

Public Policy Division  
1212 New York Ave NW  
Suite 800  
Washington, DC 20005

202.393.7737 p  
866.865.0270 f  
www.alz.org



Roderick Corriveau, Ph.D.  
Program Director  
National Institute of Neurological Disorders and Stroke  
National Institutes of Health  
Neuroscience Center, Room 2153  
6001 Executive Blvd MSC 9525  
Bethesda, Maryland 20892-9525

December 7, 2015

Re: Request for Information: Updating the Alzheimer's Disease-Related Dementias Research Priorities

Dear Dr. Corriveau,

The Alzheimer's Association appreciates the opportunity to offer comments on updating the Alzheimer's Disease-Related Dementias Research Priorities. As the largest non-profit funder of Alzheimer's research, the Association is committed to accelerating progress of new treatments, preventions and ultimately, a cure. We are grateful for our long-standing, invaluable partnership with the National Institutes of Health (NIH) on this mission. Our remarks on updating specific recommendations are followed by general comments.

**Session and Focus Area: Multiple Etiology Dementias, Differential Diagnosis**

*Recommendation 1. Develop clinical algorithms for detection of prototypical neurodegenerative dementias and VCI in (a) primary care, (b) general neurology, and (c) general psychiatry outpatient settings; and clinical algorithms for referral to specialists in appropriate cases that also might involve consultations using novel technologies (1-3 yr).*

While Recommendation 1 is relevant, it is overly broad and inclusive. The updated recommendation should be narrowed to research-level work designed for clinical settings. Intermediate steps towards success can be established from there.

*Recommendation 2. Develop imaging and fluid biomarker algorithms to detect prototypical versus atypical dementias and expand their accessibility in primary care settings (3-7 yr).*

An updated recommendation should define "prototypical" and "atypical." It should also distinguish among the multiple pathologies that can present in different forms of dementia to different degrees and topography. From there, specific goals and milestones can be established, pathologies can be measured, and their relationships or contributions to different dementias can be studied.

*Recommendation 3. Develop clinical, imaging, and fluid biomarker algorithms for the rapidly progressive and potentially treatable dementias to enable recognition and referral to specialists (1-3 yr).*

The distinctions between this recommendation and Recommendations 1 and 2 should be clarified. Because we cannot currently image or reliably detect the distinct pathologies across the spectrum of dementia, achievement of Recommendations 1 and 2 underpin this recommendation.

**Session and Focus Area: Epidemiology**

*Recommendation 1. Conduct population-based studies of dementia prevalence and incidence in diverse ethnic groups and age ranges using imaging and fluid biomarkers (1-3 yr).*

This recommendation assumes the almost immediate development of imaging and fluid biomarkers. Because the markers needed to identify contributing pathologies do not exist, the Alzheimer's Association recommends that NINDS and NIA direct their efforts accordingly.

*Recommendation 2. Develop registries for enumerating and characterizing less common dementias, dementias in younger persons, rapidly progressive dementias, and potentially treatable dementias (1-3 yr).*

The Association supports this recommendation, but is concerned that these registries are unlikely to be developed in a timely manner without identified funding. Given the many competing interests for funding, this recommendation may not be a top priority.

*Recommendation 3. Expand and broaden the accessibility of neuropathology services to cases of cognitive impairment and dementia outside of research centers. Link neuropathologic findings to development of clinical algorithms and biomarkers (1-3 yr).*

The Alzheimer's Association supports this recommendation, but notes that neuropathology is not a growing field of science. In order to implement this recommendation, NINDS and NIA should consider ways to incentivize young clinical researchers to pursue neuropathology.

### **Session and Focus Area: Health Disparities, Recruitment**

*Recommendation 1. Initiate and leverage ongoing longitudinal community-based cohort studies of incident dementia in diverse populations incorporating imaging, fluid biomarkers, and autopsy (3-5 yr).*

While the Association supports this recommendation, we note the decreasing amount of funding available for new epidemiological studies and suggest NINDS and NIA focus on the continuation of existing studies.

