to develop and promote incorporation of common data elements (CDEs) and best practices for standardized consent language to facilitate research, including by data and biologicals sharing, that addresses real world cognitive impairment and dementia in diverse populations of the United States.	*5-10 years*

MED Special Topic: Post-TBI AD/ADRD (MED Post-TBI)		
Milestone #(Priority Level) Milestone Text	**Success Criteria**	**Timeline**
1(1) Promote collaboration among TBI and dementia researchers through working groups, retrospective and prospective data and measurement harmonization, and interdisciplinary research. *AD+ADRD Research Implementation Milestone 1.N (Epidemiology/Population Studies)* *See* https://www.nia.nih.gov/research/milestones/population-studies-precision-medicine-health-disparities/milestone-1-n-0	• Convene a meeting of TBI and AD/ADRD researchers including trainees and other interdisciplinary researchers with a focus on data harmonization and data sharing. • Add TBI assessments to at least one AD/ADRD cohort study. • Add AD/ADRD assessments to at least one TBI cohort study.	*1-3 years*
2(2) Characterize the heterogeneous clinical and biological phenotypes and time course of progressive dementia following varied TBI exposure histories by developing biomarkers and methods to quantify lifetime head trauma exposure and diagnose post-TBI dementias. *AD+ADRD Research Implementation Milestone 11.K (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-11-k	• Develop and disseminate best practices for collecting and sharing clinical data in research studies of AD/ADRD outcomes following TBI. • Establish a longitudinal study of individuals with TBI to identify features of AD/ADRD risk following TBI. • Support discovery and validation of biomarkers related to AD/ADRD outcomes following TBI.	*1-10 years*
3(3) Establish research infrastructure, including multimodal longitudinal studies with autopsy endpoints that employ standardized CDEs and methodologies, to study post-TBI AD/ADRD. *AD+ADRD Research Implementation Milestone 1.O (Epidemiology/Population Studies)* *See* https://www.nia.nih.gov/research/milestones/population-studies-precision-medicine-health-disparities/milestone-1-o-0	• Develop and validate at least one TBI-related risk stratification model of dementia, including in diverse populations. • Build or enhance existing brain biorepositories to include brain tissues and biofluids from individuals with TBI for the purpose of understanding AD/ADRD outcomes. • Develop a best-practice document for using standardized common data elements (CDEs) and methods for tissue preservation of human neuropathological studies in TBI.	*1-3 years*

4(4) Basic and translational research to elucidate the mechanistic pathways, development, and progression of post-TBI AD/ADRD neuro-pathologies to better understand clinical symptom expression. *AD+ADRD Research Implementation Milestone 2.W (Disease Mechanisms)* *See* https://www.nia.nih.gov/research/milestones/disease-mechanisms/milestone-2-w-0	• To facilitate translational research, develop at least one new TBI animal model that has sustained cognitive decline and progressive changes in the brain associated with AD/ADRD cognitive impairment and dementia outcomes in humans following TBI. • At least two new projects to identify molecular mechanisms resulting from TBI that lead to cognitive impairment and dementia. • Support one project to connect preclinical data and clinical data to identify potential drug targets.	*7-10 years*

MED Special Topic: LATE (TDP-43 in Common Late-Onset Dementias) (MED-LATE)		
Milestone #(Priority Level) Milestone Text	**Success Criteria**	**Timeline**
1(1) Define LATE (pathologic, clinical, genetic, molecular) classification and diagnostic boundaries across FTLD-TDP, AD and other dementia related pathologies and their syndromes to enhance diagnosis, research, and awareness assuring diversity, inclusion, and equity. *NEW (Diagnosis, Assessment, and Disease Monitoring)*	• Develop and publish a report that defines limbic-predominant age-related TDP-43 encephalopathy (LATE) classification and diagnostic boundaries (pathologic, clinical, genetic, molecular) across FTD, AD and other dementia diagnoses, other nervous system disorders with TDP-43 proteinopathies, and in diverse populations.	*2-7 years*
2(2) Develop biomarkers, classifiers, and risk profiles to establish in-vivo diagnostic criteria for LATE in persons without cognitive symptoms and in persons with amnestic or other relevant late-life dementia syndromes, assuring diversity, inclusion and equity. *AD+ADRD Research Implementation Milestone 9.T (Diagnosis, Assessment, and Disease Monitoring)* *See* https://www.nia.nih.gov/research/milestones/biomarkers-diagnosis/milestone-9-t	• At least three new projects to develop biomarker profiles for clinical trials for TDP-43 proteinopathy in common dementias.	*2-7 years*
3(3) Build new experimental models that incorporate aging with behavioral, pathologic, and molecular phenotypes of TDP-43 proteinopathy or hippocampal sclerosis, to advance knowledge and enable testing of therapeutics. *AD+ADRD Research Implementation Milestone 4.V (Research Resources)* *See* https://www.nia.nih.gov/research/milestones/enabling-infrastructure/milestone-4-v	• Two or more validated animal models, available to the research community, that exhibit brain TDP-43 pathology aligned with the affected anatomical sites and with functional changes that occur in common human dementias that include TPD-43 pathology.	*5-8 years*
4(4) Study the intersection of hippocampal sclerosis (HS) and LATE-NC, within and across all disciplines (clinical, pathologic, diagnostic, genetic, molecular, etc.) and consider the roles of vasculopathy, senescence, and other potential contributing factors, assuring diversity, inclusion, and equity. *NEW (Disease Mechanisms)*	• At least four studies to identify molecular, genetic, clinical, and pathologic drivers of LATE-NC with hippocampal sclerosis, versus, LATE-NC without hippocampal sclerosis; studies are to be powered to understand relevant similarities and potential mechanistic differences in at least two populations that experience health disparities.	*2-7 years*

