Alzheimer's Disease and Other Related Dementias: Early Detection Initiative at the Vanderbilt Memory and Alzheimer's Center

Corey J. Bolton, PsyD

TN Department of Health

Disclosures

- None

TN Department of Health

Overview

- The Vanderbilt Memory and Alzheimer's Center
- Early Detection Initiative
  - Subjective Cognitive Decline
  - Blood-Based Biomarkers for AD
  - Predicting Dementia Risk
  - Risk Disclosure

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The Vanderbilt Memory and Alzheimer's Center (VMAC)

TN Department of Health

VMAC

Our Mission

We aim to enhance knowledge to solve the complexities underlying the pathophysiology, early identification, and treatment of Alzheimer's disease and related dementias.

Interdisciplinary Team

Tim Hohman, PhD; Leah Acosta, MD; Angela Jefferson, PhD; Katie Gifford, PhD; Taylor Davis, MD

Trans-Institutional

Vanderbilt University

Vanderbilt University Medical Center

Meharry Medical College

Investigators

61 faculty

20 clinicians

41 scientists

21 departments

Research

Risk

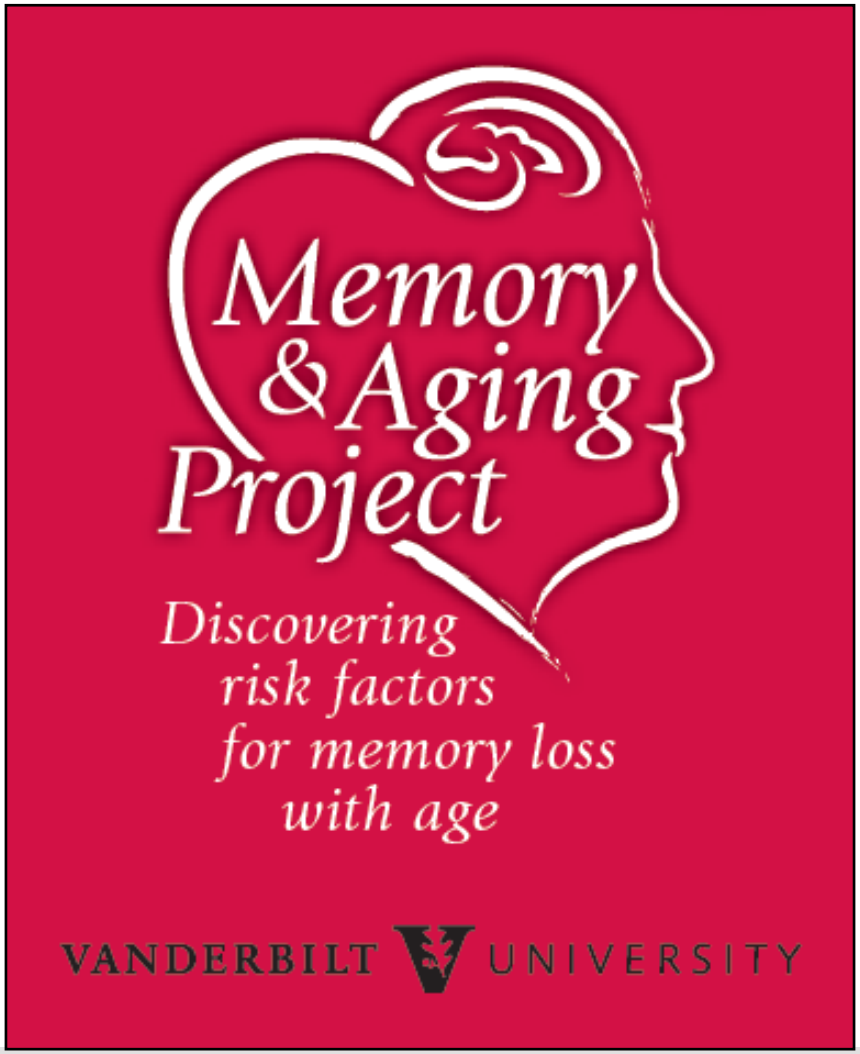
Resilience

Disparities

TN Department of Health

VMAC

- The Vanderbilt Memory and Aging Project (VMAP)
  - Longitudinal, observational cohort study launched in 2012
  - Adults age ≥60, no dementia, clinical stroke, or heart disease
  - Enriched for MCI
  - Assessing cardiovascular and cerebrovascular correlates of cognition and brain health in aging
  - Currently collecting 9-year follow-up data



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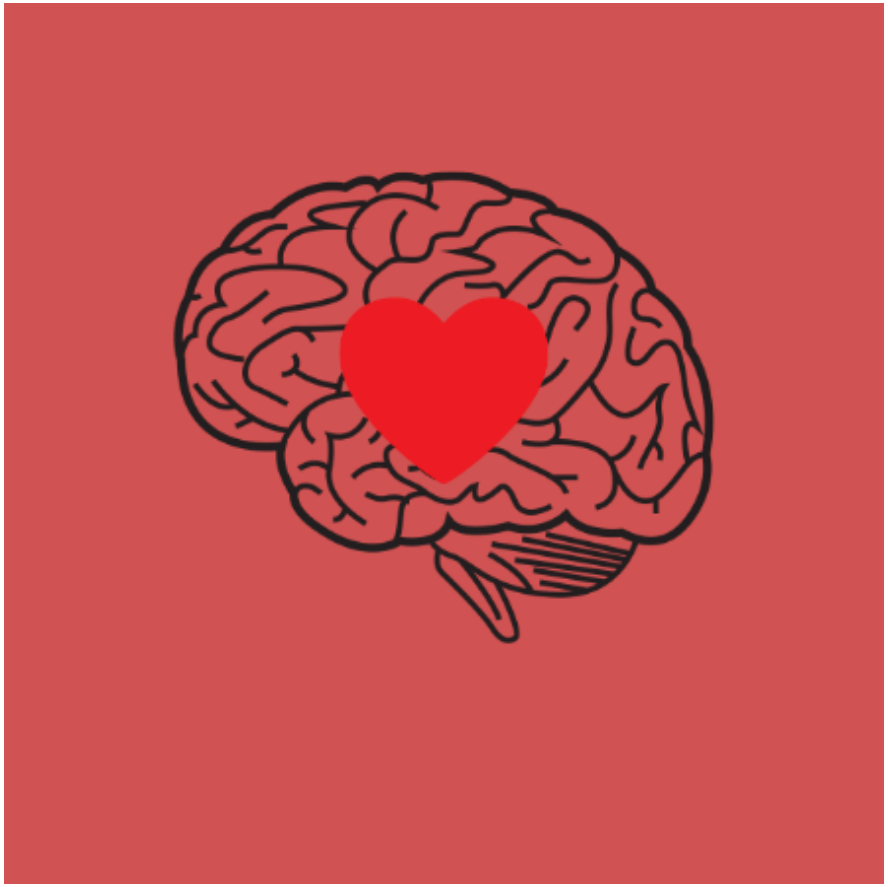
- VMAP 2.0
  - Given key findings from original cohort, funding was granted to expand the cohort to 1000 participants
  - Age dropped to ≥50
  - Currently enrolling cognitively normal participants
  - Actively recruiting