*Recommendation 2. Use mixed methodology studies to improve assessment tools for disparities populations (1-3 yr).*

Specific examples of these tools should be included in the recommendation. Without examples of tools or specific measures to be captured, this recommendation is too vague to be effectively implemented.

*Recommendation 3. Use community outreach methods to facilitate recruiting disparities populations into FTD and LBD clinical studies (5-7 yr).*

As written, this recommendation is too vague to be practicable. The recommendation should include possible outreach methods and how an approach to its implementation would be organized.

*Recommendation 4. Evaluate under-diagnosis and implement surveillance for ADRDs to detect incidence and monitor trends in disparities populations (5-7 yr).*

As noted in Recommendation 1, NIA and NINDS should focus on existing disparities surveillance rather than new studies.

### **Session and Focus Area: Health Disparities, Advancing Treatment and Prevention Strategies**

*Recommendation 1. Enhance the design of all trials of vascular health interventions to improve their application to diverse populations (5-7 yr).*

As written, this recommendation is too vague to be practicable. Again, it should discuss examples of how to enhance these trial designs and how to approach this recommendation.

*Recommendation 2. Assess lifecourse risk factors for cognitive decline and ADRDs among disparities populations (1-3 yr).*

*Recommendation 3. Estimate disparities in health burden of ADRDs and risk factors among disparities populations (1-3 yr).*

In light of decreased funding availability, NINDS and NIA should focus on existing disparities surveillance rather than new studies.

*Recommendation 4. Identify environmental and genetic factors that modify incidence, presentation, and long-term outcomes of ADRDs in disparities populations (>10 yr).*

NINDS and NIA should ensure that trials are funded and that data are made public to encourage younger investigators to mine the data and identify related and modifiable factors.

**Session and Focus Area: Lewy Body Dementias (LBD): Dementia with Lewy Bodies (DLB) and Parkinson’s Disease Dementia (PDD), Establish Longitudinal Cohorts with Common Measures, Culminating in Autopsy Studies**

*Recommendation 1. Initiate clinical trials for DLB and PDD using existing and newly developed symptomatic therapies that address key symptoms that impact patient function and the burden put on caregivers (1-3 yr).*

The Alzheimer’s Association supports this recommendation and suggests that NINDS and NIA explore public-private partnerships to fund these efforts. The updated recommendation should also include examples of the types of treatments envisioned and that are achievable.

*Recommendation 2. Create longitudinal clinical, biological, and imaging resources for DLB and PDD from the earliest stages to autopsy studies to improve the accuracy of detection and diagnosis of DLB at the pre-dementia or prodromal stage and to detect PD patients with a high risk of cognitive decline leading to PDD (1-3 yr).*

This recommendation should be a priority, as many recommendations, goals, and milestones may follow from the development of these resources. NINDS and NIA should consider a structure similar to the Alzheimer’s Disease Neuroimaging Initiative (ADNI), and discuss the kind of leadership--by a NGO, NINDS/NIA, or both--that will be required to implement this recommendation.

**Session and Focus Area: Lewy Body Dementias (LBD): Dementia with Lewy Bodies (DLB) and Parkinson’s Disease Dementia (PDD), Discover Disease Mechanisms through Brain Mapping and Genetics**

*Recommendation 3. Using well defined cohorts with DLB or PDD who have come to autopsy, systematically map disease-specific changes in the brain, spinal cord, and peripheral autonomic nervous system with state-of-the-art methods, including genomics, expression arrays, metabolomics, and proteomics to identify underlying disease mechanisms that will guide future biomarker and therapeutic approaches (1-3 yr).*

The updated recommendation should provide that longitudinal participants be followed or that a national “brain bank” be created. NINDS and NIA should also consider ways to encourage researchers to specialize in pathology.

*Recommendation 4. Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that influence the risk and clinical features of DLB and PDD (5-7 yr).*

The Alzheimer’s Association notes the significance of this recommendation for less prevalent forms of dementia. Natural history studies can advance this recommendation, as can the development of an ADNI-like structure, discussed under Recommendation 2.