MED Special Topic: Impact of COVID-19 on AD/ADRD Risk and Outcomes (MED Covid-19)		
Milestone #(Priority Level) Milestone Text	**Success Criteria**	**Timeline**
1(1) Establish research infrastructure enabling clinical, epidemiological, and basic research studies of COVID-19 impact on AD/ADRD risk and outcomes, prioritizing disproportionally affected populations and clinical trials readiness. *NEW (Research Resources)*	• At least one study to establish new or leverage existing clinical cohorts for longitudinal prospective studies to examine the impact of COVID-19 on AD/ADRD risk and outcomes. • Leverage existing resources to ensure brain, other biological samples, and standardized AD/ADRD clinical data from persons infected with SARS-CoV-2, including in populations that are disproportionally impacted, are accessible for AD/ADRD research.	*1-3 years*
2(2) Characterize the clinical phenotype and develop diagnostic criteria for neurocognitive impairment and dementia associated with COVID-19 in those with and without neurocognitive impairment/dementia prior to infection. *NEW (Diagnosis, Assessment, and Disease Monitoring)*	• Develop clinical diagnostic criteria that are specific for incident neurocognitive impairment and dementia associated with long-term outcomes, including temporal progression, following SARS-CoV-2 infection.	*1-7 years*
3(3) Explore interaction of social, structural, and systemic inequalities, comorbidities and social and medical interventions with risk and neurocognitive sequelae of COVID-19. *NEW (Epidemiology/Population Studies)*	• At least two research studies to determine and propose solutions for systemic sociocultural, economic, and health care system factors that are barriers to equitable AD/ADRD outcomes following COVID-19, including when comorbidities increase dementia risk.	*1-5 years*
4(4) Advance understanding of basic mechanisms underlying neurocognitive impairment and dementia due to COVID-19 in order to develop biomarkers, risk profiles, and the foundation for early interventional trials. *NEW (Disease Mechanisms)*	• At least three studies to determine basic mechanisms, potential biomarkers, and pathways with potential for therapeutic intervention, underlying increased risk of long-term cognitive impairment and dementia outcomes following COVID-19.	*1-7 years*

Appendix 1: Research Areas for ADRD Summit 2022 Milestones

All of the ADRD Summit Milestones and respective success criteria are integrated into the existing NIH AD+ADRD Research Implementation Milestones, which are published online in a searchable database (see https://www.nia.nih.gov/research/milestones). These milestones are organized under a classification system that was developed with stakeholder input to help define different critical areas for AD/ADRD research, which include:

- Dementia Care and Impact of Disease
- Diagnosis, Assessment, and Disease Monitoring
- Disease Mechanisms
- Epidemiology/Population Studies
- Research Resources
- Translational Research and Clinical Interventions

Key:

AD+ADRD Research Implementation Milestones Database Research Area			
Summit Session Topic	Milestone # (Priority Level)	Milestone Text	Hyperlink to Database for Milestones with 2022 Updates

