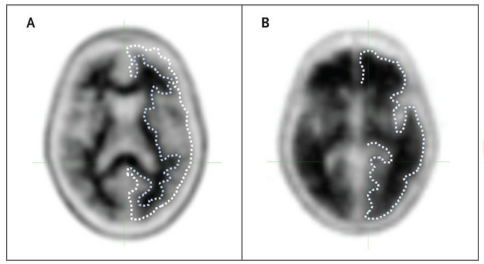

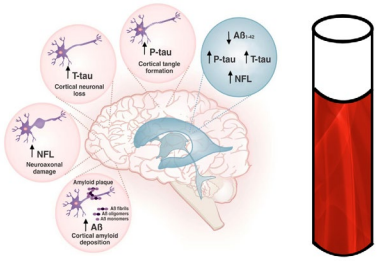

Diagnostics and risk prediction

March 6, 2025

Washington University in St. Louis
School of Medicine

Suzanne E. Schindler, MD, PhD

Associate Professor of Neurology

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Disclosures: Suzanne Schindler, MD, PhD

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- Consulting/Employment: **Dr. Schindler has received honoraria for scientific advice or presentations on biomarker testing from Eisai, Eli Lilly, and Novo Nordisk. Dr. Schindler has not received any personal compensation or direct research funding from any diagnostics companies.**
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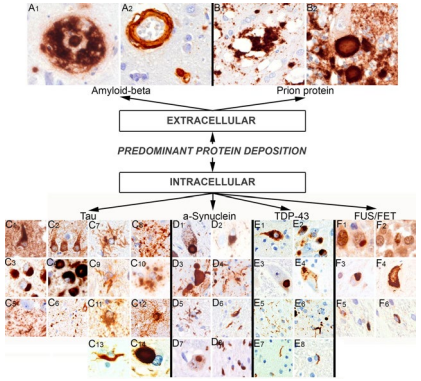
- Other: Dr. Schindler previously served as a sub-PI for the A4, DIAN-TU, and ENGAGE trials. Dr. Schindler participated in the IDEAS trial.

Diagnosing the cause of cognitive impairment

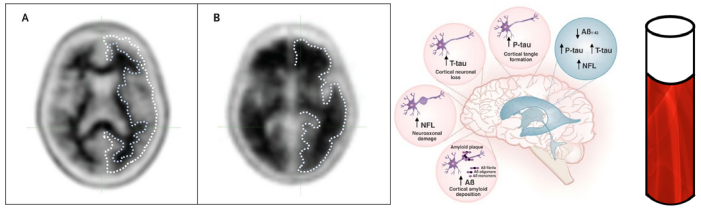


Neuropathology

Alzheimer disease, Parkinson disease, TDP-43, etc.