**Session and Focus Area: Lewy Body Dementias (LBD): Dementia with Lewy Bodies (DLB) and Parkinson’s Disease Dementia (PDD), Develop and Validate Biological and Imaging Biomarkers**

*Recommendation 5. Develop imaging approaches to enhance the diagnostic accuracy of DLB and PDD, detect latent and prodromal DLB and PDD, and monitor disease progression in natural history and treatment studies by integrating established and new imaging tools (5-7 yr).*

This recommendation should be clarified. Evaluating current technologies for feasibility may not be sufficient until ligands and assays for specific proteins, for example, have been discovered.

*Recommendation 6. Use existing or new longitudinal case-control studies of individuals with DLB and PDD to develop biomarkers for Lewy-related pathologic changes, disease progression, and the relative amount of concurrent AD. As new markers of molecular disease mechanisms are discovered, incorporate*

*them into biomarker studies for diagnosis of latent or prodromal disease and for monitoring molecular processes and their response to therapies (5-7 yr).*

These cohorts currently exist, so NINDS and NIA should design RFAs to target early-career investigators to pursue this recommendation.

**Session and Focus Area: Lewy Body Dementias (LBD): Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD), Model Disease Processes to Develop Potential Symptomatic and Disease Modifying Therapies**

*Recommendation 7. Recognizing the importance of  $\alpha$ -synuclein and AD pathophysiologic processes in DLB and PDD, new animal, cellular, and in vitro models are needed that recapitulate key features of these disorders with the ultimate goal of identifying strategies that can be carried forward into clinical trials (3-7 yr).*

The Alzheimer's Association applauds the specific identification of a marker in this recommendation. Updated recommendations should include this degree of specificity concerning all markers that contribute to pathology.

*Recommendation 8. Develop disease-modifying interventions based upon research discoveries (7-10 yr).*

The Alzheimer's Association supports this recommendation but notes the substantial research needed before disease-modifying interventions can be developed. Thus, the underlying research should be listed ahead of this recommendation as a priority.

**Session and Focus Area: FTD and Related Tauopathies, Basic Science: Pathogenesis and Toxicity**

*Recommendation 1. Clarify the mechanism of tau pathogenesis and associated neurodegeneration (3-7 yr)*

This is an important recommendation and warrants further discussion about much-needed research on tau and isoforms and funding that research. Other proteins of interest also need this discussion.

*Recommendation 2. Develop better FTD in vivo and cell-based model systems (1-3 yr)*

Similar to concerns expressed in Recommendation 1, these systems cannot be developed until more research is conducted on biomarker discovery and therapeutic development.

*Recommendation 3. Determine the molecular basis for C9ORF72 expansion- and GRN-related neurodegeneration (3-7 yr)*

*Recommendation 4. Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity (3-7 yr).*

These recommendations cannot be achieved until further underlying research is conducted. Thus, that fundamental research should be prioritized ahead of these recommendations. Meanwhile, these recommendations should also be prioritized and more defined timelines should be established. The updated recommendations should note what has been achieved in the field, particularly with regard to other protein changes and apoptosis, cell metabolism, and senescence.

**Session and Focus Area: FTD and Related Tauopathies, Clinical Science: FTD Clinical Discovery, Tools, and Cohorts**

*Recommendation 1. Expand efforts to genotype patients with FTD and identify new genes (1-3 yr).*

*Recommendation 2. Develop FTD biomarkers for diagnosis and disease progression (3-7 yr).*

*Recommendation 3. Create an international FTD clinical trial network (1-3 yr).*

*Recommendation 4. Understand phenotypic heterogeneity and natural history (>10 yr).*

The updated recommendations should reflect how work on each of these LBD-related recommendations can be combined to leverage dollars and accelerate learning about overlapping changes and pathologies and their clinical contributions.

