Behavioral and Social Science Research and Clinical Practice Implications of Preclinical Diagnosis of AD/ADRD

A NASEM Workshop

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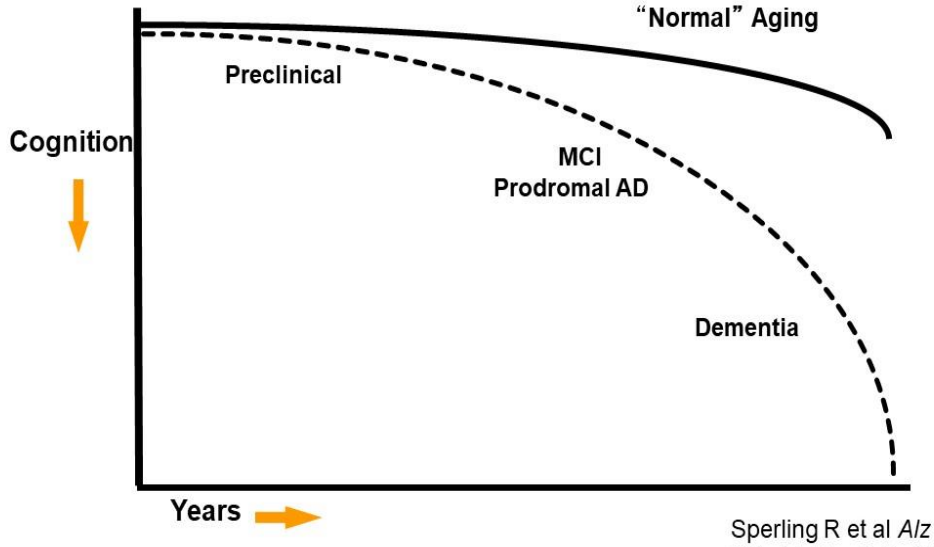
The continuum of Alzheimer's disease



Sperling R et al *Alz & Dem* 2011
NIA-AA Preclinical Workgroup
Jack C et al *Alz & Dem* 2018

Behavioral and Social Science Research in Preclinical AD/ADRD Perspective from Dr. Richard Hodes (APA interview 2020)

"To better understand the etiology of the disease (AD/ADRD)…NIA has invested in a range of approaches to elucidate and measure early psychological changes in the disease trajectory…to inform prevention and treatment strategies for maintaining cognitive health. "

"These technological advances have helped scientists discover that changes in the brain that occur during Alzheimer's are evident long before a person shows outward signs of cognitive impairment or dementia."

NASEM Workshop on Disclosure of Preclinical AD/ADRD Markers

- Two day (virtual) workshop held in late June 2021
- Planning committee:
  - Reisa Sperling, David Bennett, Nathaniel Chin, Jessica Langbaum in collaboration with Elena Fazio and Luke Stoeckel from NIA
- Workshop run by NASEM with Molly Checksfield
- Thirty-four invited speaker and discussants from range of disciplines:
  - Ethics, economics, epidemiology, preclinical markers, public health, clinical trials, participants who have received disclosure information

Structure of Workshop

- Overview and context of biomarkers and other preclinical diagnostics
- Addressing health equity issues in studies of presymptomatic individuals
- Implications of decisions about how and when to disclose a detection or diagnosis
- Public health perspective
- Perspectives of individuals who have received disclosures
- Ethical considerations related to preclinical diagnostics
- Economic impact of preclinical diagnostics
- Design and conduct of trials of preclinical diagnostics and early detection
- Closing comments: Issues and next steps

Introduction and Overview

- Speakers:
  - Reisa Sperling – Harvard
  - Howard Fillit - Alzheimer's Drug Discovery Foundation
  - David Bennett - Rush

Scope and Timeliness of Topic

- Rapidly evolving landscape for detection of preclinical AD/ADRD
  - Biomarkers (imaging, cerebrospinal fluid, fluid-based biomarkers)
  - Neuropsychological markers
  - Medical and financial records
  - Early-life risk measures (e.g., environmental exposures, personality)
- Heterogeneity in risk of decline
- Importance of investigating potential sex-based and race/ethnicity-based differences in risk
- Rights of participants to their data and transparency of findings vs. Need for more definitive results in representative populations
- Planned to be a "forward looking meeting" – but topic timely now!
  - Preclinical markers already being used in clinical trials in asymptomatic participants aiming to prevent cognitive decline and dementia
  - Controversial aducanumab approval

AD Related Dementias

- Limited discussion on ADRD – not because of lack of importance but currently lacking biomarkers available for most other pathologies
- Primarily vascular dementia (e.g., MarkVCID consortium)
  - Importance of vascular contribution to cognitive decline particularly among communities of color
  - Need for quantitative metrics to determine risk
- Unfortunate lack of validated biomarkers for other neurodegenerative dementias
  - Rare genetic forms
  - Critical need for imaging, CSF, and blood-based biomarkers for FTD, DLB and other dementias
- Digital cognitive and behavioral markers, medical records and passive monitoring of financial or other functional measures may be useful in detecting change in preclinical stages of other dementias

