Pathway to Dementia

Alzheimer’s Disease
Multiple Potential Pathways to Dementia

**Lifestyle Factors**
- physical activity
- diet
- drug/alcohol abuse

**Environmental Factors**
- education
- head trauma
- toxins/other

**Psychosocial Factors**
- depression/anxiety
- Aging
- Genetic Factors
- Sex F>M
- Other Medical Risks
  - hypertension
  - obesity
  - stroke
  - heart disease
  - diabetes
  - metabolic
  - inflammation
  - certain infectious diseases
  - certain medications
- Health Disparities Factors

*Misfolded proteins*
- amyloid
- tau
- alpha synuclein
- TDP-43

*Vascular Disorders*
- injury, infarct (stroke)
- white matter disease
- blood vessel disease

*Other Disorders*

**BRAIN CHANGES**

**Cognitive Impairment Including Dementia**
- Alzheimer’s Dementia
- Lewy Body Dementias
- Vascular Dementias
- Frontotemporal Dementias
- Limbic Predominant TDP
- Mixed Dementias
- Other Cognitive Impairment
- Other Dementias

Concept by:
Julie A. Schneider, MD, MS, Rush University &
Roderick A. Corriveau, PhD, NINDS

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The NINDS and NIA Collaborate on AD/ADRD Research

- NIA is the NIH lead for AD research and responding to the National Plan
- NINDS is the NIH lead for ADRD research (FTD, LBD, VCID), including ADRD Summits

**NAPA Goal 1: Prevent and Effectively Treat AD/ADRD by 2025**

- Triennial AD, ADRD and Care Summits*
- Research Recommendations
- Milestones
- Scientific Advances Toward Goal 1

*Dementia Care Services Research Summit NIH/NIA, March 14-15, 2020*
Alzheimer’s Disease-Related Dementias (ADRD)

**ADRD**: Types of dementias that share cognitive and pathological features with Alzheimer’s and/or commonly co-occur with typical Alzheimer’s pathology

**Vascular Contributions (VCID)**
- Vascular contributions to cognitive impairment and dementia (VCID)
- Frequently a part of typical clinical Alzheimer’s disease
- Diverse spectrum of disorders caused by cerebro- & cardio-vascular disease
- Reducing vascular risk factors may decrease dementia risk

**Lewy Body Dementia (LBD)**
- Lewy bodies, pathological hallmark of Parkinson’s disease, also present in brains of people with Lewy Body Dementia (LBD, PDD)
- Dementia occurs with problems with movement, sleep, mood, & hallucinations

**Fronto-temporal Degeneration (FTD)**
- Onset often occurs in a person’s 50s or 60s
- Progressive decline in social behavior and/or language (memory can be spared)
- Can be associated with amyotrophic lateral sclerosis (ALS)

**Mixed Dementias (MED)**
- Majority of all dementia cases (age 65+) are mixed or multiple etiology dementias, mainly Alzheimer’s pathology (beta-amyloid plaques and tau tangles) with cerebrovascular disease and/or Lewy bodies

NINDS-Led Summits Shape ADRD Scientific Priorities

**National Plan Action 1.A.6**: NINDS to regularly convene ADRD Summits to review progress & refine & add new ADRD research recommendations as appropriate based on scientific discoveries.

- Triennial ADRD Summits 2013, 2016, 2019
- Research Recommendations
- Milestones
- Scientific Advances Toward Goal 1

- ADRD Summit Scientific Chairs
  - Dr. Tom Montine (2013)
  - Dr. David Holtzman (2016)
  - Dr. Julie Schneider (2019)
NIH Investment in AD/ADRD Research (Millions)

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Source: https://report.nih.gov/categorical_spending.aspx

AD/ADRD Funding Strategy at NINDS

Additional AD/ADRD funds from NIA are used by NINDS for:

1) Research Responsive to AD/ADRD Initiatives
   • FY19 (est.): $112 M
2) Increased Investment in Investigator-Initiated AD/ADRD Research
   • FY19 (est.): $58 M
Examples of ADRD Research Initiatives: VCID, MED

- National consortium to develop and validate predictive, diagnostic, target engagement and progression biomarkers in human VCID including in clinical Alzheimer’s and other mixed dementias
- National consortium with sites in Chicago, New York, and San Francisco
- Address the unmet need to detect cognitive impairment, including dementia in primary care across the United States
- Including in populations that experience health disparities
- Proposed clinical paradigms should utilize tools that are simple to use, standardized, and ideally take five-ten minutes or less to administer in a primary care clinical setting

Examples of ADRD Research Initiatives: FTD, LBD

**Tau Center without Walls**
- Interdisciplinary, multi-institute research
- Identification and validation of molecular mechanisms that contribute to tau toxicity associated with frontotemporal degeneration (FTD)
- 2 teams funded in 2016

**The Lewy Body Dementias Biomarker Initiative**
- Supports hypothesis-driven clinical research to discover biomarkers
- 5 teams funded since 2016
Examples of NINDS AD/ADRd Trans-NIH Collaborations

**NINDS** and **NIA** are funding natural history studies in FTLD

- Study of individuals with a clinical diagnosis of FTD to help determine the clinical, genetic and biomarker profiles
- Study of families that have one of the three most common gene variants that cause FTD to learn more about natural history

- 5 awards funded by **NIA** and **NINDS**
- **M2OVE-AD** aims to gain a deeper understanding of risk phenotypes and mechanisms of VCID

- **VCID Workshops** (5/2018; 11/2019)
- **Neuropathological Impact of Sleep Deficiency & Sleep Disorders** (8/2018 workshop)
- **AD Viewed as a Neurovascular Inflammatory Disorder** (4/2017 eBriefing)

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**NINDS Investigator-Led ADRD Research is Increasing in Scale and Impact – Tauopathies (FTD, AD, PSP)**

Pathogenic tau-induced piRNA depletion promotes neuronal death through transposable element dysregulation in neurodegenerative tauopathies

Wenyan Sun\(^1,2,3\), Hanie Samimi\(^4\), Maria Gamez\(^5,6\), Habil Zare\(^7\) and Bess Frost\(^1,3,5,7\)

- ‘Jumping genes’ are ~45% of human genome
- Cells utilize defenses to limit this jumping, e.g.:
  - Piwi (nuclear protein) & small piwi-interacting RNAs (piRNA) help clear transposable element transcripts & keep chromatin condensed to prevent jumping
- Results suggest that tauopathy drives DNA decondensation, transposable element dysregulation (activation), and thus at a cellular level accelerates pathology
- This identifies transposable element regulation as potential pharmacological target in tauopathy

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* nature neuroscience 2018
NINDS ADRD Program: Summary

- **NINDS leads triennial ADRD Summits (2013, 2016, 2019)**
  - Planning effort that: (1) Delivers ADRD Milestones to the DHHS National Plan to Address AD and (2) Informs AD Bypass Budgets

- **NIH AD/ADRD budget has increased substantially; NIA shares AD/ADRD funds with the NINDS**
  - NIH ADRD research funding increased ~3-fold since 2015
  - NINDS AD/ADRD portfolio increased ~3-fold since 2015
  - NINDS has led 29 ADRD initiatives and programs since 2016
    - Including 11 NINDS ADRD initiatives in FY 2019
  - 7 additional FOA concepts approved by NINDS Council for FY2020

NINDS FY 2020 ADRD Funding Opportunity Announcement Concepts

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ALZHEIMER’S DISEASE-RELATED DEMENTIAS SUMMIT 2019

Sponsored by the
National Institute of Neurological Disorders and Stroke
In partnership with
National Institute on Aging • NIH Office of Disease Prevention • Foundation for the National Institutes of Health