**Session and Focus Area: Vascular Contributions to ADRD: Focus on Small Vessel Disease and AD/Vascular Interactions, Basic Mechanisms and Experimental Models**

*Recommendation 1. Develop next-generation experimental models of VCI and VaD (3-7y).*

*Recommendation 2. Encourage basic science research that investigates the impact of AD risk factors on cerebrovascular function (3-7 y).*

*Recommendation 3. Encourage basic science research that investigates the impact of cerebrovascular risk factors on AD-related neurodegeneration (3-7 y).*

The Alzheimer's Association supports these recommendations but notes the need to account for the interaction between these models and the normal aging process.

**Session and Focus Area: Vascular Contributions to ADRD: Focus on Small Vessel Disease and AD/Vascular Interactions, Human-Based Studies**

*Recommendation 1. Develop (1-3 y) and validate (3-7 y) noninvasive markers of key vascular processes related to cognitive and neurologic impairment.*

Markers of vascular processes may be related to normal aging. This recommendation should distinguish between those markers and markers related to dementia.

*Recommendation 2. Determine interrelationships among cerebrovascular disease and risk factors, A $\beta$ , and neurodegeneration (3-7 y).*

Longitudinal studies will be needed in order to share data, encourage research on the data, and to look for correlations that can be tested.

*Recommendation 3. Identify next generation vascular interventions to treat or prevent VCI and VaD (7-10 y).*

An updated recommendation should be more focused, both in the types of interventions to be targeted and developing a timeline based on needs and the funding models required to address those needs.

**General Comments**

While it is important for all stakeholders to bear in mind the ideal and long-term goals of treating and curing Alzheimer's disease and related dementias, the updated recommendations should reflect a more pragmatic approach. Recommendations that can lay the groundwork for long-term gains should be identified and organized accordingly.

Recommendations should also be prioritized and listed according to urgency of need and potential for realization. Though we acknowledge that the 2013 recommendations were prioritized differently among topics, the updated recommendations should be prioritized based on what is practical, realistic, and achievable. Similarly, although the timelines for the 2013 recommendations were made uniform across topic areas, the updated recommendations should include timelines that clearly establish milestones within for progress. Funding, resources, and the infrastructure needed to accomplish each recommendation should also be discussed.

Some recommendations with areas of overlap can be combined and leveraged. For example, senescence, cellular metabolic pathways, and apoptotic pathways should be included in discovery science as potential areas to find new targets that can be applied to more than one dementia. Furthermore, the recommendations should account for the normal aging process. Mechanisms common to early life, normal aging, and neurodegeneration may exist and should be explored.

The Alzheimer's Association funds the full spectrum of Alzheimer's and related dementia research areas with emphasis on (1) gaps in knowledge (e.g., non-pharmacologic interventions, biological underpinnings of genetic areas of interest, discovery and validation of novel targets), (2) early career investigators, (3) assessing commonalities across and within neurodegeneration, and (4) investments in tools for the

research community to be leveraged globally. We also work to identify emerging strategic initiatives in need of funding to accelerate and expedite progress in trials, such as the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU), the Alzheimer's Prevention Initiative (API), and the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) study.

With this experience and resources, the Association looks forward to working with NINDS, NIA, and other stakeholders to identify gap areas and synergize investments that leverage smaller pilot projects to larger federal dollars, as we have done with our Vascular and Metabolic Investigator-Initiated Research Grant award, NINDS/NIA RFAs, and DIAN-TU. We would also be pleased to explore mechanisms to collaboratively fund relevant research when appropriate.

Thank you for the opportunity to comment. The Alzheimer's Association looks forward to our continued partnership with NIH. Please contact Laura Thornhill, Manager of Regulatory Affairs, at 202-638-7042 or [lthornhill@alz.org](mailto:lthornhill@alz.org) if you have questions or if we can be of additional assistance.

Sincerely,



Robert Egge  
Executive Vice President, Government Affairs



Maria C. Carrillo, Ph.D.  
Chief Science Officer