Dementia Care and Impact of Disease			
Health Equity	8(4)	Prioritize infrastructure and policy research to understand individual, community, and societal drivers of inequities in cost of and access to treatments and care, and the impact on AD/ADRD outcomes.	13.M
MED	6(4)	Implement and evaluate outcomes for effective dementia care programs that support persons living with dementia and their caregivers, including those of socially, ethnically, and racially diverse populations.	13.L
Diagnosis, Assessment, and Disease Monitoring			
Health Equity	5(3)	Improve AD/ADRD assessment tools (cognitive, biomarkers, -omics) and analytic methods to enhance generalizability and equity of scientific research.	11.H
FTD	2(2)	Develop an array of FTD biomarkers for diagnosis, prediction, disease monitoring, target engagement, and patient stratification for clinical trials.	9.Q
	3(3)	Accelerate the evaluation of novel FTD treatments by developing new clinical trial resources and FTD-specific designs, and by conducting new prevention and treatment trials.	9.S
VCID	4(1)	Develop and validate markers of VCID in diverse populations using 1) cognitive, physical, or other functional assessments, and 2) biomarkers of key vascular processes, including in the most common scenario where VCID is accompanied by AD in human studies.	9.R
LBD	2(2)	Develop and refine neuroimaging biomarkers that track progression, assist in differential diagnosis, provide therapeutic target engagement, and relate to pathology.	9.O

	3(3)	Develop and refine biomarkers for diagnosis, prediction, and prognosis utilizing biofluids, tissues, and digital and electrophysiological methods.	9.P
	4(4)	Expand existing and develop new longitudinal LBD study cohorts, including diverse populations, from pre-symptomatic disease to autopsy to support diagnostic, epidemiologic, and therapeutic studies.	9.J
MED	1(1)	Evaluate pragmatic approaches to objectively detect cognitive impairment and link to quality care when a patient, care partner, or clinician reports cognitive, behavioral, or functional changes.	9.K
	2(4)	Evaluate the benefits, burdens, and harms of screening for cognitive impairment in older adults in the absence of a patient, care partner or clinician report of cognitive, behavioral, or functional changes.	9.N
	3(1)	Conduct multimodal clinical and translational research to support the identification of multiple etiologies in diverse populations.	9.L
	5(1)	Conduct clinical studies on approved or promising interventions and treatments to mitigate risk for cognitive decline.	11.L
	7(2)	Promote education and training on multiple etiology cognitive impairment and dementia to increase the dementia capable workforce, advance researchers including from groups underrepresented in science, and foster inclusive research practices.	11.J
MED Post-TBI	2(2)	Characterize the heterogeneous clinical and biological phenotypes and time course of progressive dementia following varied TBI exposure histories by developing biomarkers and methods to quantify lifetime head trauma exposure and diagnose post-TBI dementias.	11.K
MED-LATE	1(1)	Define LATE (pathologic, clinical, genetic, molecular) classification and diagnostic boundaries across FTLD-TDP, AD and other dementia related pathologies and their syndromes to enhance diagnosis, research, and awareness assuring diversity, inclusion, and equity.	NEW
	2(2)	Develop biomarkers, classifiers, and risk profiles to establish in-vivo diagnostic criteria for LATE in persons without cognitive symptoms and in persons with amnestic or other relevant late-life dementia syndromes, assuring diversity, inclusion and equity.	9.T
MED Covid-19	2(2)	Characterize the clinical phenotype and develop diagnostic criteria for neurocognitive impairment and dementia associated with COVID-19 in those with and without neurocognitive impairment/dementia prior to infection.	NEW
DISEASE MECHANISMS			
FTD	4(4)	Identify overlapping pathogenic mechanisms between FTD and other neurodegenerative disorders and syndromes.	NEW
	7(3)	Elucidate the mechanisms of cell type vulnerability and cell-intrinsic and –extrinsic effects on FTD pathogenesis, with the goal of accelerating development of therapeutic targets.	NEW
VCID	2(3)	Study the neurovascular unit structure and function to establish how it is impacted by VCID.	2.Q
	3(4)	Use experimental models to investigate how aging, cerebrovascular and cardiovascular disease impact myelin, white matter degeneration and neurodegeneration.	2.R
	6(4)	Understand the impact on VCID of other known dementia risk factors (e.g., aging, genetics) and co-morbid neurodegeneration along the life-course in diverse populations to establish VCID interactions with other dementia disease processes.	2.S

