Report from the ADRD summit 2019

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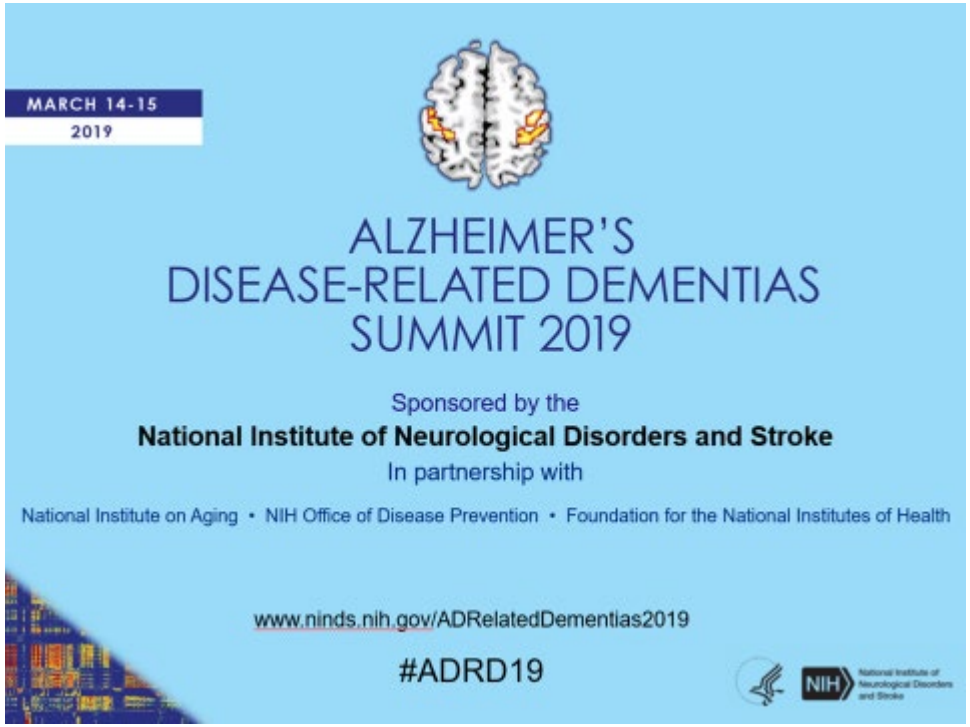

ADRD summits 2013, 2016, 2019

- Part of the **NAPA – the National Plan to Address Alzheimer's disease and related dementias** (blueprint for achieving the vision of a nation free of AD and related dementias)

- **Related dementias**: Related dementias include mixed, vascular dementias, LBD, and FTD.

- **Goal 1: Prevent and Effectively Treat ADRD by 2025**
- Identify Research Priorities and Milestones - set ambitious deadlines for achieving these milestones in order to meet this goal.

- **Action 1.A.6; Regularly convene an ADRD Summit to review progress on ADRD** research recommendations and refine and add new recommendations as appropriate, based on recent scientific discoveries.

NINDS ADRD Research Initiatives and Programs

MED and Health Disparities

- **DetectCID – consortium to develop paradigms to increase detection of cognitive impairment/dementia** in primary care & health disparity populations *[3 awards FY17]*
- **Health Disparities and AD (R01) FOA** – NINDS participating to encourage **health disparities research in ADRD** *[2 awards, one each starting in FY17 and FY18]*
- **VCID and Stroke in a Biracial National Cohort (REGARDS longitudinal study)** *[FY18]*
- **Recruitment & Retention Strategy for Clinical Research Planning Efforts led by NIA**
- **Scholarship Program for ADRD Summit 2019** *[21 recipients]*

LBD

- **Supporting biomarker discovery studies for LBD** by including data and biospecimens from patients with LBD in the NINDS PDBP *[5 awards in FY16]*
- **Leveraging existing LBD data and biospecimens in ADNI/NACC and PDBP** for research on LBD *[2 awards in FY17]*
- **Pathway and Target Identification for LBD and AD/ADRD** genes, control regions, pathways, cell types, and brain regions *[1 award in FY18]*
- **Structural Biology** of alpha-synuclein in LBD *[1 award in FY18]*