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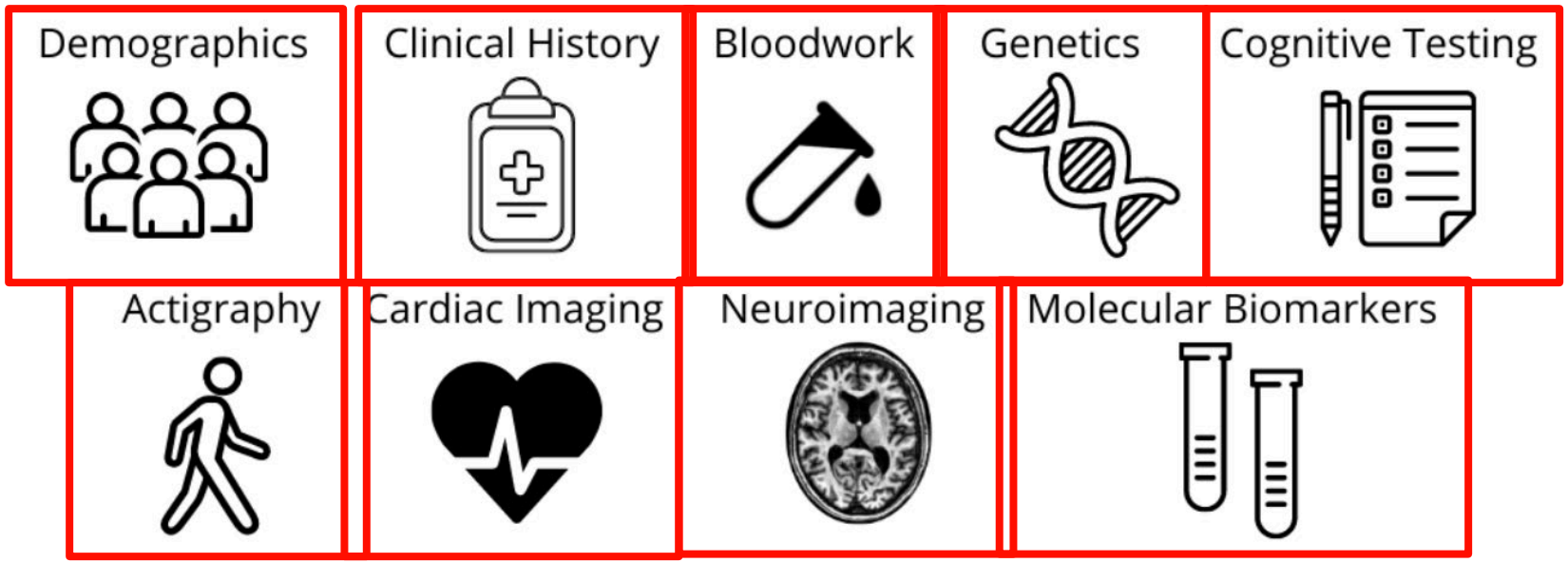
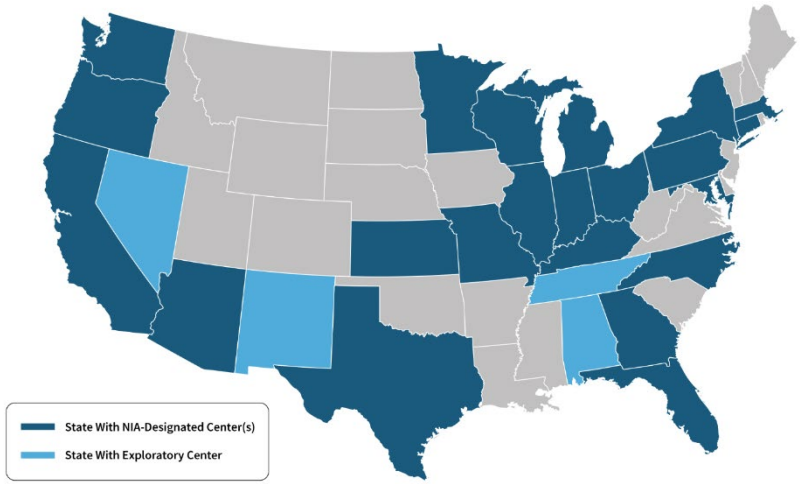

Demographics
Clinical History
Bloodwork
Genetics
Cognitive Testing
Actigraphy
Cardiac Imaging
Neuroimaging
Molecular Biomarkers

VMAC

- In August 2020, VMAC was awarded a 3-year, $3.8M grant from the NIA to establish an exploratory Alzheimer's Disease Research Center at VUMC
- One of 33 ADRCs in the country
- First in TN



VMAC

- The ADRC clinical core is recruiting for a signature cohort – the Tennessee Alzheimer's Project (TAP)
- Recruiting individuals age ≥60 with normal cognition, MCI, or mild dementia

Paul Newhouse, MD
Clinical Core Leader
Professor of Psychiatry

Katherine Gifford, PsyD
Clinical Core Co-Leader
Assistant Professor
of Neurology

VMAC

Key Research Initiatives

Risk & Prevention Initiative

Led by Dr. Angela Jefferson, this initiative examines the intersection between vascular health and Alzheimer's disease for the purposes of identifying risk factors and prevention targets. To learn more, click here.

Early Detection Initiative

This initiative, led by Dr. Katherine Gifford, focuses on identifying tools for the early detection of Alzheimer's disease. To learn more, click here.

Resilience Initiative

This initiative, led by Dr. Timothy Hohman, focuses on understanding factors underlying some people's resilience to the clinical manifestation of Alzheimer's disease. To learn more, click here.