Neuropathology is associated with biomarker values

Cognitive impairment



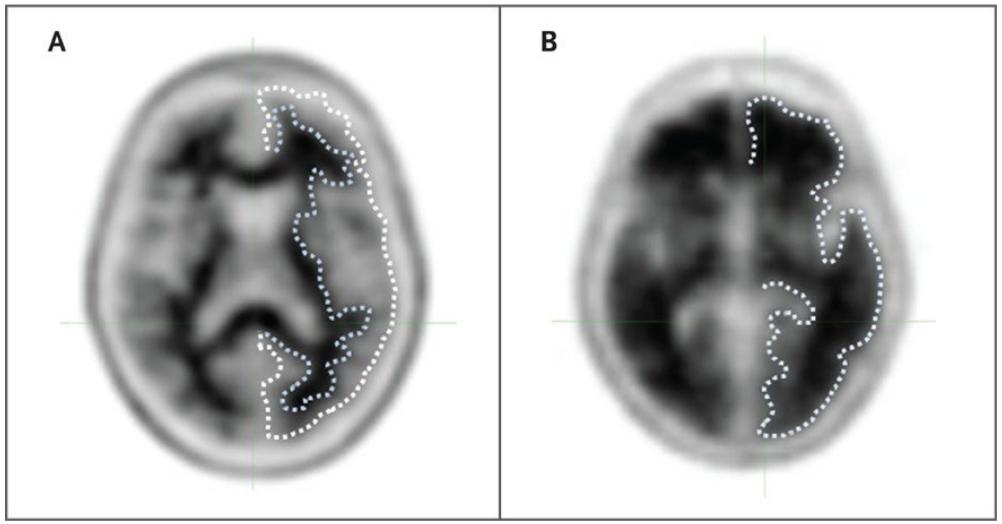
Biomarkers

Comorbidities

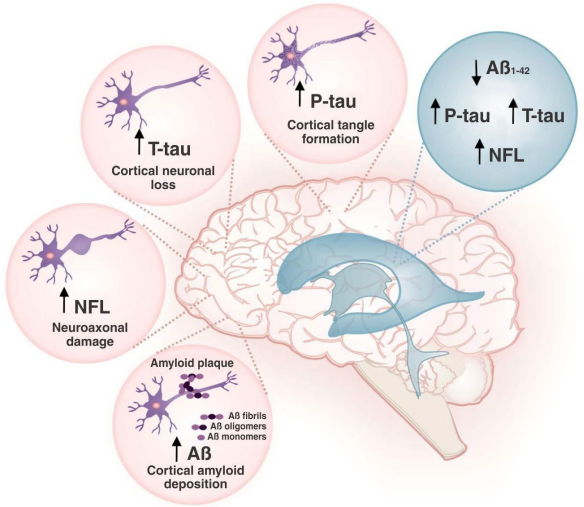
Cerebrovascular disease, sleep disorders, and mood disorders, Medication side effects, etc.

Comorbidities may affect some biomarker values

Alzheimer disease (AD) biomarker tests for clinical diagnosis



Amyloid PET



CSF tests

Blood tests

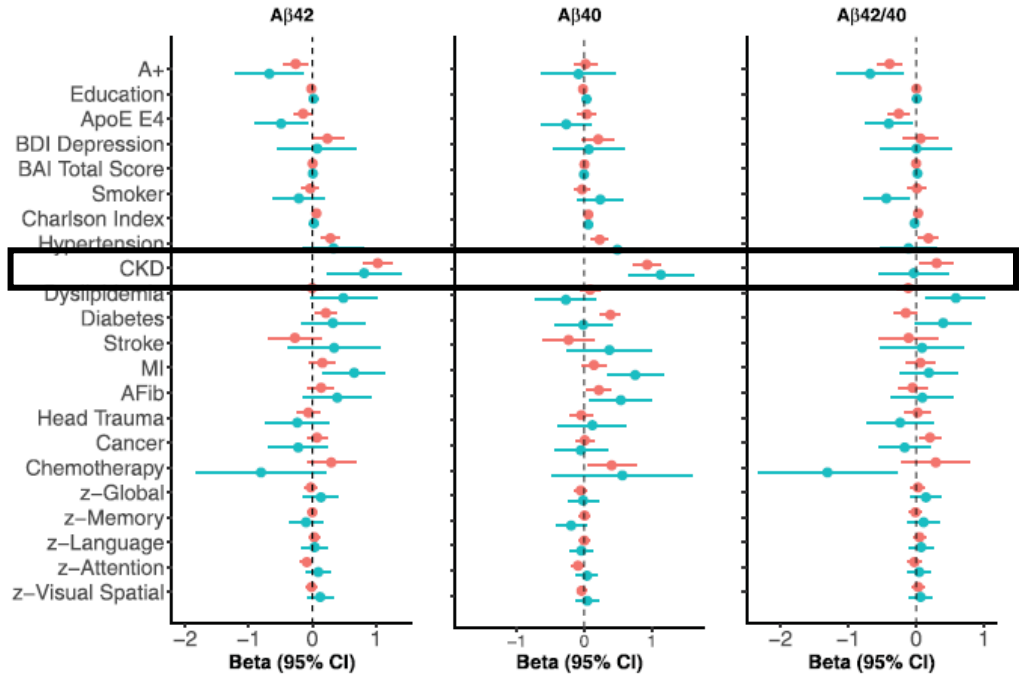
Comorbidities may affect the selection of AD biomarker test modality

Patient-specific factors	Amyloid PET	CSF tests	Blood tests
Patient is very concerned about risks from radiation	↓	↑	↑
Patient has severe claustrophobia	↓	↑	↑
Patient lacks insurance coverage for biomarker testing and cost is a concern	↓	↓	↑
Patient is treated with anticoagulant medications	↑	↓	↑
Patient is very concerned about invasiveness or risks of lumbar puncture	↑	↓	↑
Patient has risk factors for a difficult lumbar puncture such as scoliosis, prior lumbar back surgery, or severe lumbar adiposity	↑	↓	↑
Patient's differential diagnosis includes non-AD conditions that can be evaluated for with CSF tests	↓	↑	↓
Patient is a candidate for AD-specific treatments and insurance requires CSF or amyloid PET for biomarker confirmation	↑	↑	↓
Patient can only access lower accuracy or poorly validated AD blood tests	↑	↑	↓
Patient has chronic kidney disease, liver cirrhosis, or prior myocardial infarction or stroke	↑	↑	↓

