National Plan to Address Alzheimer's Disease

Ronald C. Petersen, Ph.D., M.D.
Mayo Clinic
Rochester, MN
Chair, Advisory Council on Research, Care and Services
National Alzheimer's Project Act

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National Plan to Address Alzheimer's Disease

http://aspe.hhs.gov/daltcp/napa/NatlPlan.pdf

U.S. Department of Health and Human Services
Office of Assistant Secretary for Planning and Evaluation

National Alzheimer's Project Act

Goal

To effectively treat Alzheimer's disease (delay onset, slow progression) by

2025

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National Plan to Address AD

In the introductory language of the National Plan the term "Alzheimer's Disease" is used but is intended to include AD related dementias:

FTD, DLB, VCI and related conditions

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US National Alzheimer's Plan Goals

1. Prevent and effectively treat AD by 2025
2. Enhance care quality and efficiency
3. Expand supports for people with AD and families.
4. Enhance public awareness/engagement
5. Improve data to track progress

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Research Goal

1. Identify research priorities and milestones
2. Expand research aimed at prevention and treatment of AD
3. Accelerate efforts to identify early and presymptomatic stages of AD
4. Coordinate research with international public and private entities
5. Facilitate translation of findings into medical practice and public health programs

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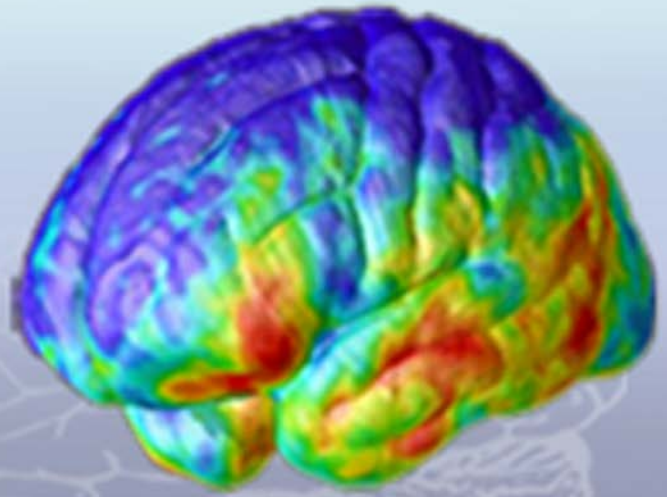
Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention

May 14-15, 2012
National Institutes of Health
Bethesda, MD



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Annual Revision of the National Plan

- NAPA requires that the Plan be updated annually through 2025
- For the 2013 revision a set of milestones to assess progress was recommended
  - Short term
  - Intermediate
  - Long term