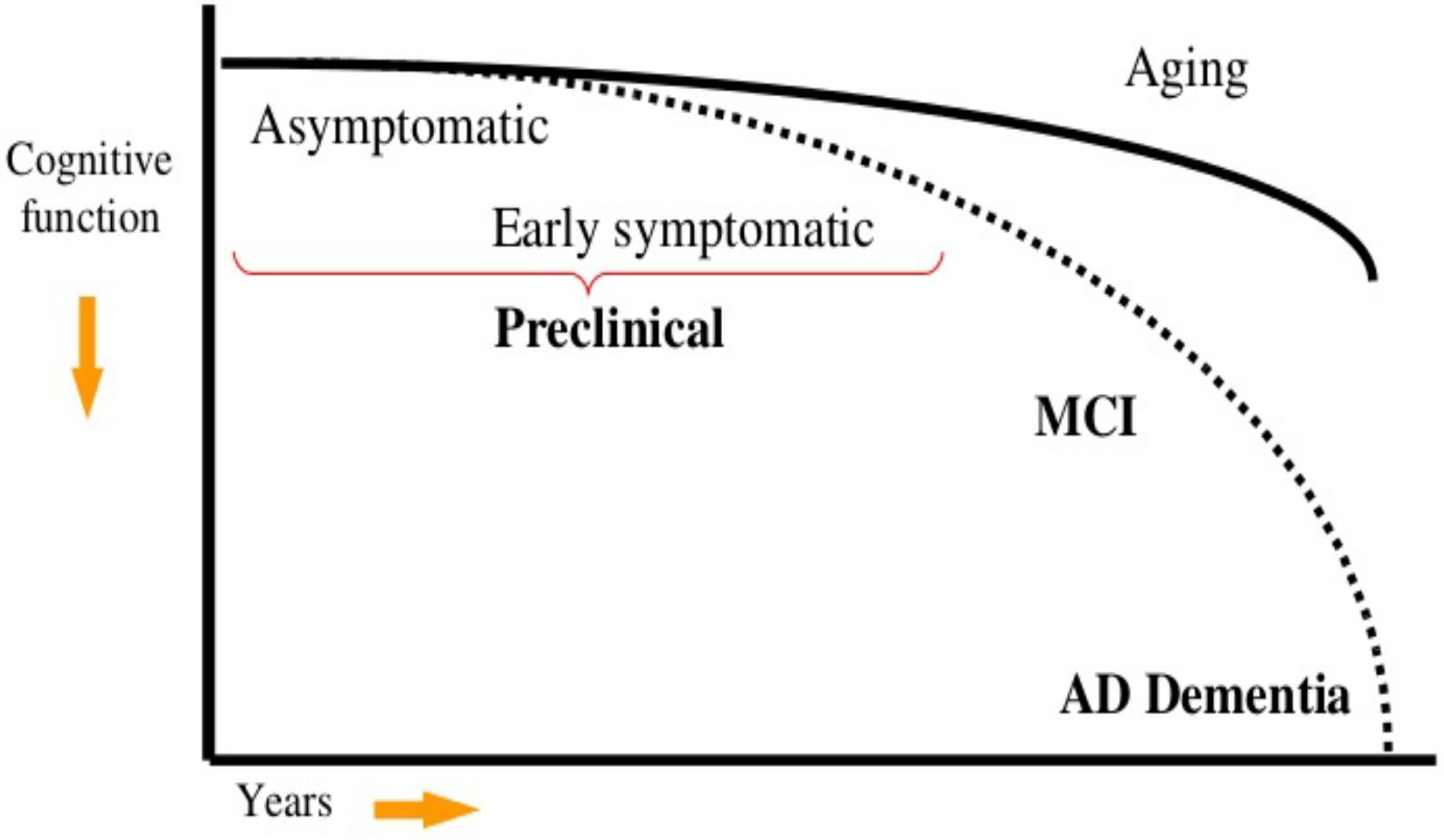
Clinical Trials Initiative

This initiative, jointly led by Drs. Angela Jefferson and Lealani Acosta, focuses on testing new drug targets to identify effective treatments for Alzheimer's disease. To learn more, click here.

Early Detection Initiative

Early Detection Initiative

- What is early detection?



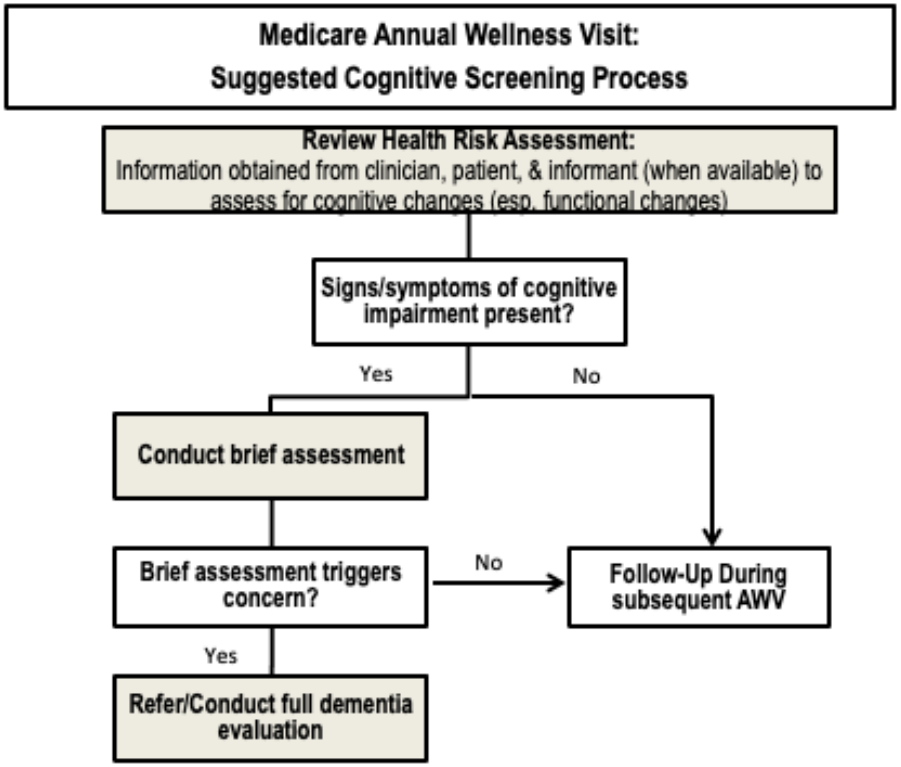
Sperling et al., 2011, *Alzheimer's & Dementia*

Early Detection Initiative

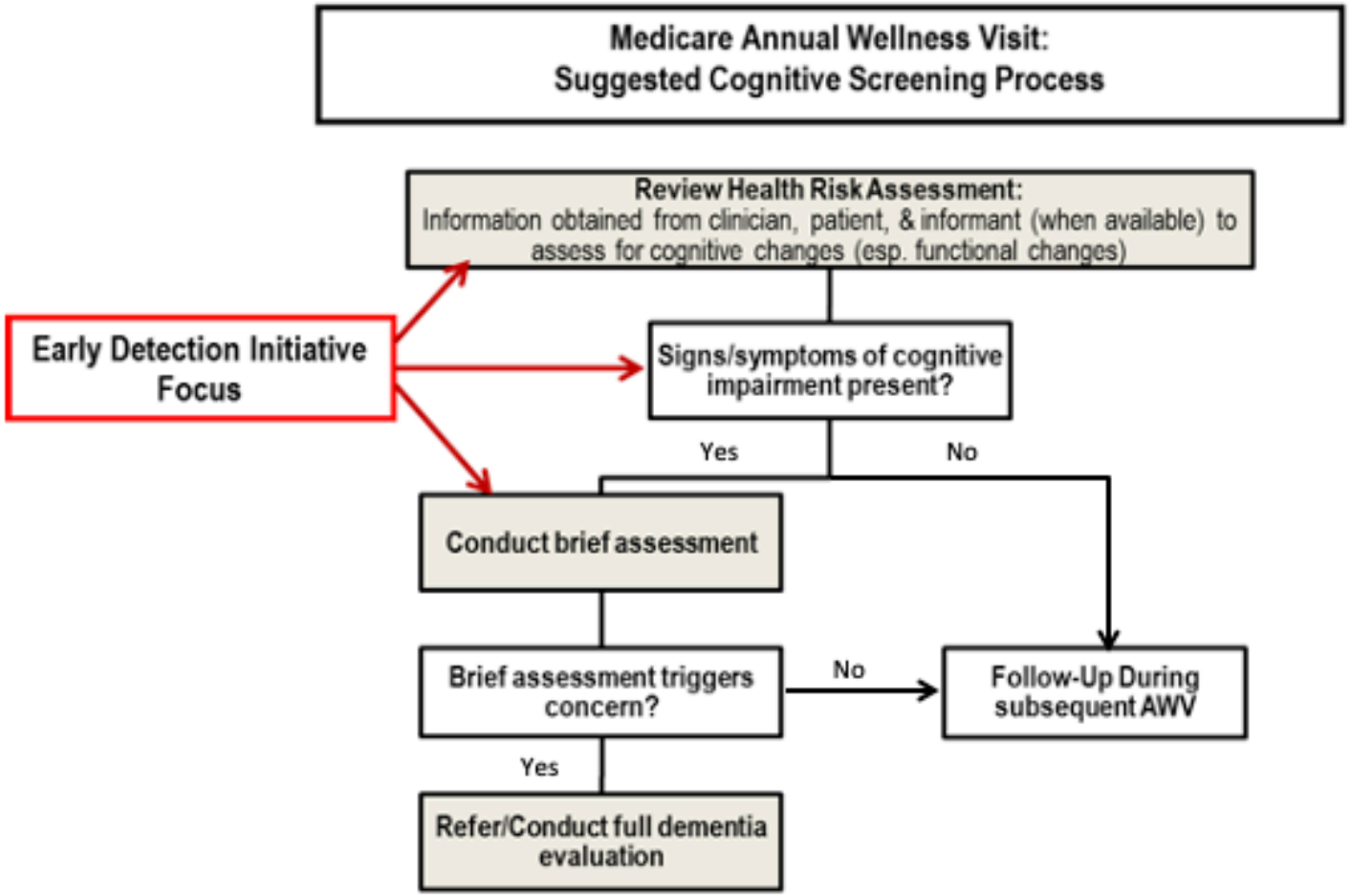
- Earlier detection of preclinical AD allows individuals and their families to…
  - Identify exacerbating factors or comorbidities
  - Initiate treatment or intervention strategies early
  - Increase safety (i.e., driving, medications, cooking)
  - Make important decisions while a loved one has cognitive capacity
    - Designate financial and medical proxies
    - Discuss wishes of the patient including living arrangements or treatment
  - Delay placement into nursing home or long-term care facility
  - Reduce healthcare costs