VandeVrede and Schindler, *Alzheimer's and Dementia 2024*

Effects of comorbidities on AD biomarkers

- We do not have sufficient data to understand how comorbidities affect CSF tests and amyloid PET scans
- Blood biomarkers of AD pathology may be affected by age, sex, race, *APOE* genotype, metabolic factors, and medical comorbidities[1-6]
- Blood biomarker ratios and mass spectrometry-based assays may have more consistent associations with AD pathology[4,7,8]



[1]Syrjanen Alzheimer's and Dementia 2021

[2]Morris *JAMA Neurol* 2019 [3]Deters *Neurology* 2021
[4]Schindler *Neurology* 2022 [5]Mielke *Nature Medicine* 2022
[6]Pichet Binette *A&D* 2022 [7]Janelidze *JAMA Neurol* 2023
[8]Bornhorst *Neurology* 2025

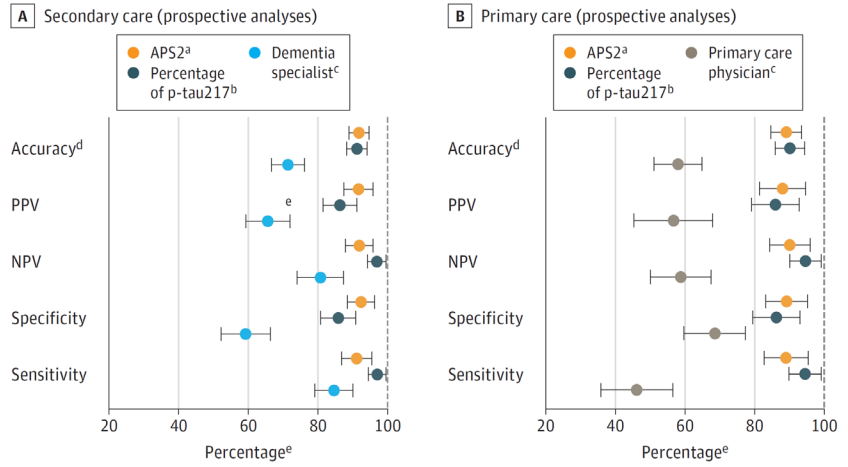
Blood biomarkers in primary and secondary care

- A mass spectrometry-based blood biomarker ratio (%-tau217) has high diagnostic accuracy, even in clinic populations with high rates of medical comorbidities
- Further studies of immunoassay tests are needed, ? if ratios of biomarkers help mitigate effects of medical comorbidities

JAMA | Original Investigation

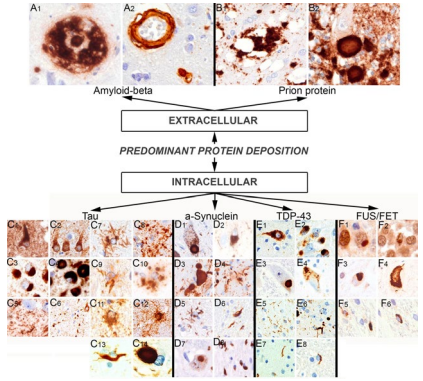
Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care

Sebastian Palmqvist, MD, PhD; Pontus Tideman, MSc; Niklas Mattsson-Carlgren, MD, PhD; Suzanne E. Schindler, MD, PhD; Ruben Smith, MD, PhD; Rik Ossenkoppele, PhD; Susanna Calling, MD, PhD; Tim West, PhD; Mark Monane, MD, MBA; Philip B. Verghese, PhD; Joel B. Braunstein, MD, MBA; Kaj Blennow, MD, PhD; Shorena Janelidze, PhD; Erik Stomrud, MD, PhD; Gemma Salvadó, PhD; Oskar Hansson, MD, PhD



	Primary care	Secondary care
Medical history, No./total (%)		
Cardiovascular disease	355/511 (69.5)	337/692 (48.7)
Hyperlipidemia	269/512 (52.5)	230/692 (33.2)
Chronic kidney disease	134/511 (26.2)	117/691 (16.9)
Diabetes	113/512 (22.1)	103/691 (14.9)

Predicting future cognitive impairment



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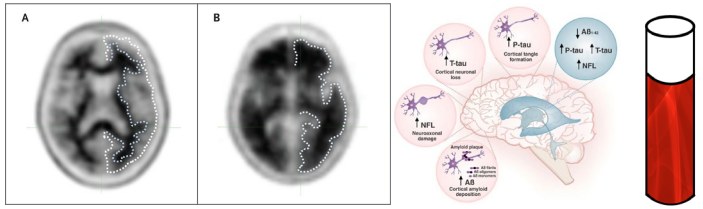
Future cognitive impairment



