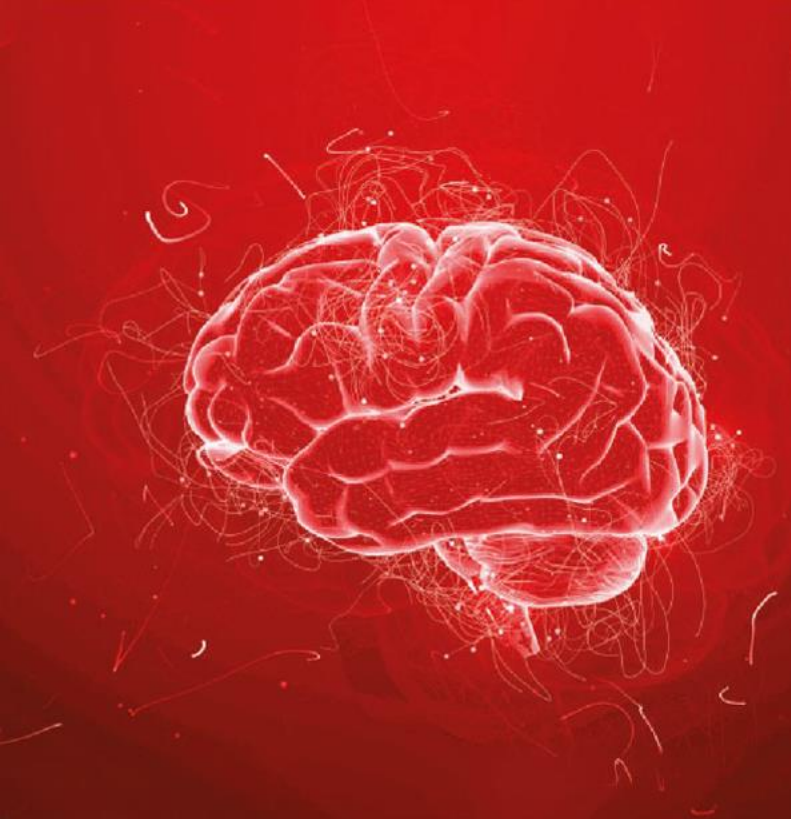

DR. SEBASTIAN PALMQVIST | MD PHD
Senior Consultant Neurologist, Skåne University Hospital, and
Associate Professor, Lund University, Sweden
GM-54571. March 2025.

THE EVOLVING JOURNEY OF ALZHEIMER'S DISEASE BLOOD BIOMARKERS IN CLINICAL PRACTICE

Lilly

Personal Disclosures

Dr. Sebastian Palmqvist acquired research support (for the institution) from Avid Technology and ki:elements/ Alzheimer's Drug Discovery Foundation.

In the past 2 years, Dr. Sebastian Palmqvist received consultancy/speaker fees from BioArctic, Biogen, Eisai, Lilly, and Roche.

Dr. Sebastian Palmqvist received no financial compensation from C_2N Diagnostics (neither privately nor to the institution).

Dr. Sebastian Palmqvist owns no stocks and has no financial interest in C_2N Diagnostics.

Acceptable Performance of AD Blood Biomarkers Recommendations from the Global CEO Initiative[1]

Required performance of the biomarker is dependent on setting and intended use:

For triaging before confirmatory testing (CSF/PET): **≥90% sensitivity and ≥75-85% specificity** (depending on availability of confirmatory testing)

For confirmatory testing of AD pathology: **≈90% sensitivity and specificity** (equivalent to CSF)

Important to consider the assumed prevalence of AD positivity (i.e., pre-test probability)

Minimum acceptable performance of blood biomarker tests for triaging or confirmation of amyloid pathology[1]

Test	Minimum acceptable performance	Predictive value according to prevalence of amyloid pathology	
		Prevalence of amyloid pathology	Predictive value
Confirmatory test	90% sensitivity 90% specificity	80%	PPV 97% NPV 69%
		50%	PPV 90% NPV 90%
		20%	PPV 69% NPV 97%
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Low-specificity triaging test	90% sensitivity 75% specificity	80%	PPV 94% NPV 65%
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Modified from: Schindler SE, et al. *Nat Rev Neurol.* 2024[1]

AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; PET=Positron Emission Tomography.

1. Schindler SE, et al. Acceptable Performance of Blood Biomarker Tests of Amyloid Pathology - Recommendations from the Global CEO Initiative on Alzheimer's Disease. *Nat Rev Neurol.* 2024;20(7):426-439.