Special thanks for assistance with outreach to:
Alzheimer’s Association
LEAD Coalition (Leaders Engaged on Alzheimer’s Disease)
Levy Body Dementia Association
Association for Frontotemporal Degeneration

2019 ADRD Summit Planning
~ 6 months by >80 scientists, physicians, and administrators

- **Scientific Chair:** Julie Schneider
- **NIH/NINDS Summit Lead:** Rod Corriveau
- **Steering Committee:** S. Dickinson, L. Gitlin, D. Holtzman, E. Masliah, T. Montine, B. Obviatele, R. Petersen

**Session Committees**
- **Overarching:** MED; Health Disparities; Nomenclature
- **Disease-Specific:** LBD; FTD; VCID; Emerging Science

**Summit Goals**
- Present rationale, including scientific progress, for draft research recommendations
- Encourage discussion among group experts
- Solicit feedback and opinions from audience
- Modify recommendations based on feedback
 Portions of this event were made possible by the

FNIH
Foundation for the National Institutes of Health

with generous support from the following contributors:

Elite

Platinum

Gold

Alzheimer’s Association

GHR Foundation

Biogen

Silver

Accelerate Cure/Treatments for Alzheimer’s Disease (ACT-AD) Coalition
Alzheimer’s Drug Discovery Foundation
American Stroke Association, a division of the American Heart Association
CurePSP
EIP Pharma
The John A. Hartford Foundation
WellMed Charitable Foundation

Thank You to NIH Leadership and Staff

- Walter Koroshetz (NINDS)
- Richard Hodes (NIA)
- Roderick Corriveau (NINDS)
- Debra Babcock (NINDS)
- Patrick Bellgowan (NINDS)
- Jue Chen (NHLBI)
- Sara Dodson (NINDS)
- Cerise Elliott (NIA)
- Jordan Gladman (NINDS)
- Amelie Gubitz (NINDS)
- Sophia Jeon (NINDS)
- Melinda Kelley (NIA)
- John Hsiao (NIA)
- Eliezer Masliah (NIA)
- Daniel Miller (NINDS)
- Claudia Moy (NINDS)
- Toya Rogers (NINDS)
- Jonathan Sabbagh (NINDS)
- Paul Scott (NINDS)
- Beth-Anne Sieber (NINDS)
- Margaret Sutherland
- Margo Warren (NINDS)
**Approved ADRD Summit Recommendations Become National Plan Milestones**

Stakeholder Input
- Public
- Academic
- Advocacy
- Patients
- Families
- Caregivers
- Care providers
- Industry

NIH National Institutes of Health

AD/ADRD Summits

Scientific Progress

AD/ADRD Research

NAPA Goal 1

Research Recommendations

Research Milestones in National Plan to Address Alzheimer’s Disease

Bypass Budget

NIH National Institute of Neurological Disorders and Stroke

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**ALZHEIMER’S DISEASE-RELATED DEMENTIAS SUMMIT 2019**

RESEARCH CHALLENGES AND OPPORTUNITIES

MARCH 14-16 2019

**ADRD Summit 2019 Results**

- FACA Committee-approved ADRD Summit 2019 Report
- FACA Committee-approved prioritized ADRD research milestones (47) with timelines that will:
  - Inform future NIH AD/ADRD bypass budgets and, as appropriated funds become available, corresponding research activities.
  - Guide the AD/ADRD research community generally, and as such, broad implementation and execution by various federal, national and international stakeholders will be vital to their impact.
Highlights of 2019 ADRD Recommendations

- Central continuing themes across the 6 committees
  - Biomarkers and Risk Profiles
  - Type of Research (Basic, Translational, Clinical)
  - Resource Infrastructure (biospecimens, bioinformatics, research tools, clinical trials)
  - Training and Workforce Needs
  - Nomenclature