Early Detection Initiative

- In 2011, the Centers for Medicare & Medicaid Services (CMS) altered their annual wellness visit (AWV) policy for all beneficiaries
  - AWV must include detection of cognitive impairment



Early Detection Initiative

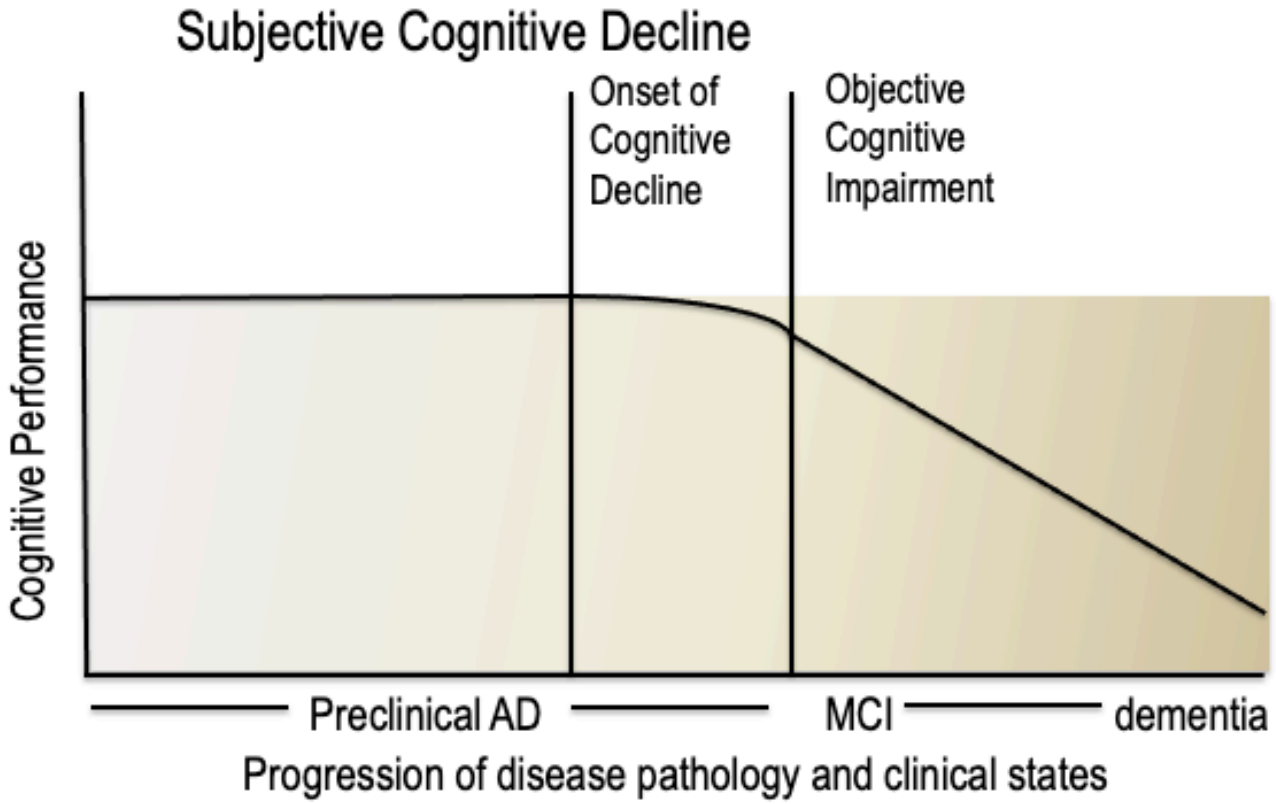


Current Research

Subjective Cognitive Decline (SCD)

SCD

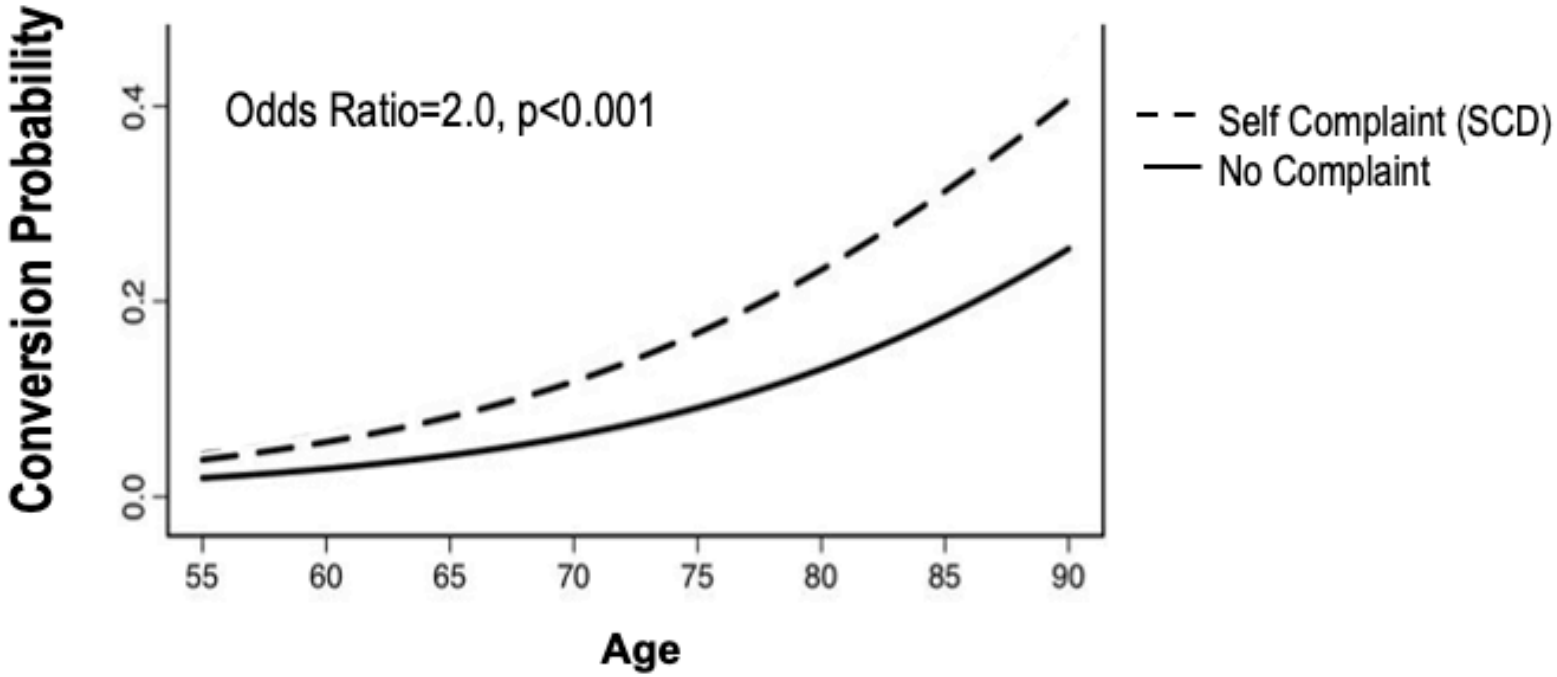
- Subjective cognitive decline (SCD) is a promising marker of early cognitive changes



Adapted from Jessen et al., 2014, *Alzheimer's & Dementia*

SCD

- Individuals with SCD are 2x more likely to be diagnosed with mild cognitive impairment or dementia after 3 years