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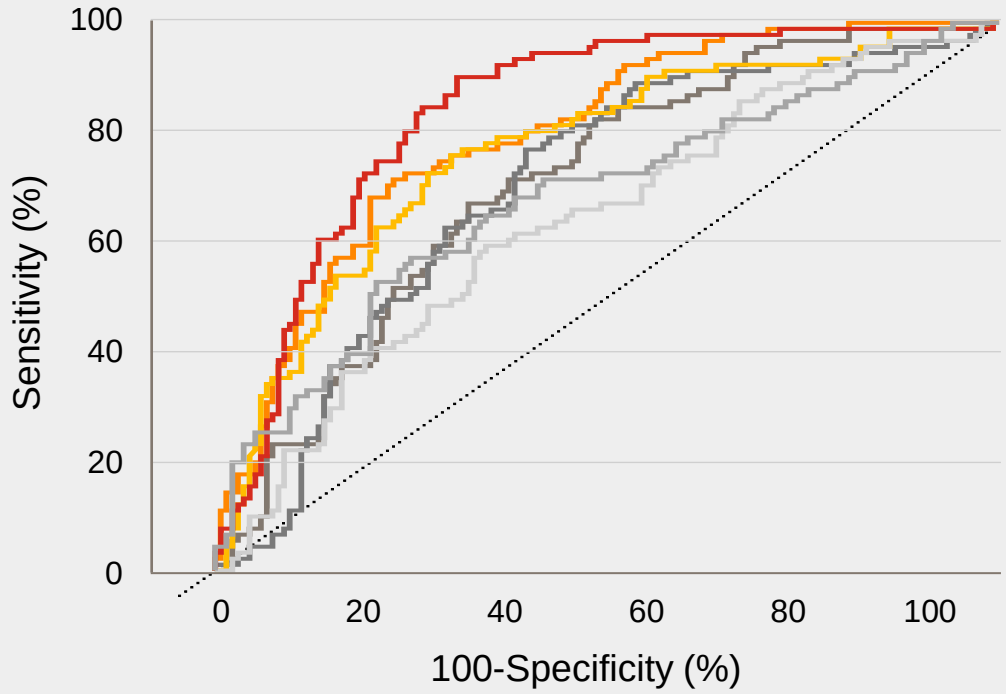
Plasma Biomarkers of Amyloid-Beta (Aβ) Pathology

The Aβ42/40 ratio

Comparison of Key Plasma Aβ42/Aβ40 Assays

ROC curve analysis for differentiating participants with abnormal and normal CSF Aβ42/40[1,*]



Plasma Aβ42/40 assays

- IP-MS-WashU: AUC, 0.84
- IA-Elc: AUC, 0.80
- LC-MS-Arc: AUC, 0.76
- IA-N4PE: AUC, 0.71
- IA-EI: AUC, 0.70
- IP-MS-UGOT: AUC, 0.68
- IA-Quan: AUC, 0.64

IP-MS-WashU had the highest discriminative accuracy.[1]

Findings may inform future clinical use of blood tests for Aβ pathology in AD.[1]

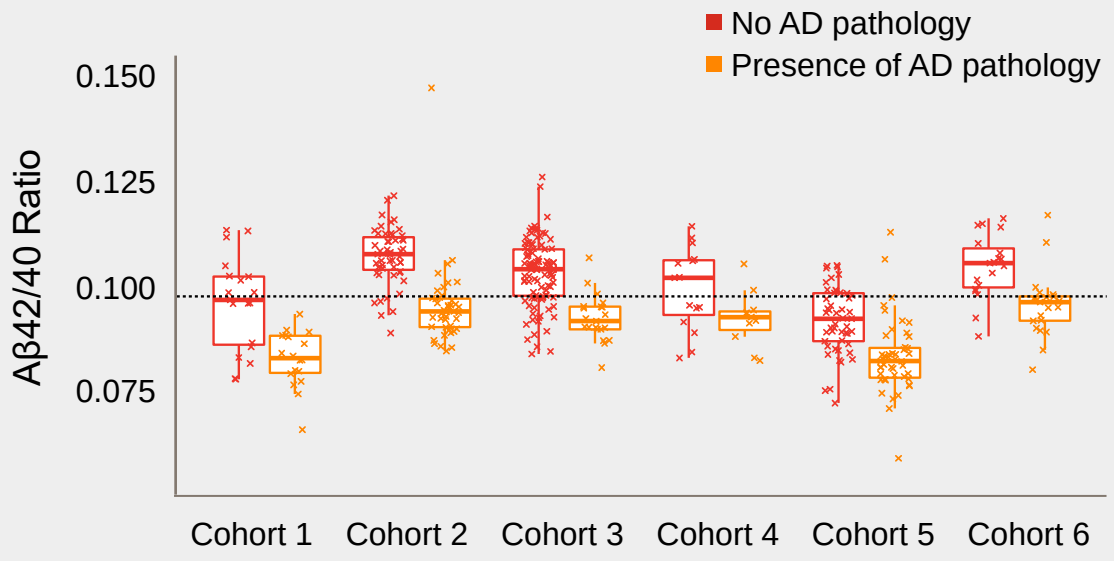
Modified from: Janelidze S, et al. *JAMA Neurol.* 2021[1]