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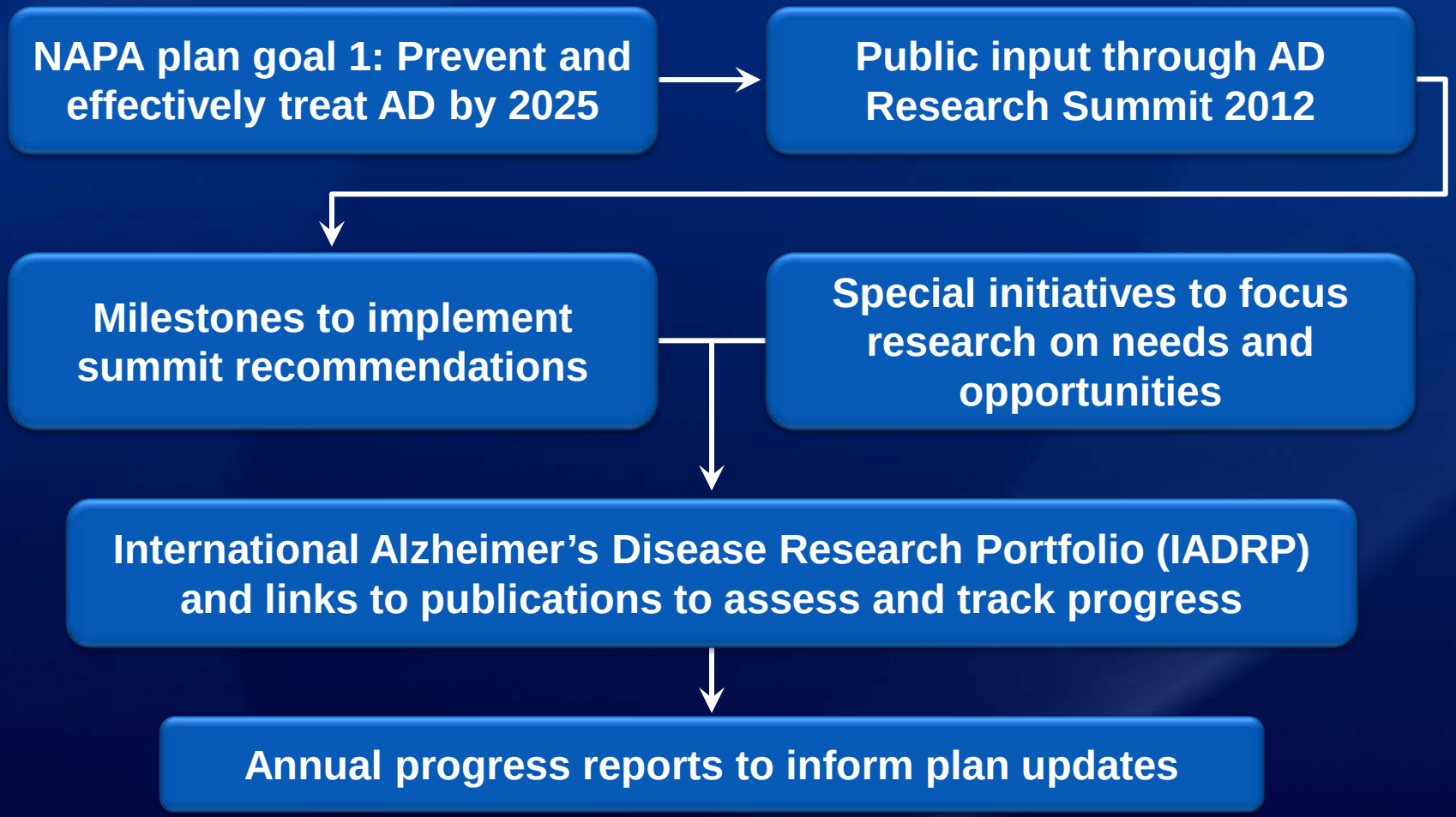
Establishing Research Milestones and Tracking Progress



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Alzheimer's Research Summit Recommendations
May 2012

Recommendations Related to Drug Trial Milestones

3.A. Initiate treatment trials in asymptomatic, at-risk individuals using uniform biomarkers and cognitive outcomes informed by data from Alzheimer's disease trials using patients with more advanced disease

3.B. Collect DNA and other biosamples from these studies to enable subsequent interrogation based on treatment response and predictors of decline in groups receiving placebo

3.F. Develop treatments for patients with symptomatic Alzheimer's disease and support proof of concept studies to validate novel targets for cognitive and neuropsychiatric symptoms across all disease stages

5.E. Develop standard outcome measures to enable data comparisons across studies; these include but are not limited to ecologically valid measures of real-world function, quality of life and physical and cognitive function

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Search Found 35 Phase II and III Drug Trials in IADRP, 2008-2011

Grant number	Grant title	PI first name	PI last name	Grant institution	Funding organization	Funding year(s)
R01AG030048	A Phase 2 Trial of AAV-NGF Gene Delivery in Alzheimer's Disease	Paul	Aisen	University of California, San Diego	National Institutes of Health (NIH)	2008-11
20101209	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Effect of PBT2 (Once Daily for 52 Weeks) on Abeta Deposition in the Brain of Patients with Alzheimer's Disease	Dianne	Angus	Prana Biotechnology Ltd	Alzheimer's Drug Discovery Foundation	2010
20101202	Safety/Tolerability and Effects on Cognitive Impairment, Impaired Cerebral Critical Metabolism and Oxidative Stress of R(+)Pramipexole Administered to Subjects with Early Alzheimer's Disease	James	Bennett	Virginia Commonwealth University	Alzheimer's Drug Discovery Foundation	2010
281206 AFTD	A Pilot Clinical Trial NAP (AL-108) for Corticobasal Degeneration and Frontotemporal Lobar Degeneration with Predicted Corticobasal Degeneration Pathology	Adam	Boxer	University of California, San Francisco	Alzheimer's Drug Discovery Foundation	2008
K23AG026752	Effect of Statins on Pathobiology of Alzheimer's Disease	Cynthia	Carlsson	University of Wisconsin Madison	National Institutes of Health (NIH)	2008
R01AG031790	Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for AD	Cynthia	Carlsson	University of Wisconsin Madison	National Institutes of Health (NIH)	2009-11
R01AG027156	Testosterone Supplementation in Men with MCI	Monique	Cherrier	University of Washington	National Institutes of Health (NIH)	2008-09