NINDS ADRD Research Initiatives and Programs

FTLD

- **Multicenter, interdisciplinary "Center without Walls" (Tau CWOW)** to study molecular mechanisms of tau toxicity in FTD *[2 awards in FY16]*
- **FTD Sequencing Consortium** to discover FTD-causing genetic mutations *[2 awards in FY17]*
- **Pathway and Target Identification for FTD and AD/ADRD** genes, control regions, pathways, cell types, and brain regions *[1 award in FY18]*
- **Structural Biology** of Tau and TDP-43 in FTD *[2 awards in FY18]*

VCID

- **MarkVCID – Small vessel VCID Biomarkers Consortium** to develop biomarkers for cerebrovascular disease for use in clinical trials *[8 awards FY16]*
- Research to better understand **the mechanistic basis of small vessel and diffuse white matter disease in VCID (R01)** *[10 awards in FY16, FY18]*
- **VCID and Stroke in a Biracial National Cohort (REGARDS longitudinal study)** *[FY18]*

NINDS ADRD Research Concepts Proposed FY 2019

VCID

- Prospective clinical research to determine the stroke and events and comorbidities that increase risk for or cause **Cognitive Impairment and Dementia in Post-Stroke Populations in the United States, Including in Health Disparities Populations** (RFA-NS-19-012)

LBD

- **Progression Markers for Cognitive Impairment** (PAS-19-210) in Parkinson's Disease Dementia
- **Lewy Body Dementia Center without Walls** (RFA-NS-19-013) to systematically and comprehensively characterize alpha-synuclein and amyloid-beta subspecies

FTLD

- **FTD Natural History, Biomarker, and Genetics Studies** (NOT-NS-18-082)(with NIA)

MED & Cross-Cutting

- **Advanced ADRD Animal and Cellular Models** (RFA-NS-19-027 and PAR-19-167)
- **PET Ligand Development (RFA-NS-19-014)** to identify ADRD proteinopathies & pathology
- **Clinical Research and Pathological Mechanisms of AD/ADRD in CTE/**TBI (RFA-NS-19-026 and RFA-NS-19-030)
- Validate novel **ADRD Druggable Targets** (RFA-NS-19-015) for development of pharmaceutical interventions
- **Training Supplements** (NOT-NS-19-003) to mentor the underrepresented groups in AD/ADRD

- **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. Obviagele, R. Petersen
- **Session Committees**
  - Overarching: MED; Health Disparities; Nomenclature
  - Disease-Specific: LBD; FTD; VCID; Emerging Science
- **ADRD Summit Goals**
  - Present rationale for draft research recommendations
  - Provoke discussion among group experts
  - Solicit feedback and opinions from audience

Multiple Etiology Dementias
Chairs: Dave Knopman, Kate Possin

Focus Area 1: Improving Detection and Diagnostic Skills in the Community
REC 1 – Priority 1. Detect cognitive impairment when a patient, care partner or clinician reports cognitive, behavioral or functional changes (3-7 y).
REC 2 – Priority 3. Improve differential diagnosis of symptomatic cognitive impairment (5-10 y).

Focus Area 2: Advancing Basic and Clinical Research in MED
REC 3 – Priority 1. Advance basic and clinical research in multi-etiology cognitive impairment (3-7 y).

Focus Area 3: Increasing the Dementia Capable Workforce
REC 4 – Priority 2. Increase education and training of health professionals and researchers focused on cognitive impairment and dementia (5-10 y).

Focus Area 4: Intervention Studies to Mitigate Reversible Causes of Dementia
REC 5 – Priority 2. Conduct intervention studies to mitigate reversible causes of cognitive dysfunction in persons with or at-risk for cognitive impairment where etiology may be uncertain or where multiple etiologies appear likely (3-7 y).