Note: National Alzheimer's Coordinating Center Data, no complaint n=2967, SCD n=585

Gifford et al., 2014, *Alzheimer's & Dementia*

SCD

- **What causes SCD?**
- 1170 men completed a measure of SCD and objective neuropsychological assessment
- Self-reported SCD was associated with memory and executive functions, but only modestly
- SCD was more strongly associated with depression and anxiety symptoms

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NIHMSID: NIHMS1742314
PMID: 34308902

How Well Does Subjective Cognitive Decline Correspond to Objectively Measured Cognitive Decline? Assessment of 10–12 Year Change

Daniel E. Gustavson,[a,b] Amy J. Jak,[c,d] Jeremy A. Elman,[c,e] Matthew S. Panizzon,[c,e] Carol E. Franz,[c,e] Katherine A. Gifford,[b] Chandra A. Reynolds,[f] Rosemary Toomey,[g] Michael J. Lyons,[g] and William S. Kremen[c,e,h]

SCD

- **Is SCD associated with AD pathology?**
  - 1842 participants from NACC
  - Examined associations between SCD and neuropathology
  - Four SCD groups
    - No complaint
    - Self-only complaint
    - Informant-only complaint
    - Mutual complaint
  - Only mutual complaint was associated with AD pathology

PLOS ONE

PLoS One. 2015; 10(11): e0141831.
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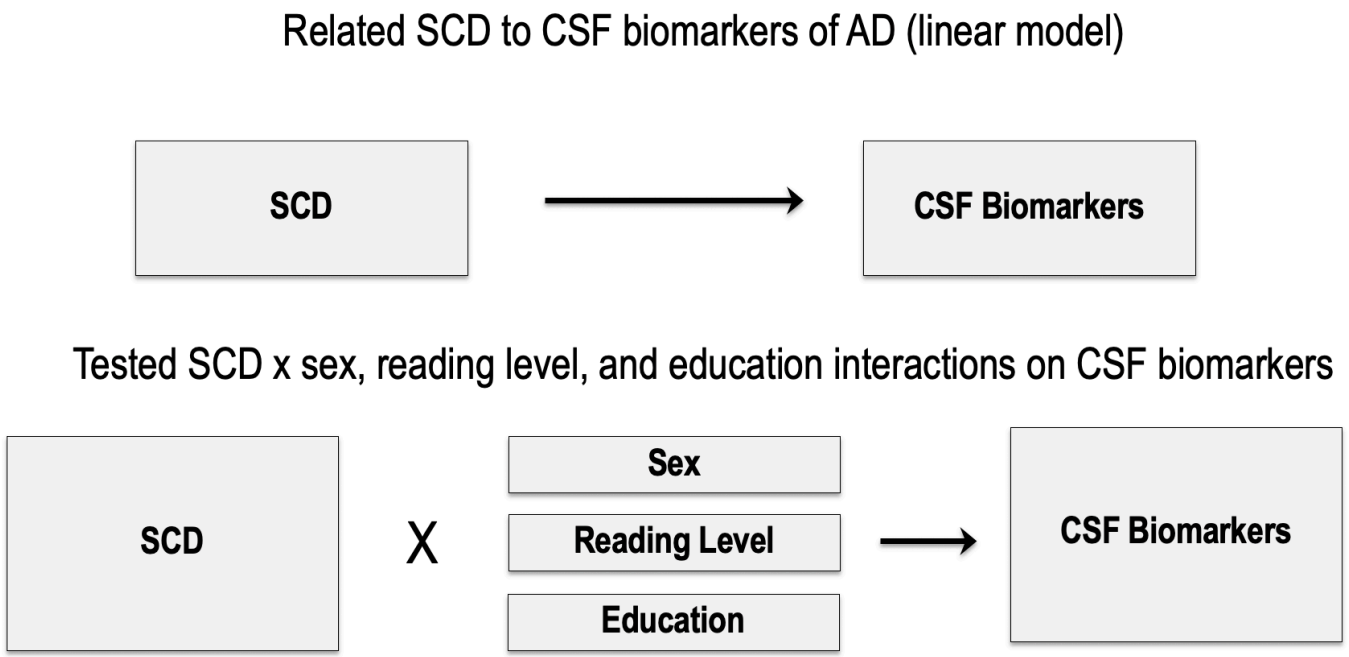
PMCID: PMC4634952
PMID: 26539829

A Mutual Self- and Informant-Report of Cognitive Complaint Correlates with Neuropathological Outcomes in Mild Cognitive Impairment

Katherine A. Gifford,[1] Dandan Liu,[2] Timothy J. Hohman,[1] Meng Xu,[2] Xue Han,[2] Raymond R. Romano, III,[1] Laura R. Fritzsche,[1] Ty Abel,[3] and Angela L. Jefferson[1,*]

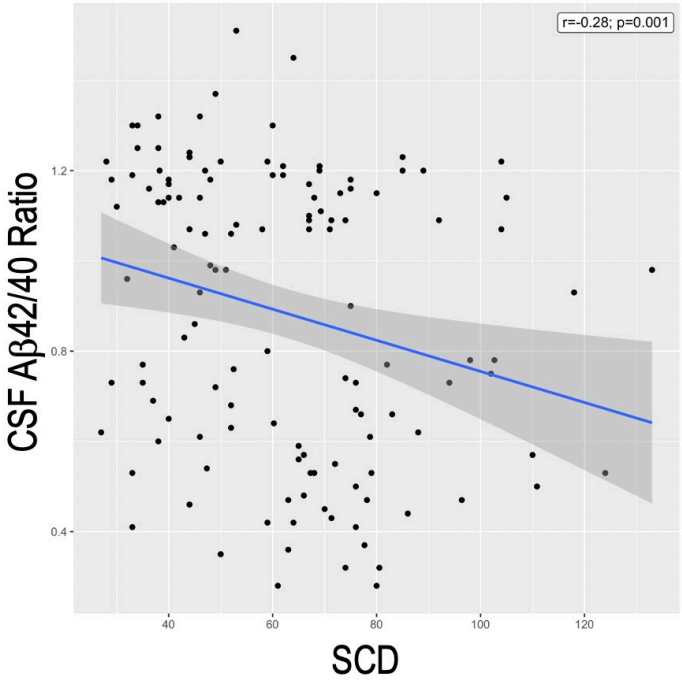
SCD

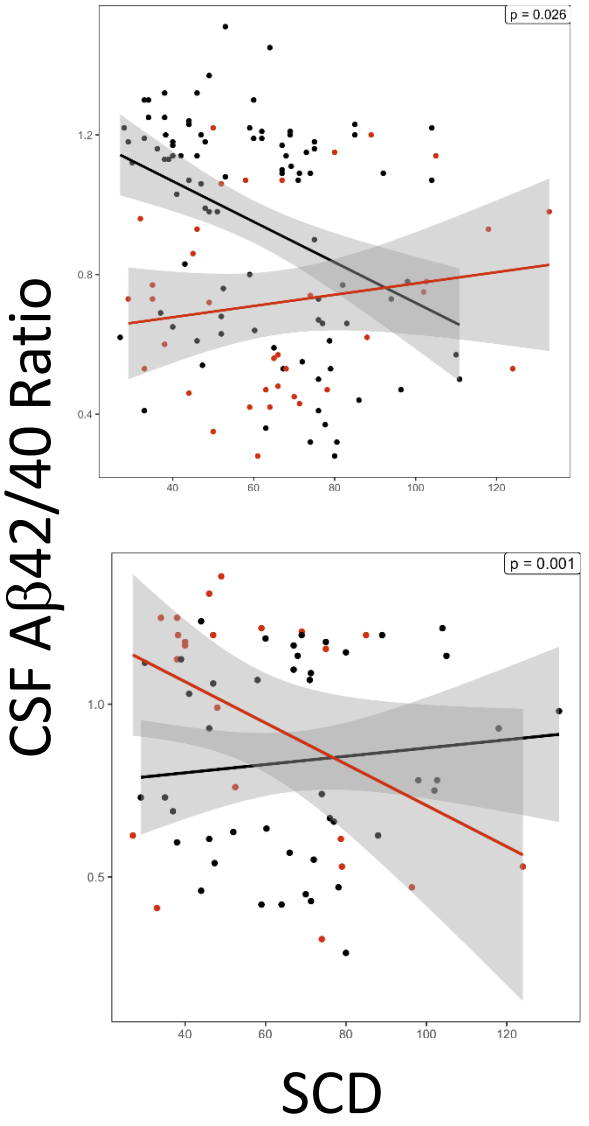
- **Is SCD associated with *in vivo* biomarkers of AD?**
  - 129 participants from VMAP
  - Used the Vanderbilt SCD scale
  - Investigating which factors influence the association between SCD and markers of AD pathology