http://iadrp.nia.nih.gov/cadro-web/

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Example

Milestone	Time to complete	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Drug development: Repurposing and combinations													
Convene an advisory meeting of experts to advance rational drug repurposing/repositioning and combination therapy	1 year												
Initiate research programs for translational bioinformatics and network pharmacology to support rational drug repositioning and combination therapy	3-5 years												
Initiate early clinical development for ≥6 repurposed drugs or drug combinations	2-4 years												
Initiate ≥3 phase 3 trials with repurposed drugs or drug combinations	3-5 years												
Drug development: Currently known targets													
Initiate phase 2 (proof of concept) drug trials for agents against 3-6 currently known therapeutic targets	2-4 years												
Initiate phase 3 drug trials for agents against ≥3 currently known therapeutic targets	3-5 years												

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Example

Drug Development: Currently Known Targets	
Milestone	Success Criteria
• Initiate phase II (proof of concept) drug trials for agents against 3-6 currently known therapeutic targets. Of these at least 2 will be for targets involved in asymptomatic stages of disease. These trials will be designed to provide or confirm proof of mechanism and/or evidence of target engagement for the therapeutic agent being tested. [Summit 3.A, 3.B, 3.F, and 5.E]	Completion of 3-6 phase II drug trials for agents against currently known targets, providing conclusive evidence of therapeutic mechanism/target engagement.
• Initiate phase III drug trials for agents against at least 3 currently known therapeutic targets. Of these at least one trial will be asymptomatic, at risk populations. These trials will incorporate a combination of biomarkers (fluid and imaging) and cognitive measures as outcomes and include collection of DNA and other bio-samples for interrogation of responsiveness. [Summit 3.A, 3.B, 3.F, and 5.E]	Comprehensive success/failure analysis of data from at least 3 phase III trials.

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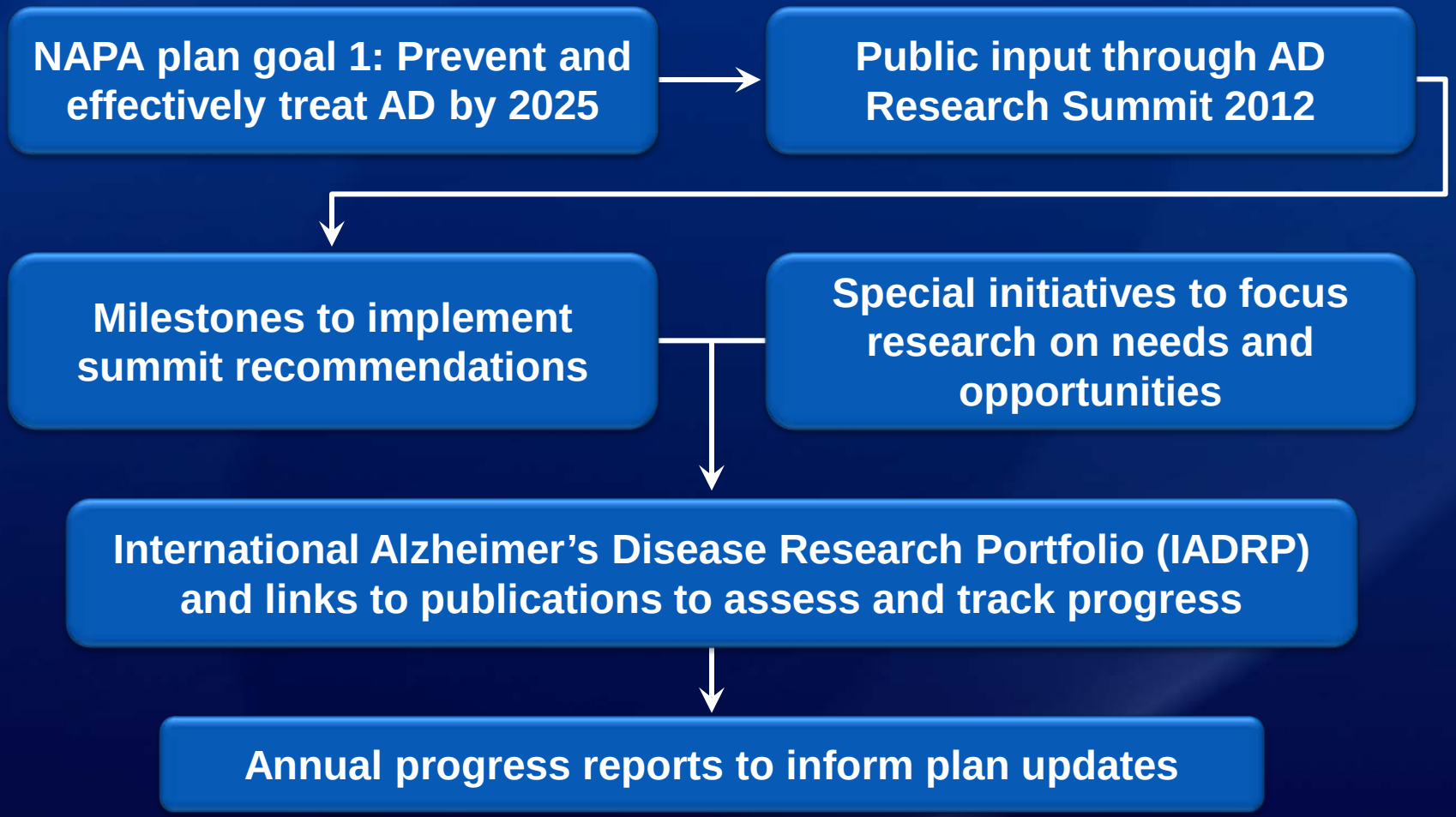
Establishing Research Milestones and Tracking Progress