Addressing Health Equity Issues in Studies of Presymptomatic Individuals

- Moderator
  - David Bennett – Rush
- Speakers
  - Jennifer Manly - Columbia
  - Lisa Barnes - Rush
  - Hector González - UCSD
- Panelist/Discussants
  - Yakeel Quiroz - Harvard
  - Keith Whitfield - University of Nevada, Las Vegas
  - Lauren Parker - Johns Hopkins
  - Crystal Glover - Rush

Diversity and Equity Shortcomings

- Vast majority of AD preclinical markers (e.g., biomarkers) and longitudinal outcome data are drawn from white, high SES cohorts
- Communities of color have unique risk factors, such as discrimination and stress, that may increase risk of decline
- Comorbidities, including diabetes, hypertension, and other vascular risk factors, and potentially altered immune function, more prevalent among some communities of color
- Evidence that genetic factors (e.g. APOE ε4) have differential impact by race on AD biomarkers

Diversity and Equity Barriers

- Legacy of distrust and lack of linkage between communities of color and researchers
- Lower levels of awareness of dementia, variable perceptions and beliefs about dementia
- Inclusion/Exclusion criteria may disproportionately screen-fail diverse participants and create bias in results
- PET scans and lumbar punctures are cost and burden barriers to large scale studies in diverse populations
- Largely ineffective approaches to diversity recruitment employed in biomarker studies to date

Diversity and Equity Potential Solutions

- Research must be community-based process from the beginning
  - Clear, culturally appropriate communication between researchers and communities
  - Specific research questions and goals relevant to people in the community
  - Mixed-methods (qualitative and quantitative) research to understand and incorporate diverse participant perspectives into research
- Expand research to identify and understand potential racial differences
  - Include other pathways that may be relevant to cognitive decline (e.g., immune function)
  - Assess associations between biomarkers and social determinants of health
  - Investigate heterogeneity both between and within racial/ethnic groups
  - Broaden eligibility criteria to maximize participant/minimize bias
- Overcoming barriers to research participation
  - Focus on equity and access
  - Work with trusted partners from community in all stages of the research process
  - Time and effort essential to connect and develop trust before research begins
  - Recruit and train a diverse research workforce
  - Increase leadership of researchers with proven experience in underrepresented groups

Implications of decisions about how and when to disclose detection or diagnosis

- Moderator
  - Nathaniel Ark Chin - Wisconsin
- Speakers
  - Ron Brookmeyer - UCLA
  - Ken Langa - University of Michigan
  - Vincent Mor - Brown
  - Carol Brayne - Cambridge
- Panelists/Discussants
  - Lauren Nicholas - University of Colorado
  - Jason Karlawish - University of Pennsylvania

Implications of decisions about how and when to disclose detection or diagnosis

- Variable lifetime risk of clinical AD dementia and imminent risk
  - 65-year-old white female with amyloidosis and neurodegeneration has 40.8% lifetime risk for AD dementia, but only 10.7% risk within 10 years
- Risk of overdiagnosis
  - Costs of screening and treating preclinical AD/ADRD would be enormous
  - Potential positive impact of disclosure
  - Studies suggest that positive biomarkers increase likelihood of willingness to accept greater risk of potential treatment
- Public health perspective
  - Dementia complex syndrome – multiple factors associated with aging

Perspectives of individuals who have received disclosures

- Moderator
  - Jason Karlawish (U Penn)
- Panelists
  - Samuel Gandy (researcher – Mt Sinai) participated in amyloid PET scan screening for prevention trial
  - Renee Saxon (music teacher – Arizona) participated in APOE genetic disclosure study
  - Helene Decoste (ambassador for prevention trials) participated in amyloid PET scan screening for AD prevention trial

Perspectives of individuals who have received disclosures

- Discussion of disclosure process
  - Flood of information
  - Importance of gaining knowledge and that risk may change over time
- Who did they tell
  - Discussions with family
  - Confidentiality and risks for employment and insurance
- Impact of disclosure
  - Increase in awareness of any memory changes
  - Change in lifestyle
  - Participation in clinical trials
- Extremely valuable to researchers to hear these perspectives

Ethical considerations related to preclinical diagnostics

- Moderator
  - Jessica Langbaum – Banner
- Speakers:
  - Josh Grill- UC Irvine
  - Emily Largent – U of Pennsylvania
- Panelists/Discussants
  - Winston Chiong – UCSF
  - Gary Marchant - Arizona State University
  - Richard Milne – University of Cambridge

Ethical considerations related to preclinical diagnostics

- Preclinical AD/ADRD is not used as a clinical diagnosis
  - Is this meaningful and actionable?
  - Can we accurately predict on individual level which people with preclinical AD/ADRD biomarkers will progress to symptomatic disease?
- Disclosure studies thus far from large AD prevention trials suggest that disclosure of APOE and amyloid markers can be done effectively and safely
  - Concerns about stigma or discrimination in relationships, employment, insurance, and housing
  - Generalizability limited by biased sample of individuals volunteering for these studies
  - Limited diversity in these large trials – race/ethnicity and socioeconomic status
- With electronic medical records (legal requirements 21st Century Cures Act) - patients may view biomarker results before their providers can help with interpretation
- Disclosure of AD/ADRD biomarker results may be different than other risk biomarkers
  - Brains and minds are seen as uniquely fundamental part of who people are
  - AD/ADRD-related cognitive decline is not a discrete event that is clearly delineated
  - Impairment may be years in the future and for some people may never occur

