

Alzheimer's Disease–Related Dementias Summit 2016: National research priorities

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ABSTRACT

Goal 1 of the National Plan to Address Alzheimer's Disease is to prevent and effectively treat Alzheimer disease and Alzheimer disease-related dementias by 2025. To help inform the research agenda toward achieving this goal, the NIH hosts periodic summits that set and refine relevant research priorities for the subsequent 5 to 10 years. This proceedings article summarizes the 2016 Alzheimer's Disease–Related Dementias Summit, including discussion of scientific progress, challenges, and opportunities in major areas of dementia research, including mixed-etiology dementias, Lewy body dementia, frontotemporal degeneration, vascular contributions to cognitive impairment and dementia, dementia disparities, and dementia nomenclature.

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GLOSSARY

AD = Alzheimer disease; **ADRD** = Alzheimer disease-related dementias; **ALS** = amyotrophic lateral sclerosis; **DLB** = dementia with Lewy bodies; **FTD** = frontotemporal dementia; **FUS** = fused in sarcoma; **LBD** = Lewy body dementia; **MED** = mixed-etiology dementia; **NGO** = nongovernmental organization; **NINDS** = National Institute of Neurological Disorders and Stroke; **NVU** = neurovascular unit; **PDD** = Parkinson disease dementia; **TDP** = TAR DNA-binding protein; **VCID** = vascular contributions to cognitive impairment and dementia.

Dementia is a major public health problem with substantial personal, social, and financial burden, affecting more than 47 million people worldwide.¹ Alzheimer disease (AD) contributes to about two-thirds of dementia cases and affects more than 5 million people in the United States alone. Although AD is the most prevalent dementia diagnosis, the majority of dementia cases among the elderly show histologic changes in addition to the classic AD pathology of β -amyloid (plaques) and tau-containing aggregates (neurofibrillary tangles).²⁻⁷ These additional non-AD pathologic changes, typically vascular, Lewy bodies, or TAR DNA-binding protein (TDP)–43 pathology, occur in individuals with clinical AD, as well as in other types of dementias, and conversely, classic AD pathology is frequently present when the dementia diagnosis is not AD, as well as in older persons without dementia.⁸⁻¹⁵ Because of such close clinical and pathologic relationships with AD, frontotemporal, Lewy body, vascular, and mixed dementias are considered AD-related dementias (ADRD) and are included in the National Plan to Address Alzheimer's Disease. ADRD contribute to millions of dementia cases^{2,7,9,11,16} in the United States. Combined, the toll of AD and ADRD on individuals, caregivers, and society is enormous and will continue to increase as the United States population ages.¹⁷⁻²² An organized, comprehensive, and multisector approach is necessary to coordinate and more effectively use national resources to mitigate physical, emotional, and economic burden of these devastating diseases. Prioritized recommendations from the ADRD Summit 2016 are now formalized, with

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success criteria, in the National Plan to Address Alzheimer's Disease as milestones²³ that will both drive critical new research and track progress toward the goal of preventing and effectively treating AD and ADRD by 2025.

A COORDINATED APPROACH TO ADVANCING AD/ADRD RESEARCH

In 2011, the National Alzheimer's Project Act was signed into law, requiring the Secretary of the US Department of Health and Human Services to create and coordinate an integrated National Plan to address AD.²⁴ First released in 2012, this Plan is updated annually and includes an ambitious research goal (Goal 1) of preventing and effectively treating AD/ADRD by 2025. To inform the national AD/ADRD research agenda toward this goal, the National Institute on Aging and the National Institute of Neurological Disorders and Stroke (NINDS) at the NIH host periodic AD and ADRD summits, inviting national stakeholders and international partners to identify and refine AD/ADRD research priorities for a 5- to 10-year time frame. Following approval by the NINDS Council, ADRD research recommendations are included in the National Plan as research milestones²³ that shape development of the annual NIH AD/ADRD bypass budget proposals and guide progress toward the goal of