LBD	7(3)	Develop models to understand the pathophysiology and normal molecular and cellular functions of α-synuclein to support drug discovery.	2.T
	8(4)	LBD Pathogenesis and Mechanisms of Toxicity: Identify mechanisms of selective vulnerability, disease heterogeneity, disease spread/propagation, and interaction with other age-related pathologies as therapeutic targets.	2.M
MED	4(2)	Advance basic research on the common and interacting risk factors and mechanisms of multiple etiology cognitive impairment and dementia in diverse populations.	2.L
MED Post-TBI	4(4)	Basic and translational research to elucidate the mechanistic pathways, development, and progression of post-TBI AD/ADRD neuro-pathologies to better understand clinical symptom expression.	2.W
MED-LATE	4(4)	Study the intersection of hippocampal sclerosis (HS) and LATE-NC, within and across all disciplines (clinical, pathologic, diagnostic, genetic, molecular, etc.) and consider the roles of vasculopathy, senescence, and other potential contributing factors, assuring diversity, inclusion, and equity.	NEW
MED Covid-19	4(4)	Advance understanding of basic mechanisms underlying neurocognitive impairment and dementia due to COVID-19 in order to develop biomarkers, risk profiles, and the foundation for early interventional trials.	NEW
EPIDEMIOLOGY/POPULATION STUDIES			
Health Equity	4(2)	Assess the social, economic, and structural impediments to equity in AD/ADRD assessment, diagnosis, and referrals, and impacts on health and economic outcomes.	NEW
	6(3)	Apply existing and novel surveillance methods to assess inequities, including trends in inequities, in AD/ADRD prevalence, incidence, diagnosis, treatment and care.	1.J
	7(4)	Identify life course and multi-level mechanisms of and pathways to AD/ADRD inequities and use the discoveries to reduce these inequities.	1.I
FTD	1(1)	Understand FTD epidemiology and genetics in diverse populations, including how socioeconomic and ethnocultural status affects disease risk and manifestations.	NEW
LBD	5(1)	Delineate genetic loci and their functions contributing to the onset and progression of LBDs using genetic, transcriptomic, epigenetic, and environmental characterization analyses.	1.L
	6(2)	Enhance and standardize the techniques for neuropathologic characterization of LBD and the use of LBD pathology cohorts including more diverse cohorts.	1.K
MED Post-TBI	1(1)	Promote collaboration among TBI and dementia researchers through working groups, retrospective and prospective data and measurement harmonization, and interdisciplinary research.	NEW
	3(3)	Establish research infrastructure, including multimodal longitudinal studies with autopsy endpoints that employ standardized CDEs and methodologies, to study post-TBI AD/ADRD.	1.O

MED Covid-19	3(3)	Explore interaction of social, structural, and systemic inequalities, comorbidities and social and medical interventions with risk and neurocognitive sequelae of COVID-19.	NEW
RESEARCH RESOURCES			
Health Equity	2(1)	Increase training support and capacity of an AD/ADRD scientific workforce of persons historically under-represented in biomedical, behavioral, and social sciences.	4.S
	3(2)	Promote career development of biomedical, behavioral, and social scientists conducting AD/ADRD health equity research.	NEW
FTD	5(1)	Advance understanding of FTD and identify therapeutic targets through the creation, validation, and use of pre-clinical and translational tools and resources.	4.Q
VCID	1(1)	Establish and refine experimental models and technologies to identify disease-relevant mechanisms underlying VCID.	4.R
	7(2)	Incorporate VCID mechanisms derived from basic science animal/human studies into the design of human trials targeting prevention or treatment of dementia/mild cognitive impairment.	4.U
	8(3)	Validate hypothesized mechanisms of VCID in large-scale, including community-based diverse, human studies leveraging existing and in-process biospecimens, genomics, and imaging data.	4.T
MED	8(3)	Conduct research to improve pre- and post-data collection harmonization and sharing practices across multiple etiology cognitive impairment and dementia studies.	NEW
MED-LATE	3(3)	Build new experimental models that incorporate aging with behavioral, pathologic, and molecular phenotypes of TDP-43 proteinopathy or hippocampal sclerosis, to advance knowledge and enable testing of therapeutics.	4.V
MED Covid-19	1(1)	Establish research infrastructure enabling clinical, epidemiological, and basic research studies of COVID-19 impact on AD/ADRD risk and outcomes, prioritizing disproportionally affected populations and clinical trials readiness.	NEW
TRANSLATIONAL RESEARCH AND CLINICAL INTERVENTIONS			
Health Equity	1(1)	Advance equity in AD/ADRD research via inclusion science to improve representative sampling and retention of diverse communities.	NEW
FTD	6(2)	Accelerate pre-clinical disease-modifying and symptomatic therapeutic development in FTD.	NEW
	8(4)	Define genetic and molecular modifiers of FTD (including in diverse populations).	6.I
VCID	5(2)	Identify and apply 1) interventions (medication, lifestyle, or a combination of these) that reduce cardiovascular and cerebrovascular risk and 2) care models to test their efficacy for prevention and treatment of VCID across the spectrum of severity and in diverse populations.	8.E
LBD	1(1)	Prepare for and initiate clinical trials that aim to alleviate or slow the course of LBD symptoms, and delay or prevent the onset of disease.	5.D