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FY 2013 Alzheimer's Disease Request for Funding Announcements

RFAs	$ in 2013 – up to
Interdisciplinary Approach to Identification and Validation of Novel Therapeutic Targets for Alzheimer's Disease (101)	23 M
Alzheimer's Disease Therapeutics Program (U01)	1 M
Alzheimer's Disease Prevention Trials (U01)	45 M
Alzheimer's Disease Phase I Clinical Trials (R01)	4 M
Total	73 M

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Newly Funded Alzheimer's Projects

$45M awarded Sept. 18, 2013

- Alzheimer's Prevention Initiative
  - ApoE4 Trial: Eric Reiman, Pierre Tariot
- Allopregnenolone for MCI/AD Phase 1
  - Roberta Brinton, Lon Scheider
- Pathway Discovery, Validation and Compound Identification for AD
  - Philip DeJager, David Bennett

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Newly Funded Alzheimer's Projects

- Integrative Biology Approach to Complexity of AD
  - Eric Schadt
- Systems Approach to Targeting Innate Immunity in AD
  - Todd Golde
- DIAN-TU Trial
  - Randy Bateman

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National Plan 2012

- **Action 1.A.4: Convene a scientific workshop on other dementias in 2013**
- **HHS will expand the work undertaken in Actions 1.A.1 and 1.A.2 to address non-Alzheimer's dementias. NIH will hold a scientific workshop in 2013 to solicit input on special research priorities and timelines for addressing related dementias**

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Alzheimer's Disease-Related Dementias: Research Challenges and Opportunities

Conference and Recommendations Report to the NINDS Council

12 September 2013

Scientific Chair: Thomas Montine, MD, PhD
University of Washington

Background

National Alzheimer's Project Act (NAPA) signed by President in January 2011

- National Plan to Address Alzheimer's Disease
  - Goal of preventing and effectively treating Alzheimer's disease, including Alzheimer's disease-related dementias, by 2025
- NIA sponsored "Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention"
- NINDS sponsored "Alzheimer's Disease-Related Dementias: Research Challenges and Opportunities" (May 2013)

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Timeline

- Steering committee formed September 2012
- Pre-conference work from October 2012 to April 2013

Alzheimer's Disease-Related Dementias: Research Challenges and Opportunities, May 1-2, 2013

- Post-conference work from May to July 2013
- Draft Report in August 2013
- Present to NINDS Council 12 September 2013
- NAPA Council in October 2013

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Alzheimer's Disease-Related Dementias: Research Challenges and Opportunities

Research Challenges and Opportunities

Sponsored by the
National Institute of Neurological Disorders and Stroke
in cooperation with