Ethical conundrums

- What is the risk-benefit ratio that favors disclosure when there are still many unknowns to inform individual risk?
- Do participants from epidemiologic cohorts who did not sign consent for preclinical marker disclosure want to know their results? Should we at least offer the option?
- Do we disclose preclinical marker results to diverse individuals without additional evidence that findings from largely white cohorts are (or are not) generalizable to other communities?

Economic impact of preclinical diagnostics

- Moderator
  - David Bennett - Rush
- Speakers
  - Julie Zissimopoulos - USC
  - Amitabh Chandra - Harvard
  - Michael Hurd - RAND
- Panelists/Discussants
  - Gary Mottola - FINRA Foundation
  - Norma Coe - University of Pennsylvania

Economic impact of preclinical diagnostics

- Economic effects of preclinical diagnosis could arise through different pathways:
  - Treatment could prevent or delay onset of disease
  - Health care system could be incentivized to deliver better care
  - Patients could have more quality-adjusted life years
  - Direct and indirect costs could be reduced (e.g., medical care, employment productivity losses, long-term care)

- Three major policy questions surrounding preclinical diagnostics:
  1. How will these diagnostics affect the sustainability of health care spending?
  2. How will they affect society's well-being?
  3. How will they affect the pricing of medicines?

- The value of a preclinical diagnostic depends in large part on positive predictive value, that is, how well a diagnostic identifies those who will get symptoms of the disease and progress to clinical dementia

Design and conduct of trials of preclinical diagnostics and early detection

- Moderator
  - Jessica Langbaum – Banner
- Speakers:
  - Oskar Hansson - Lund University
  - Randall Bateman - Washington University
  - Jeff Burns - University of Kansas
- Panelists/Discussants
  - Rhoda Au - Boston University
  - Jeffrey Kaye - Oregon Health and Science University
  - Paul Aisen - University of Southern California

Design and conduct of trials of preclinical diagnostics and early detection

- Algorithms with AD biomarkers (blood or CSF), APOE, and cognitive tests show predictive accuracy for clinical decline of >.9 in research settings
- Large community-based studies with blood-based biomarkers and phone assessments ongoing
- Pragmatic studies evaluating health records and lifestyle interventional trials exploring disclosure
- Potential for primary prevention trials (age 45?) that employ genetic and blood biomarkers to determine risk and utilize novel outcomes that may precede AD neuropathology

Cognitive and functional preclinical markers

- Digital biomarkers may be closer to real change in cognitive function and track intra individual change
- Ecological frequent assessment of neuropsychological function
- Monitoring of financial errors may detect early decline and could protect against financial consequences
- Digital biomarkers differ from traditional biomarkers
  - Validation with biological markers and standard clinical assessments
  - Regulatory approval issues

Discussion - Thorny Issues

- We still do not have adequate data for individual prediction of dementia risk, especially over short time frame
  - Some people with multiple markers apparently resilient, some decline without substantial pathology on current biomarkers
- Most of the data on risk of decline and impact of preclinical marker disclosure acquired in non-representative populations
  - Primarily in highly educated people willing to undergo multiple imaging and cognitive testing in intensive studies at academic centers, increased concern about developing AD symptoms with family history or subjective decline
  - Very little data available in diverse populations, esp. race and ethnicity, unknown impact of educational, cultural, and systemic health issues
- There is no legal protection for discrimination (job, long term insurance, etc. related to biomarkers. We have GINA, Not BINA!

Work Needed

- Need to understand heterogeneity, resistance to pathology, resilience to manifesting symptoms
- Very likely that multiple preclinical markers needed to accurately predict who will decline and when
- Need to study whether preclinical markers and disclosure in broader populations (epidemiologic cohorts, racial and ethnically diverse groups, people not actively seeking treatment or risk information) have similar impact to less representative prevention trial populations
- Need to understand impact of disclosure not just on person themselves but their family, health care, economic care systems

Summary and Next Steps

- Very productive and thought-provoking meeting
  - Has already informed plans for introducing blood-based markers into NIA supported preclinical AD prevention trials
- Summary report available:
  - https://www.nia.nih.gov/sites/default/files/2021-08/final-report-bsr-biomarkers-preclinical-diagnostics-of-ad-adrd.pdf
- Potential white paper to highlight key issues that need urgent attention in broader communities
- Start of conversations that will be critically important if any of these preclinical AD prevention trials are successful!

Gratitude

- NASEM - Molly Checksfield Dorries
- NIA – Luke Stoeckel, Elena Fazio, Lis Nielsen
- Planning Committee members – Bennett, Chan, Langbaum
- Workshop speakers and panelists
- All of the research participants and their study partners who allow us to learn