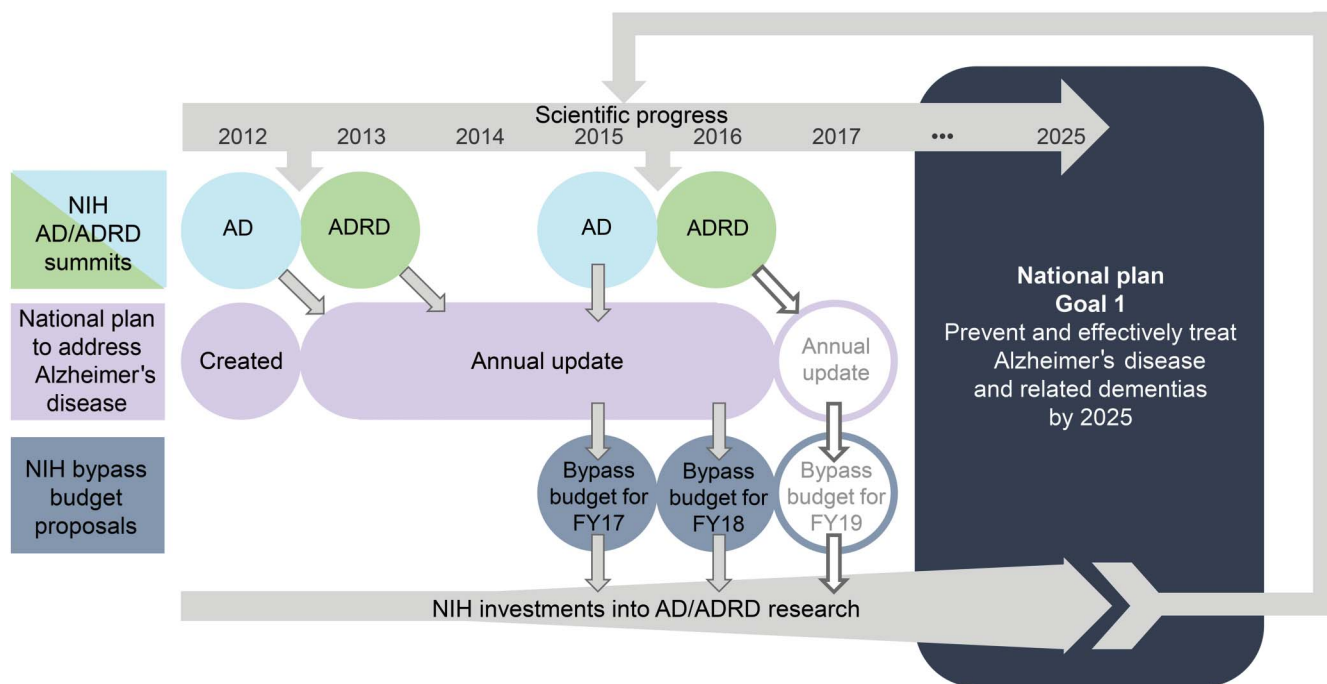
preventing and effectively treating AD/ADRD by 2025 (figure 1).^{25,26}

In 2013, the initial detailed ADRD-specific research priorities were established by the ADRD Conference 2013.²⁷ Three years later, NIH hosted the second ADRD Summit on March 29–30, 2016, to visit progress and refine recommendations as needed (figure 2). The 2016 Summit also included a session led by nongovernmental organizations (NGOs) to broaden stakeholder input and increase public-private partnership. The remainder of these proceedings will focus on the ADRD Summit 2016 by presenting the updated research recommendations that reflect the most important opportunities in ADRD research based on scientific progress, broad stakeholder input, and research gaps, and will highlight ADRD-scientific advances since the 2013 conference.

MIXED-ETIOLOGY DEMENTIAS: THE COMPLEXITIES OF DIAGNOSING DEMENTIA WITH MULTIPLE ETIOLOGIES IN THE 21ST CENTURY

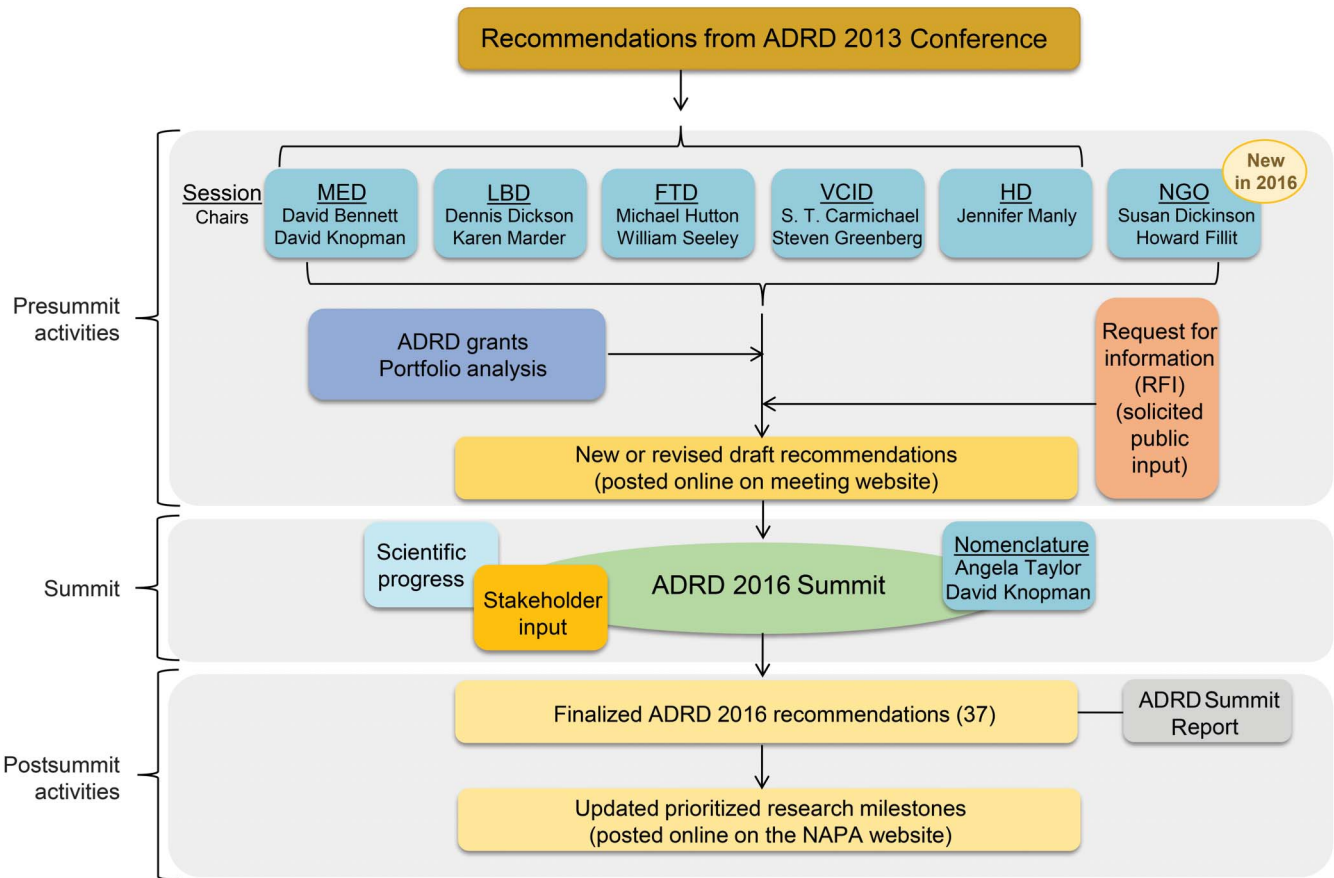
The first step in diagnosis of dementia disorders is detection of cognitive impairment. Although cognitive assessment is included in the annual wellness visit covered by Medicare,²⁸ identifying cognitive impairment, including dementia, continues to be a substantial challenge in the current health care system even