SCD

- SCD and CSF biomarkers of AD
  - SCD is related to CSF levels of amyloid, not other AD biomarkers
  - This relationship is stronger in men and in individuals with higher educational level



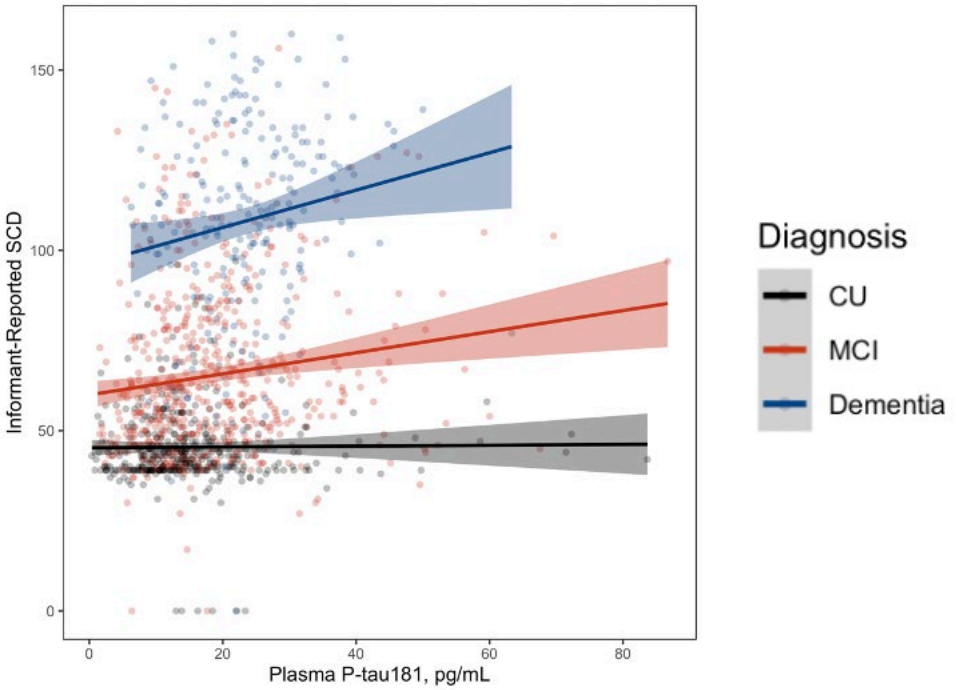


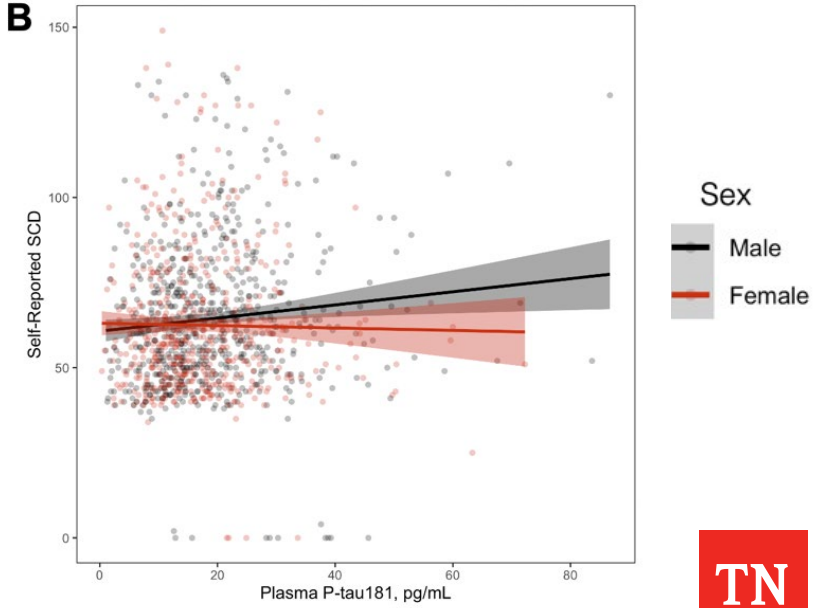
Men
Women

Lower Education
Higher Education

SCD

- Plasma p-tau181 and SCD
  - 1185 adults from ADNI
  - Investigated associations between plasma levels of ptau181 and self- and informant-reported SCD
  - Examined several clinical/demographic factors to determine what influences this association





SCD

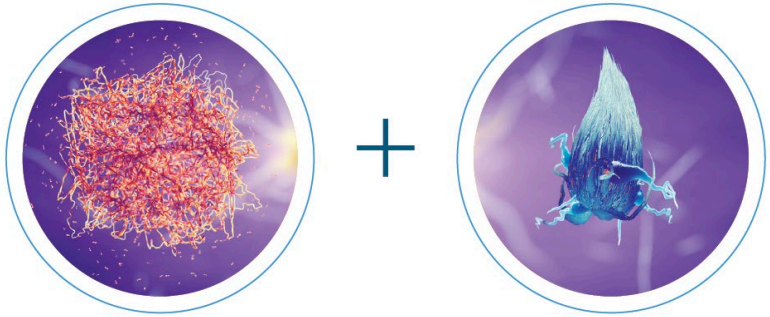
- Summary of SCD findings
  - SCD is associated with AD, but this association can depend on several factors
  - Likelihood of SCD being related to underlying AD pathology is increased when:
    - Absence of excessive symptoms of anxiety/depression
    - Patient and informant are both reporting SCD
    - Patient is highly educated, male (due to decreased comorbidities?)

- Future Directions
  - Understanding sex differences, role of other medical conditions
  - Integrating SCD with other accessible biomarkers

Blood-Based Biomarkers

Blood-Based Biomarkers

- Alzheimer's disease is made up of two proteins: amyloid and tau
- Detection and measurement of these proteins typically requires CSF analysis or PET imaging
- Recent advances have allowed for detection and quantification of these proteins in the blood



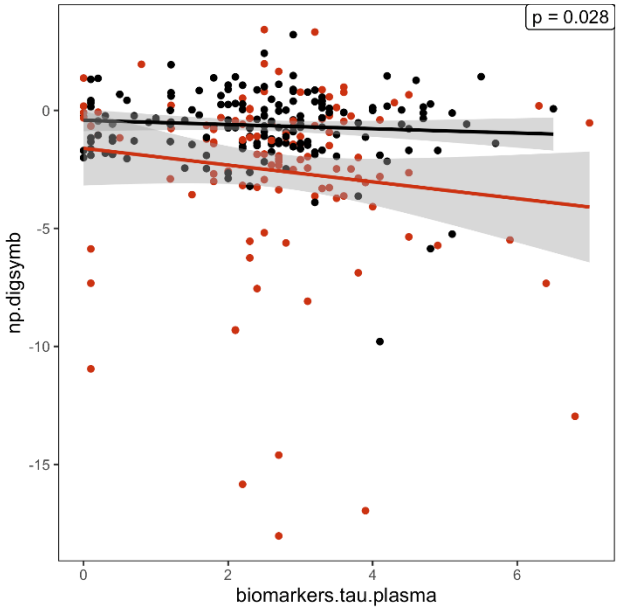
Plaques: made up of a protein called *amyloid*