- Evolving and new recommendations
  - MED: trials for reversible causes; bridge science/clinical practice gap
  - HD: policy relevant research and work force training in health disparities
  - Nomenclature: proposes process to achieve common nomenclature
  - VCI: Forward translation from basic science and reverse from clinical/trials
  - LBD: expanded basic science recs (further testing hypothesis of propagation)
  - FTD: Database resource

- Expansion in topics
  - New emerging topics session
    - TDP proteinopathy, Traumatic brain injury

Natchez Auditorium, NIH Campus, Bethesda, MD

Thursday, March 14, 2019

8:00 am Welcoming Remarks and Introduction: Walter Koroshetz, MD, Director, NINDS
8:10 am Perspective: Laura Gitlin NAPA Chair
8:20 am Progress and Updating Research Recommendations
  Julie Schneider, MD, MS, Scientific Chair, and Rod Corriveau, PhD, NIH Summit Lead
8:40 am Multiple Etiology Dementias – Diagnosing in the 21st Century
  Chairs: David Knopman, MD, and Kate Possin, PhD
10:40 am Health Disparities in AD/ADRD
  Chairs: Lisa Barnes, PhD and Hector Gonzalez, PhD
1:20 pm Lewy Body Dementias
  Chair: Bradley Boeve, MD and Carol Lippa, MD
3:20 pm Dementia Nomenclature
  Ronald Petersen, MD, PhD and Angela Taylor, BMus

Friday, March 15, 2016

8:00 am Vascular Contributions to Cognitive Impairment and Dementia
  Chairs: Donna Wilcock, PhD and Jeff Williamson, MD, MHS
10:10 am Frontotemporal Lobar Degeneration
  Chairs: Leonard Petrucelli, PhD and Adam Boxer, MD, PhD
12:40 pm Emerging Scientific Topics
  Chairs: Kristen Dams-O’Connor, PhD and Julie Schneider, MD, MS
2:30 pm Scientific Chair’s Highlights and Cross-Cutting Themes
  Julie Schneider, MD, MS, Scientific Chair

NEW - Emerging Topics:
* TDP-43 Pathology in Common Dementias
* TBI and AD/ADRD Risk

>3 Hours Open Microphone Time
Perspective on Prioritization of the Recommendations

1. All recommendations in the the report represent very important research goals.
2. Each committee was required to assign priorities starting at #1.
   - However, for a research recommendation to be included in this report, it must be among the top priorities in its field.
3. Timelines do not in any way reflect prioritization, but rather serve to guide planning and implementation logistics.
4. Finally, ordering of sessions in no way reflects prioritization – all sessions (MED, HD, NGO, LBD, FTLD, VCID, Nomenclature, Emerging Scientific Topics) are of equally high priority.

Multiple Separate Pathways AND Cross-Cutting Scientific Areas of Investigation Needed Across AD/ADRD

Protein aggregation and neurodegeneration
Protein clearance and degradation
Vascular mechanisms, hypoxia, neurovascular unit, BBB
Innate immune system and inflammation
Axonal and synaptic injury and repair
Circadian & sleep function/dysfunction
Neurogenetics
Systems and computational biology
Cross-Cutting Science

CRITICAL NEED for AD and ADRD biomarkers/risk profiles

Biomarkers that can discriminate underlying pathologies
assessment of pre-symptomatic and symptomatic
assessment of therapeutic response
clinical screening
pathology progression
cognitive progression

Need multiple biomarkers or markers of common processes

Role for genetic, person-specific, multifactorial risk profiles

Health Disparities
Chairs: Lisa Barnes, Hector González

REC 1 – Priority 1. Generate and/or improve cognitive assessment tools for populations facing AD/ADRD health disparities (1-3 y).

REC 2 – Priority 1. Increase availability and utilization of harmonized culturally- and linguistically-valid assessment tools within ongoing and newly generated studies of AD/ADRD and cognitive health intervention trials (1-3 y).