- National Institute on Aging
- Alzheimer's Association
- USAgainst Alzheimer's
- Alliance for Aging Research, ACT-AD
- Association for Frontotemporal Degeneration

www.ninds.nih.gov/ADRelatedDementias2013

Conference

Natcher Auditorium, NIH Campus, Bethesda, MD

May 1, 2013

8:00 am	**Welcoming Remarks: Story Landis, PhD, Director, NINDS**
8:05 am	**Introduction: Ronald Petersen, PhD, MD, Mayo Clinic**
8:25 am	**Developing Researching Recommendations and Timelines for the AD-Related Dementias** Thomas Montine, MD, PhD, Scientific Chair
8:30 am	**Session 1: Non-AD and Multiple Etiology Dementias** Chairs: Bruce Miller, MD and David Knopman, MD
9:30 am	**Session 2: Lewy Body Dementias (LBD, PDD)** Chairs: Dennis W. Dickson, MD and Karen S. Marder, MD, MPH
1:15 pm	**Session 3: FTD and AD-Related Tauopathies** Chairs: Michael Hutton, William Seeley

May 2, 2013

8:30 am	**Session 4: Vascular Contributions to AD-Related Dementias** Chairs: Steen Greenberg, Berislav Zlokovic
12:30 pm	**Session 5: Health Disparities in AD-Related Dementias** Chairs: Maria Glymour, ScD and Jennifer Manly, PhD
2:45 pm	**Final Panel Discussion and Questions**
4:00 pm	**Closed Session: Session Chairs, NIH Leads, Steering Committee**

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Conference

Goals

- Each topic area presents rationale for prioritized research recommendations and timelines
- Provoke discussion among group experts
- Solicit feedback and opinions from audience

Outcomes

- 567 registrants: 322 in-person, >200 on-line
- Lively 2-day public session with many comments
- Culminated with “open mike” and review of all suggested revisions
- Closed session to plan post-conference work

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Executive Summary
Overall

Topic area	Focus area (number of prioritized research recommendations)			
1. Multiple etiology dementias (MED)	Differential diagnosis (3)		Epidemiology (3)	
2. Health disparities (HD)	Recruitment (4)		Advancing Treatment and Prevention Strategies (4)	
3. Lewy body dementias (LBD)	1. Establish longitudinal cohorts with common measures, culminating in autopsy studies (2)	2. Discover disease mechanisms through brain mapping and genetics (2)	3. Develop and validate biological and imaging biomarkers (2)	4. Model disease processes to develop potential symptomatic and disease modifying therapies (2)
4. Frontotemporal dementia and other tauopathies (FTD)	Basic Science: Pathogenesis and Toxicity (4)		Clinical Science: Discovery, tools, and cohorts (4)	
5. Vascular contributions to ADRD – focus on small vessel disease and AD/vascular interactions (VAS)	Basic Mechanisms and Experimental Models (3)		Human-Based Studies (3)	

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Executive Summary
High

High priority recommendations 1-3 year		
Topic area	**Focus area**	**Recommendation**
1-MED	Differential diagnosis	Develop clinical algorithms for detection of prototypical and 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
	Epidemiology	Conduct population-based studies of dementia prevalence and incidence in diverse ethnic groups and age ranges using imaging and fluid biomarkers
3-LBD	Establish longitudinal cohorts with common measures	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
		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
4-FTD	Clinical Science	Expand efforts to genotype patients with FTD and identify new genes
5-VAS	Human-based studies	Develop noninvasive markers of key vascular processes related to cognitive and neurologic impairment (Part 1 of 2)
High priority recommendations 3-7 year		
Topic area	**Focus area**	**Recommendation**
2-HD	Recruitment	Initiate and leverage ongoing longitudinal community-based cohort studies of incident dementia in diverse populations incorporating imaging, fluid biomarkers and autopsy
	Treatment and prevention strategies	Enhance the design of all trials of vascular health interventions to improve their application to diverse populations
4-FTD	Basic Science	Clarify the mechanism of tau pathogenesis and associated neurodegeneration
5-VAS	Basic Mechanisms and Experimental Models	Develop next-generation experimental models of VCI and VaD
	Human-based studies	Validate noninvasive markers of key vascular processes related to cognitive and neurologic impairment (Part 2 of 2)

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Executive Summary
Intermediate