Focus Area 5: Research to Implement Effective Dementia Care
REC 6 – Priority 3. Bridge the science-practice gap for dementia care programs with proven efficacy that support persons with dementia and their caregivers (3-7 y).

Multi-etiology dementia Q/A

- **Add more on basic mechanism/cell biology/animal models.**
- Use **predictive phenotypic and genetic modelling to identify/detect specific persons with a diagnosis of interest?**
- **Add more on role of other diseases** such as PD, ALS and prions in the spectrum.
- Add more focus on early and (before complaints? Prodromal?) **preclinical diagnosis** (before complaints).for research? Not sure if this is an actionable comment here. Future, after more progress is made on being able to follow-up when people have cog complaints. Technology may come into this.
- Add **clinical pathways** for referrals (e.g. toward prion or FTD) add bullet to rec one and rec 2 to make clear this is a priority.
- Education of PCP/attention towards/**caregiver risk/trauma**? Add bullet to rec 6?also recs 1 and 2.

Health Disparities in AD/ADRD Draft Recommendations

Chairs: Lisa Barnes, Hector González

Focus Area 1: Assessment

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

REC 2 – Priority 1. Increase availability and utilization of harmonized culturally- and linguistically-valid assessment tools within cognitive health intervention trials (1-3 y).

Focus Area 2: Culturally Appropriate Pathways to Effective Prevention and Treatments

REC 3 – Priority 2. Test mechanistic pathways that may account for disparities (3-7 y).

REC 4 – Priority 2. Implement culturally-tailored multimodal intervention trials and drug therapy trials to reduce AD/ADRD burden in disparities populations (3-7 y).

Focus Area 3: Monitoring Changes in AD/ADRD Disparities

REC 5 – Priority 3. Clarify the epidemiology of disparities in prevalence and incidence by documenting and monitoring trends over time (ongoing).

REC 6 – Priority 3. Increase policy-relevant research on disparities in care access, awareness, stigma, costs of care for persons with AD/ADRD, their families and caregivers (ongoing).

Focus Area 4: A diverse and Inclusive AD/ADRD Workforce

REC 7 – Priority 4. Improve and increase training, including for individuals who are members of underrepresented minorities, of scholars of different career levels who conduct health disparities research in AD/ADRD (3-5 y).

REC 8 – Recruitment Recommendations (combine 2 related to this from 2016?)

Health Disparities Q&A

- More information on how to **develop resources for recruitment**?
- Recommend need for **precision medicine add bullet (to rec 3?)**
- Recommend studying the **interactions of pathologiesadd bullet**.
- Recommend **study of early life factors**//prematurity more common in minorities.
- Requested clarity for when to use **self-identified race/ethnicity vs. genetic admixture**. Mixed heritage – how do we account for them in ADRD research//how do people self identify? Add a bullet about the need to capture self-identified as well as genetic ancestry separately, as two separate variables. Depends on the question which is the most needed. Social determinates are another separate factor.
- Requested to consider encouraging diversity researchers to be more open to being involved in **scientific reviews**. bullet under recommendation 7
- Recognition of need for disparity information on the **younger onset dementias and non-Alzheimer's diseases**. Need for engaging specific groups to get younger persons. Rec 5 bullet
- Encourage more **mentoring**
- Encourage more efforts to **helping woman navigate childcare** to allow their careers to flourish
- Specifically call out **better follow-up** of persons in disparities studies.

Lewy Body Dementias Draft Recommendations

LBD Chairs: Bradley Boeve, Carol Lippa

Focus Area 1: Clinical Science

REC 1 – Priority 1. Initiate clinical trials to target or prevent LBD symptoms, and prepare for trials which target slowing/delaying/preventing disease onset (1-7 y).

REC 2 – Priority 2. Longitudinal antemortem LBD characterization (3-5 y).

REC 3 – Priority 3. Neuroimaging characterization of LBD (3-7 y).

REC 4 – Priority 4. Neuropathologic characterization of LBD and use of LBD pathology cohorts (2-7 y).