Tangles: made up of a protein called *tau*

Blood-Based Biomarkers

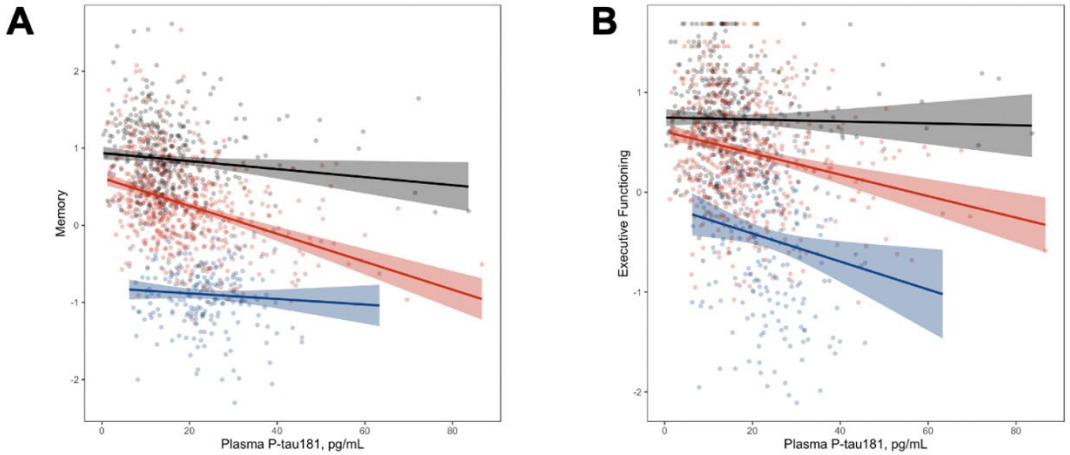
- Plasma total tau
  - Measures the amount of the protein tau in the blood – not specific to AD-type hyperphosphorylated tau protein

- **Do plasma total tau levels predict changes in cognition?**
  - 332 participants from VMAP
  - Tau was associated with longitudinal declines in processing speed, but not associated with other measures of cognition
  - Associations were stronger in individuals with MCI at baseline



Blood-Based Biomarkers

- Plasma Phosphorylated Tau (ptau181)
  - New technology has allowed for quantification of phosphorylated, AD-specific tau protein in the blood
- **Is elevated plasma ptau181 associated with cognitive impairment?**
  - 1185 participants from ADNI
  - Plasma ptau181 is associated with tests of memory, executive functions, language
  - Associations are stronger in individuals with MCI or dementia



Blood-Based Biomarkers

- Summary of Blood-Based Biomarkers Findings
  - Plasma total tau is a nonspecific marker of neurodegeneration that predicts longitudinal declines in speed of information processing
  - Plasma ptau181 is much more specific to AD and is associated with changes in AD-related cognitive domains cross-sectionally

- Future Directions
  - Investigate longitudinal clinical changes to brain structure, cognition, and functional abilities associated with plasma ptau181
  - Identify clinical and/or demographic variables that modify associations between plasma ptau181 and clinical outcomes

Predicting Dementia Risk

Predicting Dementia Risk

- We have identified several accessible tools to predict risk for dementia
  - Self- and informant-reported measures of SCD
  - Blood-based biomarkers
  - *APOE* genotyping
  - Cognitive screening

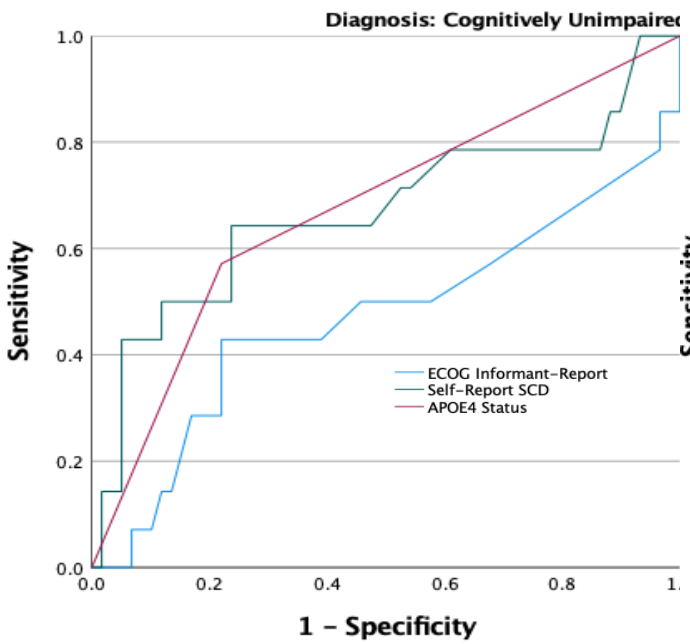
- The next step is to integrate these tools to efficiently and accurately predict dementia risk

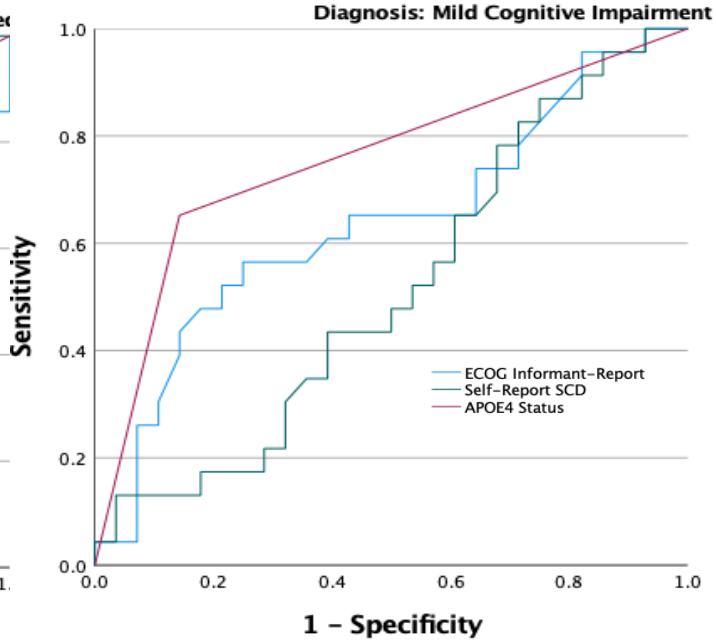
Predicting Dementia Risk

- **Which accessible measures add value beyond demographic factors and cognitive screening?**
- 288 participants from VMAP
- Examined multiple predictors of conversion to dementia and amyloid status
  - *APOE* status
  - Plasma total tau, plasma neurofilament light (neurodegeneration)
  - Self- and informant-reported SCD on ECOG measure
  - Self-reported SCD on Vanderbilt SCD scale
- *APOE* was the most robust predictor
- Plasma markers of neurodegeneration added value to models when examining participants with MCI only

Predicting Dementia Risk

- Measures of SCD added value to combined models
  - Self-report SCD was useful in cognitively unimpaired participants
  - Informant-report SCD was useful in MCI participants





Predicting Dementia Risk

- Future Directions
  - Identify which combination of predictors is most effective at predicting dementia risk
  - Add plasma ptau181 into these models
  - Validate models in external cohorts