Figure 1 Role of Alzheimer disease (AD) and Alzheimer disease-related dementias (ADRD) summits in the National Plan to Address Alzheimer's Disease



National Plan to Address Alzheimer's Disease hosted AD and ADRD summits review progress in AD/ADRD research and generate or refine recommendations based on recent scientific discoveries and input from a wide range of stakeholders, including the public. These recommendations inform research milestones that are included in the annually updated national plan. The milestones not only help guide and track progress, but also inform the annual bypass budget proposals developed each year by the NIH and delivered to congress that estimate additional funding needed to reach Goal 1 of the National Plan.

Figure 2 Organization structure of the Alzheimer's Disease-Related Dementias (ADRD) Summit 2016 broken down into the pre-Summit activities, the Summit, and post-Summit activities



FTD = frontotemporal dementia; LBD = Lewy body dementia; MED = multiple etiology dementia; NGO = nongovernmental organizations; VCID = vascular contributions to cognitive impairment and dementia.

when a person or his or her relative or caregiver voices a concern to a health care provider. Important barriers are financial (e.g., reimbursement for neurologic and neuropsychological evaluation),²⁹ technical (e.g., lack of simple, accurate, rapid, culturally appropriate, and standardized detection paradigms),³⁰ and social (e.g., stigma for patients and families; reluctance of medical professions to whom the value of detection is unclear).³¹ As a result, cognitive impairment, including dementia, often goes undetected, and even when it is detected, follow-up resulting in a diagnosis occurs only about half of the time.^{32,33} When cognitive complaints and other warning signs are evident but there is no diagnosis it can delay or prevent treatment of reversible conditions, use of appropriate medical and support services, and care planning in a critical time window. Nowhere are these barriers more evident than in primary care, the main locus of care for older people in the United States. This need is addressed by mixed-etiology dementias (MEDs) Recommendation 1 (table 1).

After incident cognitive impairment is detected, differential diagnosis among dementia syndromes

and differentiation of these from medical conditions that may be reversible is a high priority (table 1; MED Recommendation 2). Even though accurate diagnosis is possible to a significant (although imperfect) extent, only a subset of highly specialized clinicians has the requisite tools and training. Many in the United States do not have access to such specialists. Some patients would also benefit from improved diagnostic means to identify reversible causes of cognitive impairment (including, but not limited to, medication side effects, sleep disorders, normal-pressure hydrocephalus, substance abuse, anxiety, and depression). Relatively accurate diagnostic criteria for Lewy body dementia (LBD) are available, but underused, resulting in initial misdiagnosis, potentially harmful treatment with bradykinesia-causing antipsychotics, and delaying benefit from effective pharmacologic management.³⁴ Revised diagnostic criteria are also available for the behavioral variant of frontotemporal dementia (FTD), which may also benefit from specific treatments.³⁰

Accurate clinical diagnosis of the specific type of dementia is challenging because multiple pathologies

Table 1 Research recommendations for Alzheimer disease-related dementias (ADRD) named in the national plan^a