Multiple Etiology Dementias
Chairs: Dave Knopman, Kate Possin

REC 1 – Priority 1. Detect whether cognitive impairment is objectively present when a patient, care partner, or clinician reports cognitive, behavioral, or functional changes (β-7 y).

REC 3 – Priority 1. Advance basic & clinical research on common mechanisms of multi-etiopathy cognitive impairment and dementia (β-7 y).
Brain Pathology is Common Late in Life; Mixed Pathologies are the Rule in Common Dementias

Clinical Diagnosis
No Cognitive Impairment
ROS/MAP (N = 360)

Clinical Diagnosis
Probable AD Dementia
ROS/MAP (N = 447)

PIE CHART KEY:
AD = neuropathologic dx (plaques/tangles)
OD = other neurodegenerative pathology
TDP = pathology beyond amygdala
LB = neocortical pathology
V = vascular pathology
- infarcts (macro/micro)
- vessel disease (athero, arteriolosclerosis, CAA)
0 = no pathology detected


Clinical Diagnosis = No Cognitive Impairment
ROS/MAP (N = 360)

Clinical Diagnosis = Probable AD Dementia
ROS/MAP (N = 447)

No Dementia
Dementia

Alzheimer’s Disease (All)

Alzheimer’s Disease (Pathological)


Alzheimer’s Disease (Pure)

Dementia Nomenclature

Chairs: Angela Taylor, Ron Petersen

Focus Area 1: Dementia Nomenclature Working Groups

REC 1 - Priority 1. Form research, clinical practice and public stakeholder dementia nomenclature working groups (1-2 y).

Focus Area 2: Integration and Interoperability of Dementia Nomenclature

REC 2 - Priority 1. Integrate and refine recommendations from the Research, Clinical Practice, and Public Stakeholder Working Groups into standardized, acceptable and accurate nomenclature that works across the spectrum of stakeholders (2-4 y).

LBD Chairs: Bradley Boeve, Carol Lippa

REC 1 - Priority 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 (1-7 y)

REC 5 - Priority 1. Biomarker development (3-7 y)

FTLD Chairs: Adam Boxer, Leonard Petrucelli

REC 1 - Priority 1. Clarify cellular and converging cellular mechanisms related to tau pathogenesis, C9orf72 hexanucleotide repeat expansions, GRN mutations, and other targets and pathways contributing to FTD neurodegeneration (2-10 y)

REC 5 - Priority 1. Develop FTD biomarkers for diagnosis, prediction and disease monitoring (2-7 y)

VCID Chairs: Donna Wilcock, Jeff Williamson

REC 1 - Priority 1. Develop next generation experimental models and translational imaging methods for VCID (3-5 y)

REC 4 - Priority 1. Develop, validate, and longitudinally track: (1) cognitive, physical, or other functional assessment components that indicate the presence of VCID; (2) VCID biomarkers, including when VCID is accompanied by pathological AD (3-5 y)
Emerging Scientific Topics
Chairs: Kristen Dams-O’Connor, Julie Schneider

REC 1 – Priority 1. Develop biomarker/risk profiles to establish in vivo diagnostic criteria for TDP-43 pathology in persons without cognitive symptoms or amnestic syndromes (6-7 y).

REC 5 – Priority 1. Encourage cross-talk and interdisciplinary collaboration between TBI and dementia researchers (1-3 y).

All recommendations in the NINDS Council-Approved ADRD Summit 2019 Report represent critical national research pathways that are top scientific priorities toward the goal of achieving effective prevention and treatment of AD and ADRD.

On behalf of the committee co-chairs, members, and with input from multiple stakeholder and the public, we respectively submit the ADRD Summit 2019 Report and Milestones to the NAPA Council.

Questions? Comments?
HIGH BLOOD PRESSURE IS EVEN RISKIER

Stroke and dementia are more likely to affect people with high blood pressure. Understand the links and learn what you can do to minimize your risk.