Focus Area 2: Basic Science

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

REC 6 – Priority 2. Genetic, epigenetic & environmental characterization (3-7 y).

REC 7 – Priority 3. Understanding the molecular biology of α-synuclein in the context of non-motor brain areas (2-4 y).

REC 8 – Priority 4. Identify Lewy body disease spreading mechanisms between and that affect different brain regions and interact with other pathologies (5-7 y).

Lewy body dementias Q&A

- Recommend use of **genome data from Alzheimer's disease centers** for LBD
- Recommend **biomarkers for progression for LBD clinical trials**
- Recommend to **include specifically immune mechanisms** given role and given apoE e4 and AD? Need to include this more directly in basic science aims bullet under rec 8
- Recommended **biomarker validation studies first using autopsy cohorts**
- Recommend investigating **LBD and vascular pathology relationship separate bullet about "understanding interactions with vascular and other biological and disease processes that are relevant" bullet under rec 8**
- Recommend "sprinkling" in **peripheral biomarkers**
- **Rec 7: wording changes – add pathophysiology of synuclein to go with normal function of synuclein**

Dementia Nomenclature Draft Recommendations

Chairs: Angela Taylor, Ronald Petersen

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).

Nomenclature Q/A

- **Reframe** (field's approach to both science and nomenclature) so scientifically accurate but also **includes those under 60**.
- **Recommend more public health campaigns** to reduce stigma//changing behaviors?
- Needs to include necessity for it to be translated to the **electronic medical record**
- Include process for **choosing membership** in working groups
- Recommend calling out that there is **heterogeneity among patients reactions** to diagnosis (not all react negatively)
- Question about **Sponsorship/ownership** – Angela mentioned there will likely be layers of investment from multiple stakeholders.
- Discussion guidelines for how and when to **disseminate** – need to make it work into current framework.

VCID Draft Recommendations
Chairs: Donna Wilcock, Jeff Williamson

Focus Area 1: Basic Mechanisms and Experimental Models

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

REC 2 – Priority 3. Basic science research on neurovascular unit function and how it is impacted by the following: aging, cardiovascular disease, AD pathology and genetics (3-5 y).

REC 3 – Priority 4. Basic science research on dementia-related neurodegeneration and myelin biology to determine the impact of cardio- and cerebro-vascular risk & genes (5-7 y).

Focus Area 2: Human-Based Studies

REC 4 – Priority 1. Develop, validate and longitudinally track: (1) clinical assessment; & (2) biomarkers, including when VCID is accompanied by AD (3-5 y).

REC 5 – Priority 2. Test for efficacy across the spectrum of VCID severity: (1) interventions proven to reduce cardio- and cerebrovascular risk; & (2) established care models, (3-5 y).

REC 6 – Priority 4. Determine interrelationships among cardio- & cerebrovascular disease, neurodegeneration, other risk factors, and VCID plus resilience to it along the life-course (3-5 y).

Focus Area 3: Translational Studies

REC 7 – Priority 2. Use data and other resources from large-scale clinical research and trials to test hypothesized mechanisms of human VCID based on basic science findings (3-5 y).

REC 8 – Priority 3. Incorporate VCID findings from basic science into the design of clinical research and trials targeting VCID-relevant cognitive impairment and dementia (5-7 y).