| Multiple etiology dementias and diagnosis | |
|--|---|
| Focus area 1: Improved diagnostic skills in the community | |
| 1. | Detect cognitive impairment when a patient or relative voices a concern to health care providers |
| 2. | Improve differential diagnosis of symptomatic cognitive impairment |
| 3. | Increase training of health professionals to meet the demand for cognitive impairment and dementia diagnosis, care, and need for human-based research |
| 4. | Develop diagnostics/biomarkers in asymptomatic individuals |
| Focus area 2: Basic and clinical research in interactions between dementia pathophysiologies | |
| 5. | Promote basic and clinical research in multi-etiology dementia |
| Focus area 3: Determining the role for screening for cognitive dysfunction | |
| 6. | Determine the value of screening for clinically relevant cognitive impairment in the absence of a cognitive complaint |
| Lewy body dementias | |
| Focus area 1: Establish longitudinal diverse cohorts with common measures, culminating in autopsy | |
| 1. | Initiate clinical trials for LBD in diverse populations using therapies that address symptoms that have the greatest effect on patient function and caregiver burden |
| 2. | Create longitudinal clinical, biological, and imaging resources to improve detection and diagnosis of DLB at the prodromal or prodromal stage including patients at high risk of PD |
| Focus area 2: Discover disease mechanisms through brain mapping and genetics | |
| 3. | Characterize nervous system changes in LBD cohorts that have come to autopsy to identify disease-specific underlying mechanisms to guide biomarker and therapeutic approaches |
| 4. | Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that affect the risk for and clinical features of LBD |
| Focus area 3: Develop and validate biological and imaging biomarkers | |
| 5. | Develop and validate imaging approaches to enhance the differential diagnostic accuracy of LBD, detect latent and prodromal LBD, and monitor disease progression in natural history and treatment studies |
| 6. | Develop biomarkers for pathologic changes, disease progression, and diagnosis; incorporate markers for diagnosis of latent or prodromal disease and for monitoring therapeutic responsiveness |
| Focus area 4: Model disease processes to develop potential symptomatic and disease-modifying therapies | |
| 7. | Develop LBD animal, cellular, and in vitro models that recapitulate key features, including clinical pathophysiologic heterogeneity to identify mechanistic candidates for interventions |
| 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 |
| Frontotemporal lobar degeneration | |
| Focus area 1: Basic science: Pathogenesis and toxicity | |
| 1. | Clarify the mechanism of tau pathogenesis and associated neurodegeneration |
| 2. | Determine the molecular basis for C9ORF72 expansion and GRN mutation-related neurodegeneration |
| 3. | Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity |
| 4. | Develop better FTL in vivo and cell-based model systems |
| Focus area 2: Clinical science | |
| 1. | Expand efforts to genotype patients with FTD and identify new genes and their functional relationship to FTL pathogenesis |
| 2. | Develop FTD biomarkers for diagnosis and disease progression |
| 3. | Create an international FTD clinical trial network |
| 4. | Understand phenotypic heterogeneity and natural history |

Continued

can give rise to similar clinical syndromes.^{9,15} Further complicating matters, multiple pathologies frequently occur in an individual with a single dementia diagnosis.^{9,15} Classic AD pathology (plaques and tangles) in the elderly, for example, is often accompanied by additional disease processes that may contribute independently to cognitive decline and dementia. Contributing further to diagnostic complexity is a lack of tools to gauge the degree to which different underlying brain pathologies (e.g., AD pathology, cerebrovascular disease, Lewy bodies, TDP-43opathy) contribute to observed cognitive decline and dementia.¹⁵ The current AD trials targeting amyloid attempt to include patients with pure Alzheimer pathology. Should these trials prove successful, attention will shift to understand how, or if, the treatment benefit generalizes to the elderly population with a mix of etiologies.

Two clinical-pathologic studies of aging and AD provide some insight into the relationship of common pathologies to dementias and offer implications for study and clinical management of MEDs. The Religious Orders Study, begun in 1993, follows 1,350 older nuns, priests, and religious brothers, without known dementia at enrollment, from across the United States. The Memory and Aging Project, begun in 1997, involves 1,850 lay people from northeastern Illinois. Participants in each study have consented to annual clinical evaluation and brain donation. These studies indicate that the effects of cerebrovascular disease, Lewy body pathology, TDP-43, and hippocampal sclerosis on cognition are independent of AD pathology. Moreover, clinically diagnosed probable AD and mild cognitive impairment are pathologically mixed and heterogeneous disorders that typically exhibit other pathologies in addition to β -amyloid and tau pathology.^{35,36} Recognition that the common clinical diagnosis of AD is actually heterogeneous in its pathologic etiology points to the need for biomarkers that reflect the underlying biology.

Learning from a series of unsuccessful clinical trials for AD, researchers are now using genetic and imaging-based biomarkers to define, recruit, and stratify participants eligible for clinical trials, and have shifted their focus to primary prevention or very early stages of dementia. Examples include the A4 trial³⁷ using amyloid imaging as a biomarker as well as the Alzheimer's Prevention Initiative³⁸ and the Dominantly Inherited Alzheimer's Network³⁹ using genetic markers. Increased and earlier detection of impending cognitive impairment, including in primary care, followed by more accurate differential diagnosis that leverages genetic, imaging, and fluid-based biomarkers will be essential to successfully treat the different disease processes within and across individuals with neurodegenerative disorders. This emerging consensus is reflected

Table 1 Continued

| VCID, including vascular cognitive impairment and vascular dementia | |
|---|---|
| Focus area 1: Basic mechanisms and experimental models | |
| 1. | Develop models that reproduce small vessel disease, are relevant to VCID and AD, address white and gray matter VCID, or include genetic and acquired VCID. Verify models, including via imaging |
| 2. | Encourage basic science research that investigates the effect of aging, AD pathology, and genes on perivascular and paravascular clearance mechanisms, the NVU, and cerebrovascular function |
| 3. | Encourage basic science research that investigates the effect of cerebrovascular risk factors/genes and atherosclerosis on AD-related neurodegeneration |
| Focus area 2: Human-based studies | |
| 1. | Develop and validate longitudinally tracked noninvasive markers of key vascular processes related to cognitive and neurologic impairment |
| 2. | Determine interrelationships among aging, cerebrovascular disease, and risk factors, resilience factors, genetic variants, amyloid, tau, and neurodegeneration |
| 3. | Identify lifestyle and vascular interventions to treat, prevent, or postpone VCID. |