Intermediate priority recommendations 1-3 year		
Topic area	**Focus area**	**Recommendation**
1-MED	Epidemiology	Develop registries for enumerating and characterizing less common dementias, dementias in younger persons, rapidly progressive dementias and potentially treatable dementias
2-HD	Recruitment	Use mixed methodology studies to improve assessment tools for disparities populations
	Treatment and prevention	Assess lifecourse risk factors for cognitive decline and ADRDs among disparities populations
		Estimate disparities in health burden of ADRDs and risk factors among disparities populations
3-LBD	Discover disease mechanisms through brain mapping and genetics	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
4-FTD	Basic Science	Develop better FTD in vivo and cell-based model systems
	Clinical Science	Create an international FTD clinical trial network

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Executive Summary
Intermediate

Intermediate priority recommendations 3-7 year		
Topic area	**Focus area**	**Recommendation**
1-MED	Differential diagnosis	Develop imaging and fluid biomarker algorithms to detect prototypical vs atypical dementias and expand their accessibility in primary care settings
2-HD	Recruitment	Use community outreach methods to facilitate recruiting disparities populations into FTD and LBD clinical studies
3-LBD	Discover disease mechanisms	Identify novel common and rare genetic variants, epigenetic changes and environmental influences that influence the risk and clinical features of DLB and PDD
	Develop and validate biological and imaging biomarkers	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
		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
4-FTD	Basic Science	Determine the molecular basis for C9ORF72 expansion- and GRN-related neurodegeneration
	Clinical Science	Develop FTD biomarkers for diagnosis and disease progression
5-VAS	Basic Mechanisms	Encourage basic science research that investigates the impact of AD risk factors on cerebrovascular function
	Human-based studies	Determine interrelationships among cerebrovascular disease and risk factors, Aβ and neurodegeneration

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Executive Summary
Additional

High priority recommendations 1-3 year		
Topic area	**Focus area**	**Recommendation**
1-MED	Differential diagnosis	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 to initiation)
	Epidemiology	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 (timeline 1-3 yr for initiation and ongoing)
Additional recommendations 3-7 year		
Topic	**Focus area**	**Recommendation**
2-HD	Recruitment	Evaluate under-diagnosis and implement surveillance for ADRDs to detect incidence and monitor trends in disparities populations
3-LBD	Model disease processes to develop therapies	Recognizing the importance of α-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
4-FTD	Basic Science	Determine the mechanisms of TDP-43 and FUS pathogenesis and toxicity
5-VAS	Basic Mechanisms	Encourage basic science research that investigates the impact of cerebrovascular risk factors on AD-related neurodegeneration
Additional recommendations 7-10 year		
Topic	**Focus area**	**Recommendation**
3-LBD	Model disease processes to develop therapies	Develop disease-modifying interventions based upon research discoveries
5-VAS	Human-based studies	Identify next generation vascular interventions to treat or prevent VCI and VaD
Additional recommendations >10 year		
Topic	**Focus area**	**Recommendation**
2-HD	Treatment and prevention	Identify environmental and genetic factors that modify incidence, presentation and long-term outcomes of ADRDs in disparities populations
4-FTD	Clinical Science	Understand phenotypic heterogeneity and natural history

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Executive Summary
Overlap

Although ordering of priorities and timelines differed, several recs applied across ADRD (and AD)

- **All recs within HD**
- **Training and education**
- **Fundamental research**
- **Improved diagnostics**
- **Optimized repositories**
- **Culmination of research in effective interventions**

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Conclusion

Our charge has been met

- Effort spanning 12 months by >80 scientists, physicians and administrators

36 prioritized research recommendations

- Covering 5 selected topics
  - Overarching: HD and MED
  - Disease-specific: LBD, VBI, FTD
- Developed by experts and honed but public scrutiny
- Stratified by
  - Topic area
  - Priority Level: High, Intermediate, Additional
  - Approximate timeline for completion or full implementation
- Overlapping recommendations highlighted

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Next Steps

- 2013 update release June 14, 2013
- Includes additional steps to meet goals
- Ongoing input from Advisory Council and Public
- Available at http://aspe.hhs.gov/daltcp/napa

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So, Is NAPA Having an Impact?

- Early to tell, but maybe
  - 2012 $50M NIH repurposed funds
  - 2013 Anticipated $80M from President's budget, didn't happen, sequestration
  - But, $40M from Dr. Collins and $5M from NIA to fund RFA's
  - 2014, $100M proposed in President's budget, but…
- Recommendations still contend that $2B is needed

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