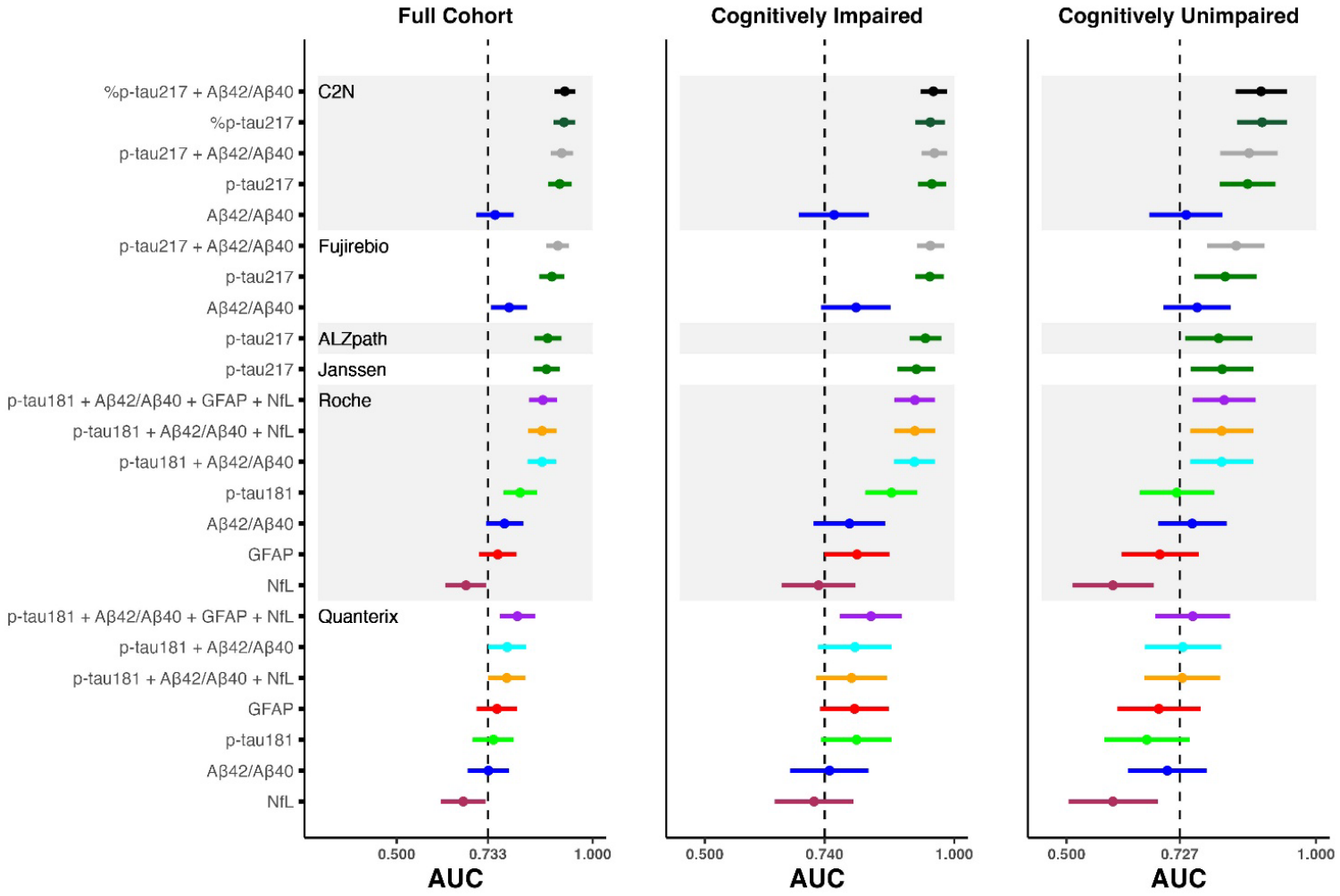
Biomarkers

Comorbidities

Cerebrovascular disease, sleep disorders, and mood disorders, Medication side effects, etc.