Abbreviations: AD = Alzheimer disease; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia; FTLN = frontotemporal lobar degeneration; FUS = fused in sarcoma; LBD = Lewy body dementia; NVU = neurovascular unit; PD = Parkinson disease; TDP = TAR DNA-binding protein; VCID = vascular contributions to cognitive impairment and dementia. ^a Short form recommendation; for full recommendations, see National Institute of Neurological Disorders and Stroke report.

both in the ADRD Summit 2016 recommendations reported here (table 1; see LBD Recommendation 4, FTD Clinical Science Recommendation 4, VCID Human-Based Studies Recommendation 1; table 2; see HD Recommendation 1) and in reviews regarding unsuccessful clinical trials in dementia.^{40,41}

LBD: CLINICAL TRIALS REMAIN TOP RESEARCH PRIORITY LBD, including both dementia with Lewy bodies (DLB) and Parkinson disease dementia

Table 2 Health disparities recommendations for Alzheimer disease (AD)/ Alzheimer disease-related dementias (ADRD)^a

| Health disparities | |
|--|---|
| Focus area 1: Treatment and prevention strategies | |
| 1. | Assess epidemiology and mechanistic pathways of disparities in health burden of AD/ADRD |
| 2. | Enrich the design of trials of vascular health interventions to improve their application to AD/ADRD among aging diverse populations |
| Focus area 2: Monitoring changes in AD/ADRD disparities | |
| 3. | Develop a system to monitor the magnitude and trends in health disparities in incidence of AD/ADRD |
| Focus area 3: Assessment | |
| 4. | Improve tools for assessment of risks, preclinical characteristics, and costs among health disparities populations by leveraging existing data/cohorts, designing targeted studies, and using psychometric analyses |
| 5. | Increase utilization of culturally and linguistically appropriate assessment tools within ongoing and newly generated studies of AD/ADRD and vascular health intervention trials |
| Focus area 4: Community partnerships, recruitment, and retention | |
| 6. | Generate a Health Disparities Task Force to provide guidance and expertise for community engagement, study design, recruitment, and retention to ensure diverse representation |
| 7. | Develop novel and identify existing community engagement and outreach methods to facilitate engagement, understanding, and partnership with health disparities populations |

^a Short form recommendation; for full recommendations, see National Institute of Neurological Disorders and Stroke report.

(PDD), features include dementia with some combination of visual hallucinations, fluctuation in level of alertness or consciousness, parkinsonism, and sleep abnormalities such as REM sleep behavior disorder.³⁴ Cognitive dysfunction and signs of dementia occur either before or close to the onset of first motor symptoms. Diagnostic criteria for DLB were recently updated and continue to emphasize these features.⁴² In contrast, in PDD, disabling cognitive dysfunction and dementia appear at least a year after the onset of typical Parkinson disease indications including motor symptoms.^{37,38} Pathologically, these disorders are characterized by aggregates of α -synuclein that are indicative of neurodegeneration in specific but widespread brain regions with affected dopaminergic neurons and their terminals. Individuals with LBD commonly have a MED that also includes components of both Alzheimer and vascular pathology.⁴³

Recent research has led to a better understanding of the role of genetics, brain network changes, and cell biology in LBD.^{44,45} Cell to cell trans-synaptic spread of aggregates of α -synuclein potentially explains the widespread Lewy body pathology in PDD and DLB.^{46,47} Substantial progress is also reflected by publication of a large-scale genetic association study with evidence that genetic risk for LBD shares similar degrees of overlap with genetic risk factors for both AD and PD. This includes a strong association of both AD and LBD at the *APOE* locus.^{44,48} Additional large whole-genome association, whole-exome sequencing, and targeted resequencing studies are ongoing.

Effective clinical trials based on a strong foundation of research remains the top priority in LBD research (table 1; LBD Recommendation 1), as it was in 2013, following the first ADRD conference.²⁷ Since 2013, 4 DLB trials have been completed. Three have been open-label or open-label extensions, with only one randomized, double-blind, placebo-controlled trial.⁴⁹⁻⁵¹ Most of these studies focused on Food and Drug Administration–approved drugs for AD, and at least one trial contributed to the approval of donepezil for DLB in Japan in September 2014. In LBD clinical trials, there is growing interest in new types of primary outcome measures for cognition, as reflected in results reported for a memantine intervention.⁵² Three PDD trials have been completed since 2013, featuring drug formulation (rivastigmine patch vs oral pill),⁵³ caregiver burden/secondary analysis of a memantine trial,⁵⁴ and psychosis in PD (randomized, double-blind trial with pimavanserin).⁵⁵

LBD OUTCOMES ARE EMBLEMATIC OF THE CROSS-CUTTING CHALLENGE, IMPORTANCE, AND BENEFIT OF ACCURATE DIAGNOSIS EVEN IN THE ABSENCE OF DISEASE-MODIFYING THERAPY The committees of all 6 sessions of the Summit believed that accurate differential diagnosis of the many forms of dementia is of the utmost

importance. LBD, which represents a significant proportion of dementia diagnoses,^{12,56,57} can clinically mimic not only AD but also Parkinson disease, commonly leading to underdiagnosis, misdiagnosis, or a delayed diagnosis. The challenges of differential diagnosis are clearly illustrated by the fact that about three-quarters of people with LBD received a different initial diagnosis before ultimately learning they had LBD, and the process required, on average, visits to 3 different physicians.^{58–60} Misdiagnosis or no diagnosis is problematic in terms of planning and medical management across the AD/ADRD spectrum. In LBD, misdiagnosis or no diagnosis is especially dangerous because of potential adverse reactions, such as heavy sedation, increased hallucinations, and parkinsonism in response to medications (e.g., typical neuroleptics) used in care settings for behavioral management of disabled elderly. Moreover, improving differential diagnosis among dementias will facilitate better clinical research and trials. To improve diagnostic capabilities as well as useful measures to test target engagement in clinical trials, NINDS issued a funding opportunity announcement for studies of LBD biomarkers.^{e1,e2}