Disclosing Risk for Dementia

Disclosing Risk for Dementia

- Overwhelmingly, patients want to know their risk status for developing dementia
- Patients who are told their risk status are more likely to engage in preventive health behaviors

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PMCID: PMC2483341
NIHMSID: NIHMS57712
PMID: 18317253

Health Behavior Changes After Genetic Risk Assessment for Alzheimer Disease: The REVEAL Study

Serena Chao, MD, MSc,[*] J. Scott Roberts, PhD,[†] Theresa M. Marteau, PhD,[‡] Rebecca Silliman, MD, PhD,[*§] L. Adrienne Cupples, PhD,[ǁ] and Robert C. Green, MD, MPH[¶#§]

TABLE 3

Logistic Regression Analysis Predicting any Health Behavior Change for AD Prevention

Variable	Adjusted Odds Ratios	95% CI	*P*
Test result (ε4+ vs. ε4−)	2.73	1.14, 6.54	0.02
Age	0.97	0.93, 1.01	0.18
Sex	0.39	0.14, 1.11	0.08
Years of education	0.98	0.80, 1.20	0.83
Modifiable comorbidity? (yes/no)	1.17	0.49, 2.80	0.73

Disclosing Risk for Dementia

- Aduhelm (aducanumab) was recently awarded FDA accelerated approval, the first new AD drug since 2003
- Appropriate use requires confirmation of amyloidosis
- Must be administered early in disease process
- More anti-amyloid therapies in pipeline
- Patients will have to know their risk status

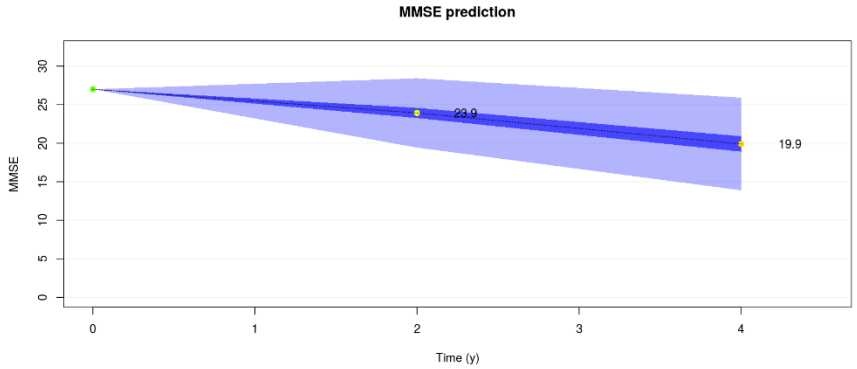
Disclosing Risk for Dementia

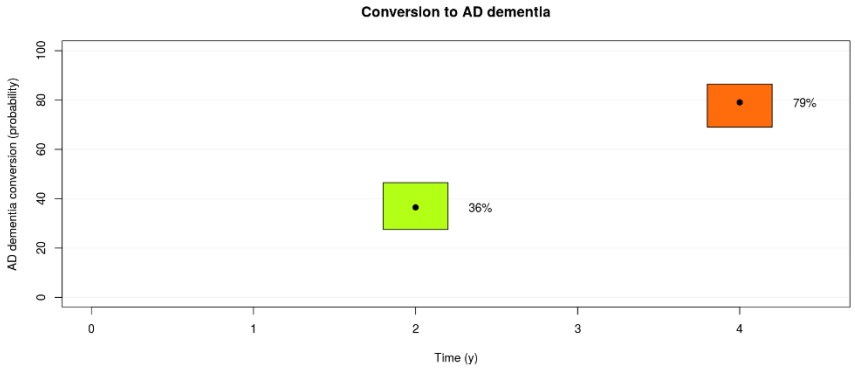
- **How do we disclose complex test results to patient with cognitive impairment in a safe and comprehensible way?**
- Study underway to develop educational materials to aid in risk disclosure to patients with MCI
- Collaboration with CEHC
- Focus groups will be conducted in August and September 2022

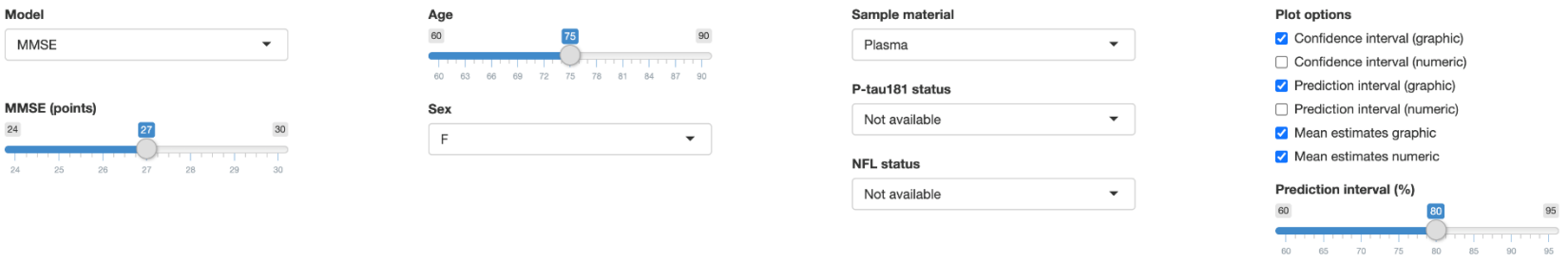
Vanderbilt Center for
Effective Health Communication

Disclosing Risk for Dementia

- Using these educational materials, a randomized trial will be conducted to disclose four-year risk of dementia to patients with MCI based on:
  - Age, sex, education, MMSE score, plasma p-tau181 results







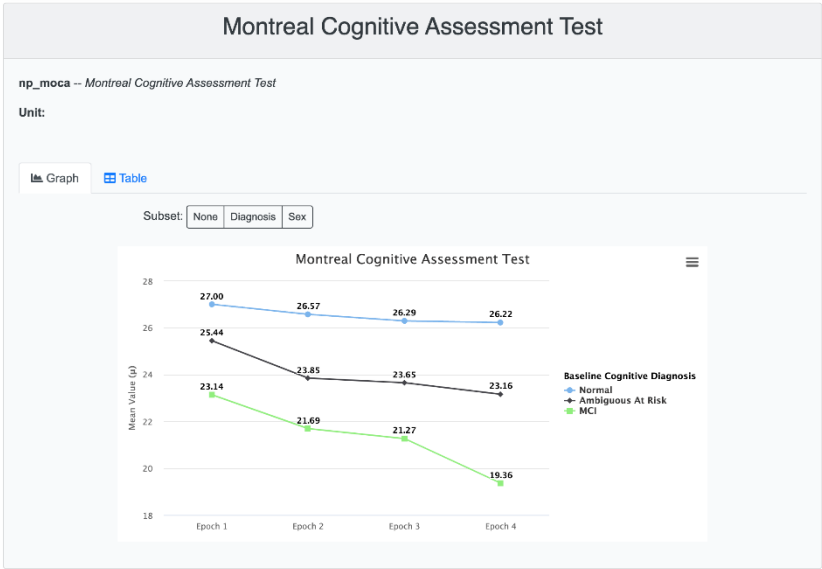
- predictprogression.com

Disclosing Risk for Dementia

- Outcomes include:
  - Psychological response
    - Anxiety, Depression, Hopelessness, Event-related Distress
    - Assessed immediately following disclosure and again at 6-month follow-up
  - Patient Comprehension
    - Ability to accurately ”teach back” their personalized dementia risk estimate
    - Assessed during risk disclosure session and again at 6-month follow-up

- Future Directions
  - Does risk disclosure increase research participation?
  - Does response to risk disclosure vary in diverse patient populations?
  - Does risk disclosure to participants with MCI influence health behaviors, and if so, does that actually reduce their risk?

vmacdata.org



Thank You!

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