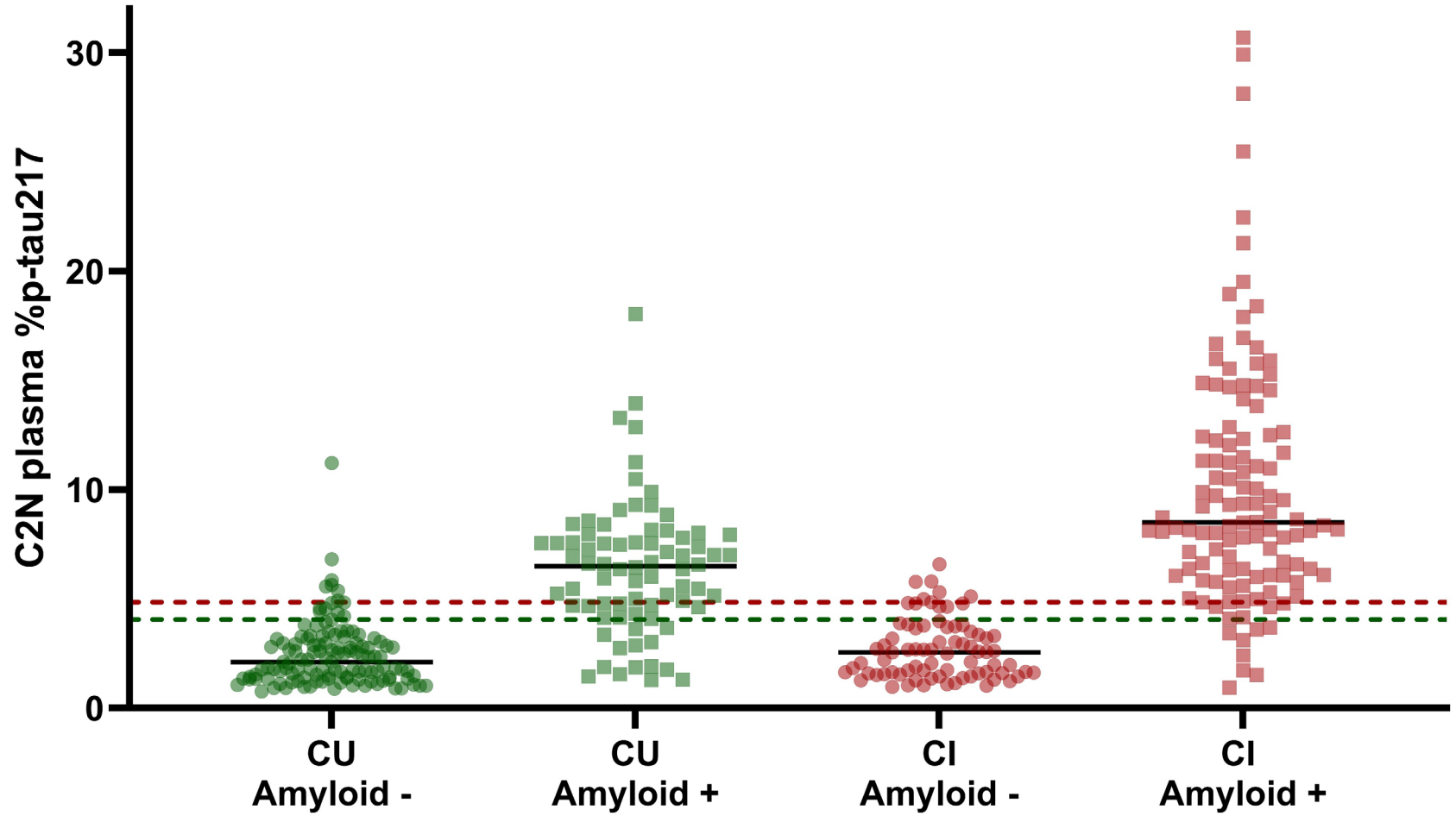
Comorbidities may affect some biomarker values

Classification of amyloid PET status (>20 versus <20 Centiloids) in cognitively impaired (CI) versus unimpaired (CU) individuals



Schindler *et al., Alzheimer's and Dementia 2024*

Distinguishing amyloid PET status (Centiloid 20) in CU and CI



Data and cut-offs from Schindler *et al., Alzheimer's and Dementia 2024*

Comorbidities add additional complexity to AD diagnosis and prediction of future cognitive impairment

- Comorbidities can directly impair cognition and complicate the diagnosis of AD
- Comorbidities can affect AD blood tests and the use of blood biomarker ratios may partially mitigate these effects
- The effects of comorbidities on CSF tests and amyloid PET scans have not been well studied
- Accurately detecting AD pathology is even more challenging in cognitively unimpaired individuals because the magnitude of difference is smaller
- Blood tests less accurately classify amyloid status in cognitively unimpaired individuals
- Models that accurately predict future cognitive impairment, which could be used to identify patients who may benefit from preventative treatments, will likely require consideration of medical comorbidities