FRONTOTEMPORAL LOBAR DEGENERATION: GENETIC DISCOVERIES INCREASE UNDERSTANDING OF MECHANISMS Among rare early age at onset dementias, FTD is a prevalent clinical diagnostic category that encompasses diverse clinical syndromes.^{e3} The average age at onset is in the middle to late 50s,^{e4} making FTD a condition with much greater midlife burden compared to typical late age at onset AD. In most patients with FTD, the pathologic correlate is frontotemporal lobar degeneration, a heterogeneous category in which neurons and glia form inclusions containing tau, TDP-43, or fused in sarcoma (FUS). FTD has an autosomal dominant genetic cause in 10%–20% of patients. Despite this complexity, considerable progress has been made since 2013, including new insights into the pathogenic mechanisms and clinical symptomatology of FTD and the FTD/amyotrophic lateral sclerosis (ALS) disease spectrum.^{e5}

Recent research has provided new insights into the disease mechanisms of FTD/ALS caused by a hexanucleotide repeat motif expansion in the chromosome 9 open reading frame 72 gene^{e6} (*C9ORF72*; see below). For example, recent studies led to the discovery of disruptions in ribonucleoprotein granule function due to liquid-to-solid phase transitions of TDP-43 and FUS.^{e7} Scientists now also have a better understanding of the molecular mechanisms underlying FTD due to tau pathology.^{e8–e10} Aiding this investigation are new techniques to study the propagation of synthetic tau strains in vitro and in vivo. Such

methods have been shown to recapitulate features of human disease pathology in animal models. Ongoing research efforts responsive to the recommendations from the 2013 ADRD Conference include 3 NIH-funded longitudinal cohort studies of Mendelian, genetically influenced, and sporadic FTD to better understand disease progression, to identify new biomarkers for diagnosis, progression, and prognosis, and to establish a clinical research consortium to support FTD therapy development. In 2016, NIH issued a funding opportunity announcement to stimulate research on tau pathogenesis as it relates to FTD.^{e1,e2}

ROLE OF C9ORF72 IN FTD/ALS The so far most common mutation associated with familial or sporadic FTD/ALS is an expanded hexanucleotide repeat motif (GGGGCC) located in intron 1 of the *C9ORF72* gene. Three main hypotheses are currently being tested to explain how this repeat expansion causes disease. One possibility is that decreased expression of the *C9ORF72* mRNAs leads to a loss-of-function phenotype, as a result of the expanded repeats interfering with transcription or translation. Another possibility is that foci of RNAs formed by the repeat-expanded sense or antisense transcripts sequester essential RNAs, leading to neurotoxicity. Finally, toxic dipeptide repeat proteins produced by repeat-associated non-ATG-initiated translation of the expanded sense and antisense transcripts could be pathogenic. These putative disease mechanisms are not mutually exclusive and require further exploration.^{e6} This mechanistic uncertainty led the FTD committee to include research on the molecular basis of *C9ORF72* repeat expansion–related neurodegeneration in Basic Science (table 1; FTD Recommendation 2).

VASCULAR CONTRIBUTIONS TO COGNITIVE IMPAIRMENT AND DEMENTIA: UNDERSTANDING MECHANISMS AND DEVELOPING BIOMARKERS FOR BETTER DEMENTIA OUTCOMES Because diagnoses of pure vascular dementia are comparatively infrequent in the United States, vascular contributions to cognitive impairment and dementia (VCID) is frequently underestimated both in terms of disease burden and potential for understanding and preventing dementia. The most common picture of brain pathology in older persons with dementia includes vascular pathology together with varying amounts of classic AD plaques and tangles. Numerous studies report that cardiovascular and cerebrovascular risk factors, cerebral arteriosclerosis, diffuse white matter disease, and infarcts increase risk for cognitive impairment and dementia in humans as well as in animal models.^{e11–e16} In addition, recent epidemiologic studies report downward trends in the prevalence of

dementia in high-income countries that parallel downward trends in the incidence of stroke that occurred due to improved control of vascular risk factors.^{e17,e18} These findings are consistent with the hypothesis that addressing cardiovascular and cerebrovascular risk factors in midlife will prevent cerebrovascular disease and stroke in later life with consequent decreased risk of dementia. Therefore, health care providers should be aware of cardiovascular and cerebrovascular risk factors and the potential importance of their management to prevent cognitive impairment and dementia.