VCID Q&A

- How to best study the big **cardiovascular risk factors across the life span**? Shouldn't now we looking at **birth cohorts (for us to note, not bullet: ECHO cohort, NIH supported) rec 6 bullet (or part of a bullet) and make them incorporate biomarkers**. Push for creativity with cohort studies across life span and better measurements; need to dig deeper
- What will it take to **translate from animals to humans for perivascular drainage, glympatics, IPAD**? Methods to study flow out of the brain are needed. Role of gadolinium? rec 8 bullet
- Is there any **opportunity to do research into cardiac and renal clinics**? Learn from other specialities? Complication of the **co-existing diseases** manifested before the brain changes. What aspects of risk factors lead you one way or the other? Edit rec 4 bullet?
- Should we add **life course for animals** too. Make sure age appropriate consideration is in bullet(s). Sex.
- Need for models looking at **function of neurons that are chronic**. Maybe more on chronic inflammation in rec 3 bullet? Rec 1 bullet? Chronic (chronicity) low level disease factors. **Minimum to trigger the ischemic cascade**. There are chronic models but the cell function should be explored more? Does not have to be animal model. Can be **computer models of energetics**? ----------
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- Need to **explore distinctions across vascular changes** reactivity, flow, and other vascular changes. Functional aspects of vasculature. Both models and human. Bullets. R1, R4, R6?
- **Hypertension can be taken further**, e.g. morning surges, evening dips Human based research Recs, nocturnal BP and WM. Add bullet(s). Rec 6? Also: Rec 8 (reverse transl)
- **Microbleeds and microinfarcts** may occur together
- **Need for more substantive theoretical hypotheses generation**. (need to state them more clearly)
- We should consider genetic factors in parallel with other **biomarkers**
- 3d models: Rec 1

Frontotemporal Lobar Degeneration Draft Recommendations FTLD Chairs: Adam Boxer, Leonard Petrucelli

Focus Area 1: Science: Pathogenesis and Toxicity

REC 1 – Priority 1. Clarify cellular mechanisms related to tau pathogenesis, C9orf72 expansion, GRN mutations, and other targets/pathways (2-10 y).

REC 2 – Priority 2. Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity (3-10 y).

REC 3 – Priority 3. Develop data/resource infrastructures to support analysis of diverse clinical, imaging, genetic, molecular and biomarker data/resources (1-3 y).

REC 4 – Priority 4. Develop better FTD in vivo and cell-based model (1-3 y).

Focus Area 2: Clinical science

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

REC 6 – Priority 2. Advance FTD clinical trial design and execute new prevention and treatment studies (1-5 y).

REC 7 – Priority 3. Expand efforts to genotype patients with FTD, identify new risk factor genes and epigenetic modifiers (1-5 y).

REC 8 – Priority 4. Understand phenotypic heterogeneity and natural history including in health disparities populations (>10 y).

FTLD Q/A

- Need to figure out how to **incorporate minority populations**
- Should include **specifically mitochondrial DNA**; (recognized difficult to do in brains; but can do in blood) Suggest **clarifying time-lines**, e.g. why some 2-10 years
- Questions about **when to intervene**
- How to **improve the pipeline** for patient registry for FTD mentioned in bullets, it may not be reaching all relevant people. Is there a bullet that could ask for this to be done?
- Need for **post-mortem studies** in order to study the clinical heterogeneity and cellular basis of different types of atrophy? Whole range needs to be covered.
- Recommend **computational modelling** to be used as term rather than informatics, etc.
- **Discussion** retinal biomarkers, lifestyle factors, programs for families with mutations, strategies can we use for animal models to recapitulate the behavioral/cognitive phenotype of the disease, clinical trials/therapeutic strategies need for tailored according to molecular genetics and sex.

Emerging Scientific Topics Draft Recommendations

Emerging Scientific Topics (TBI, TDP):

TBI Chair: Kristen Dams-O'Connor

TDP-43 (LATE) Chair: Julie Schneider

Focus Area 1: TDP-43 Pathology in Common Dementias

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 (5-7 y).

REC 2 – Priority 2. Determine pathobiologic & molecular mechanisms of cellular TDP-43 displacement, phosphorylation, & pathology in pre-symptomatic & common dementias (3-5 y).

REC 3 – Priority 3. Examine the pathologic phenotype(s) of TDP-43 pathology in asymptomatic persons and those with common dementias (5-7 y).

REC 4 – Priority 4. Develop animal models that reproduce clinical-pathologic-molecular aspects of the human TDP-43 pathology in common dementias (7-10 y).

Focus Area 2: TBI and AD/ADRD Risk

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

REC 6 – Priority 2. Establish infrastructure to study TBI as a risk factor for AD/ADRD (1-5 y).