Recognizing this scientific nexus between vascular disease and dementia, and the potential for a positive influence on public health through research in this area, in 2014 the NIH started tracking VCID in its Research, Condition, and Disease Categorization, a classification system that NIH uses to report funding. Recent scientific progress in VCID features new animal models exhibiting different types of ischemia, cerebrovascular disease, and white matter pathology as well as comorbidity with relevant human conditions. For example, AD-transgenic mice with diet-induced hyperhomocysteinemia^{e19} exhibit increased amyloid deposition in arterioles.^{e20} In hypertensive stroke-prone rats, researchers were able to study the relationship among age, small-vessel disease, parenchymal β -amyloid, and tau pathology. In 2015, the NIH established the M²OVE AD Consortium, a project that funds interdisciplinary research to understand the vascular etiology of AD.^{e21}

Updates to the VCID recommendations included identifying emerging areas of research such as the study of perivascular and perivascular clearance mechanisms,^{e22,e23} translational brain imaging, and the role of aging, resilience factors, and genetic factors as well as the relationship of cerebrovascular disease to tau-related neurodegeneration.^{e20} The research community also emphasized the need for a new generation of human-based VCID studies that interrogate not only the known vascular risk factors contributing to dementia, but also the complex and diverse roles of the different aspects of late-life changes in cerebral blood vessels (table 1). This can only be accomplished if new clinical research recruits and stratifies research participants from high-risk, high-burden populations with racial, ethnic, geographic, socioeconomic, and other real-life diversity that reflects the spectrum of vascular pathology in United States populations. One potential strategy to achieve this is by adding relevant VCID components to existing population cohort studies.

REDEFINING THE NEUROVASCULAR UNIT FOR VCID AND BEYOND An area of increasing focus and a critical part of VCID research is the neurovascular

unit (NVU). The concept of the NVU highlights the close interaction between brain and vascular cells in development, normal function, and disease. Scientific interest and cognate publications have increased dramatically since the NVU was first defined at the 2002 NINDS Stroke Progress Research Group. The concept has continued to evolve and grow in importance, including following a 2010 call for reevaluation of the NVU's role in health and disease, and in particular, in VCID.^{e12} Increased study of the NVU has shed light on the blood-brain barrier, highlighting roles of paracellular movement, including transcytosis. These insights have pointed to new roles for astrocytes, microglia, and extracellular matrix proteins after injury, including brain clearance of potentially toxic agents.^{e24}

From a conceptual standpoint, the NVU was initially static, but now it is very clear that the exact makeup of the NVU differs in different brain regions. It has become important to revisit the NVU with our increased understanding of its complex interactions with multiple neuronal and vascular cell types such as astrocytes, neurons, myocytes, pericytes, and endothelial cells. At each level of the cerebrovascular tree, the architecture of the NVU changes to meet the functional requirement of delivering blood to the brain. Thus, understanding the NVU at the extraparenchymal arteriole is different from understanding the NVU at the capillary. Understanding how the function of the NVU changes with age, hypertension, atherosclerosis, and concomitant proteinopathies, including AD, is critical to understanding and preventing VCID.

HEALTH DISPARITIES: RECOGNIZING DEMENTIA DISPARITIES, ADVANCING UNDERSTANDING AND SOLUTIONS

There is evidence that the prevalence of cognitive impairment is higher in nonwhite populations in the United States, including African American, Hispanic, and Latino populations.^{e25–e32} At the same time, people from certain racial and ethnic groups, along with socioeconomically disadvantaged and rural populations, are less likely to have dementia diagnosed, and diagnosis is typically at later stages of disease, with more neuropsychiatric symptoms present than among whites.^{e33,e34} There are also geographic disparities in the burden of dementia. For example, African Americans and whites born in the United States stroke belt are at higher risk of dementia mortality than those born in other states, even for people that at some point move out of this southern region of the country.^{e35} Finally, more women are affected than men.^{e36–e39} Due to disparities in access to specialty diagnostic care, current AD/ADRD datasets are lacking in research data from diverse populations. This is because of insufficient diversity in most

Table 3 Nongovernmental organization (NGO) session recommendations^a

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|--|
| Nongovernmental organizations |
| Focus area 1: Catalyzing research through unique programs and partnerships |
| 1. Establish more effective annual communication between NIH and NGOs on activities and progress toward Alzheimer disease-related dementia goals |

^a Short form recommendation; for full recommendations, see National Institute of Neurological Disorders and Stroke report.

cohort studies, and data capture methods that are typically composed of registries with limited catchment areas. As a result, there are important gaps in the AD/ADRD research and evidence base, which is built largely from non-Latino white participants.

Nonetheless, since the 2013 ADRD conference, research progress has been made. Existing studies of diverse cohorts have been leveraged to include neuropsychological and biomarker assessments. Researchers are engaging local expertise to evaluate AD/ADRD in diverse communities, developing assessment tools for use in disparate populations, and studying molecular mechanisms for health disparities. To help further close the disparity gap, NIH also released 2 targeted funding initiatives that address health disparities in AD and AD-related dementias.^{e1,e2} Because culturally appropriate assessment, approaches, validation, and community partnerships are critical to address dementia disparities, these figure prominently in the recommendations (table 2).

RECRUITMENT IS CRITICAL TO ANY SUCCESSFUL APPROACH FOR ADDRESSING DEMENTIA HEALTH DISPARITIES There are substantial barriers to recruitment of minorities as well as persons affected by health disparities to clinical trials and clinical research. These include inadequate connection with health systems, lack of community-based participatory research, lack of engagement and partnership with the community, and cultural differences in beliefs such as about the body after death.^{e40} Mistrust of scientific research in disparate populations has historical roots (e.g., atrocities such as the Tuskegee Syphilis Study) as well as current realities (e.g., minorities continue to have experiences of

Table 4 Nomenclature session recommendations^a

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| Nomenclature |
| NGO focus area 2: Nomenclature standards when discussing dementia |
| 2. Organize a working group of stakeholders, including health disparities communities, to develop more consistent nomenclature in dementia research and care |
| MED focus area 4: Revisiting the nosology of cognitive impairment in late life |
| 7. Develop a consistent nomenclature in dementia research and care |

Abbreviations: MED = mixed-etiology dementia; NGO = nongovernmental organization.
^a Short form recommendation; for full recommendations, see National Institute of Neurological Disorders and Stroke report.

discrimination in medical settings).^{e41,e42} Despite these and other challenges, including stigma associated with cognitive impairment and dementia, there is potential to address health disparities in AD/ADRD, as indicated by the many Latino and African American people, as well as those living in rural areas and those with lower socioeconomic status, who report interest in participation in research and clinical trials but are not routinely eligible or asked to participate.^{e43} The Health Disparities Session embraced the task of solving these critical challenges (table 2; Focus area 4) by recommending that a Health Disparities Task Force be established to focus exclusively on recruitment issues in AD/ADRD research.

NGO: CATALYZING RESEARCH THROUGH UNIQUE PARTNERSHIPS The 2016 ADRD Summit included a session led by representatives from NGOs in the AD/ADRD field that fund biomedical research among other activities. The NGO committee highlighted the value of partnerships and collaborations in AD/ADRD research. Collaborations among NGOs, government, industry, and academia can foster unique research opportunities across diseases, national borders, and stakeholders. Members of the committee discussed shared principles of NGO research funding, including flexibility, swift turnaround, focus, and an emphasis on collaboration. These allow NGOs to provide research funding that is both complementary to and synergistic with federal support (table 3).

WHAT'S IN A NAME? NGO AND THE MED SESSION FOCUS ON NOMENCLATURE A joint session of the NGO and MED committees highlighted the need for developing AD/ADRD nomenclature standards for use among researchers and other stakeholders, including individuals living with dementia and their families, caregivers, health care providers, and government agencies (table 4). There are many factors that contribute to unclear and inconsistent nomenclature: undirected evolution of terminology, reductionist tendencies, confounding of clinical syndromes and etiologies, and lack of consensus regarding how to refer to the mildest symptomatic phases of cognitive impairment and dementia. In addition, AD is often used synonymously with or instead of the term dementia. The result is that some patients and families have not heard of the ADRD diagnoses, and thus lack context for making a connection between AD care and service and their own needs. A generalized lack of clarity in dementia terminology is counterproductive to the goals of all stakeholders; better clarity in terminology should increase clinicians' ability to engage in meaningful discussions. This is critical because misdiagnosis, changing diagnoses over disease progression,

and lack of clarity in communicating a diagnosis can create tremendous confusion for patients and their family members. In the community at large, lack of both a basic understanding of dementia and an accurate vocabulary to address this contributes to stigma and confounds efforts to develop effective systems for appropriate, empathic care. It is time for an open national dialogue toward developing a universal lexicon that meets the needs of all. Several efforts are underway to achieve this goal: Dementia Friendly America,^{e44} the dementia language guidelines,^{e45} and the Dementia Engagement & Empowerment Programme^{e46} are 3 examples.

DISCUSSION Rapid progress has been made in AD/ADRD research in the last few years and dedicated funding has accelerated its pace. However, continued attention to cross-cutting areas will be necessary to uncover poorly understood relationships among different diagnoses and pathophysiologic mechanisms. Notable areas of interdisciplinary scientific interest include the relationship among proteinopathies, genetics, metabolism including diabetes, immune signaling, neural circuits, circadian rhythms and sleep, and the NVU and blood–brain barrier.

Discussion at the ADRD Summit 2016 also called for a more effective cross-sector dialogue about activities and progress toward achieving ADRD research goals, especially in the years between the NIH-hosted ADRD Summits. Plans are in process to develop consensus and harmonization in AD/ADRD nomenclature that is effective for the broad range of stakeholders. Continued collaborative efforts from government, industry, and nonprofit organizations will be essential to meet the goal of preventing and effectively treating AD/ADRD by 2025.

Here we have characterized in some detail recent progress and research recommendations in the main ADRD focal areas: LBD, FTD, VCID, and multiple etiology dementias. Frequent assessment and recalibration of research directions is being accomplished through periodic and complementary AD and ADRD summits. A full listing of the ADRD Summit 2016 recommendations, with further comments and rationale not detailed here, is available online.^{e47}

AUTHOR CONTRIBUTIONS

R.A.C., J.T.G., A.K.G., S.J., W.J.K., and D.M.H. organized pre-Summit activities, participated in the ADRD Summit 2016, and contributed to post-Summit activities and drafting a substantial portion of the manuscript. D.B., D.A.B., T.C., S.L.-J.D., D.W.D., M.E., H.F., S.M.G., M.L.H., D.S.K., J.J.M., K.S.M., C.S.M., C.H.P., C.L.T., P.A.S., W.W.S., B.-A.S., N.B.S., M.L.S., A.T., and S.P.W. organized pre-Summit activities, participated in the ADRD Summit 2016, and contributed to post-Summit activities.

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