REC 7 – Priority 3. Promote basic and clinical research examining the development and progression of TBI AD/ADRD neuropathologies and clinical symptoms (2-10 y).

REC 8 – Priority 4. Promote basic and clinical research examining the development and progression of TBI AD/ADRD neuropathologies and clinical symptoms (2-10 y)

TDP-43 in Common Dementias Q/A

- What kind of **biomarkers** do we envision?
- Relationship between **TDP-43 and aging**
- How will people understand that TDP-43 proteinopathy exists, what it is, and why should they care?
- Why from a scientific standpoint is TDP-43 in common dementia **important**?
- How will **models of TDP-43** (loss of function/gain of function) that are relevant to common dementia be developed so that they are most relevant for common dementias, i.e. dementias that occur late in life?

TBI and Dementia Q/A

- Role of repetitive head trauma and role of CTE; dose effect and how it relates to dementia/and the need for longitudinal and more pathologic studies CTE is in scope. Do not need to call out.
- Interventional trials – most have been for severe (diffuse axonal injury) and not successful. Neurobehavioral interventions as we await for targeted treatment.
- Discussion of models and translation to human disease given life course and white matter.
- Recommend work on immune mechanisms; peripheral immune influx//anti-inflammatory drugs. Bullet under rec 7.
- Long term effects of comorbid TBI and PTSD; recognize need for causal inference models. Bullet under rec 8.
- Military mention

ADRD Summit 2019 Timeline	Deliverables and Action items
November All Chairs Call	discuss charge, updates, timelines and deliverables, any materials committees would find helpful, cross-talk among committees,
Due Nov 16, 2018	• Finalize Session Committee members • Begin monthly iterative discussions about existing recommendations with your Committee members
December All Chairs Call	Updates, bring up and discuss recommendations that could complement recommendations from other committees, determine order of sessions, travel logistics
Due Dec 28, 2018	• RFI responses, milestone progress report/analysis to be provided to the committee by NINDS (Sophia & Jordan) • Template slides for presentations to be sent to Committees
Due Jan 11, 2019	• Draft revised and updated recommendations
January All Chairs Call	Updates, go over draft recommendations, discuss RFI responses, session agendas & speakers
Due Feb 11, 2019	• Finalized draft recommendations and draft agendas
February All Chairs Call	Discuss draft agendas, presentations content, coordinate presentations, harmonize recommendation slides
Due Feb 25, 2019	• Finalized agenda
March All Chairs Call	Discuss post-Summit activities, meeting day logistics, executive session
Due Mar 11, 2019	• Final presentation slides – (NO EXCEPTIONS)
Mar 14-15, 2019	ADRD SUMMIT & Executive Session
Due April 15, 2019	• FINAL recommendations
Due April 24th	• **Final recommendations fully edited and finalized and in Word file in Report to Council (2016) format**
Due August 28, 2019	• **FINAL Report to NINDS Council (1 wk before Sept Council)**
Due November 2019	• **Deliver ADRD Research Milestones to NAPA Council**
Due February 15, 2020	• **Presentation to NAPA council; Submit ADRD Summit paper for publication**

Attendance and Media Coverage

Attendance:

- 709 people registered
- 481 people attended the summit in person
- 815 Live views of day one (and 358 view after to date)
- 422 Live view of day two (and 176 views after to date)

Media:

ADRD Summit 2019 with press briefing. Additional coverage included:

- 3/18/2019, NPR: Is It Alzheimer's Or Another Dementia? The Right Answer Matters
- 3/19/2019, PLOS Neuro Community Blog: A path forward for dementia research: Highlights from the 2019 ADRD Summit
- 3/22/2019, AlzForum: NIH Summit Sets Agenda for AD-Related Dementias
- 4/8/2019, New York Times: The Diagnosis is Alzheimer's. But that's Probably Not the Only Problem.
- 4/30/2019, Associated Press: It seems like Alzheimer's but peek into brain shows a mimic

Thank you!

Questions?