*Analysis in the subcohorts where IPMS-UGOT and IA-Quan Aβ42/40 were available (n=227). The cutoff for abnormal CSF Aβ42/40 was 0.0597.
Aβ=Amyloid-Beta; AD=Alzheimer's Disease; AUC=Area Under the Curve; CSF=Cerebrospinal Fluid; IA-EI=Immunoassay from Euroimmun; IA-Elc=Elecsys Immunoassay from Roche Diagnostics; IA-N4PE=Neurology 4-Plex E Simoa Immunoassay from Quanterix; IA-Quan=Immunoassay from Quanterix; IP-MS-UGOT=Immunoprecipitation-Mass Spectrometry–based Method from the University of Gothenburg; IP-MS-WashU=Immunoprecipitation-Coupled Mass Spectrometry Method from Washington University; LC-MS-Arc=Antibody-Free Liquid Chromatography-Mass Spectrometry Method from Araclon; ROC=Receiver Operating Characteristic.
1. Janelidze S, et al. Head-to-Head Comparison of 8 Plasma Amyloid-β 42/40 Assays in Alzheimer Disease. *JAMA Neurol.* 2021;78(11):1375-1382. Erratum in: *JAMA Neurol.* 2023;80(4):422.

Levels of Plasma Aβ42/40 Ratio in Alzheimer's Disease

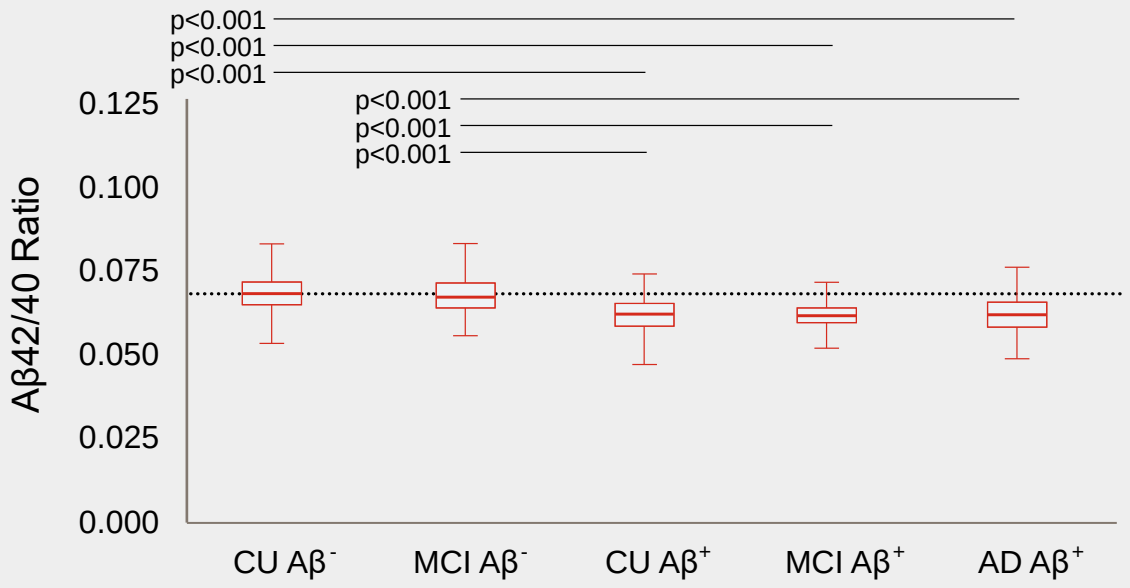
- Similar to other plasma Aβ studies, plasma Aβ42/40 showed a decrease of only ~10-20% in AD (compared to ~40-60% in CSF).[1-3]
- This may affect accuracy using a single cutoff over time and in different populations.[2,3]

Scatter-Box-Whisker plot of plasma Aβ42/40 for brain amyloid negative or positive status[4,*]



Modified from: West T, et al. *Mol Neurodegener.* 2021[4]

Boxplot of plasma Aβ42/40 stratified by CU, MCI, and AD Aβ status[1]



Modified from: Palmqvist S, et al. *JAMA Neurol.* 2019[1]

*Banked plasma samples were collected from six independent cohorts (N=37, 94, 121, 26, 96, 40 for Cohorts 1-6, respectively). Plasma $A\beta_{42/40}$ ratios are separated by brain amyloid status.
Aβ=Amyloid-Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; CU=Cognitively Unimpaired; MCI=Mild Cognitive Impairment.

1. Palmqvist S, et al. Performance of Fully Automated Plasma Assays as Screening Tests for Alzheimer Disease-Related β-Amyloid Status. *JAMA Neurol.* 2019;76(9):1060-1069. 2. Hansson O. Biomarkers for Neurodegenerative Diseases. *Nat Med.* 2021;27(6):954-963. 3. Brand AL, et al. The Performance of Plasma Amyloid Beta Measurements in Identifying Amyloid Plaques in Alzheimer's Disease: A Literature Review. *Alzheimers Res Ther.* 2022;14(1):195. 4. West T, et al. A Blood-Based Diagnostic Test Incorporating Plasma Aβ42/40 Ratio, ApoE Proteotype, and Age Accurately Identifies Brain Amyloid Status: Findings from a Multi Cohort Validity Analysis. *Mol Neurodegener.* 2021;16(1):30.

Blood Biomarkers as Indicators of Neurodegeneration

Neurofilament Light Chain

Lilly

Plasma NfL in Differential Diagnosis

NfL as plasma biomarker

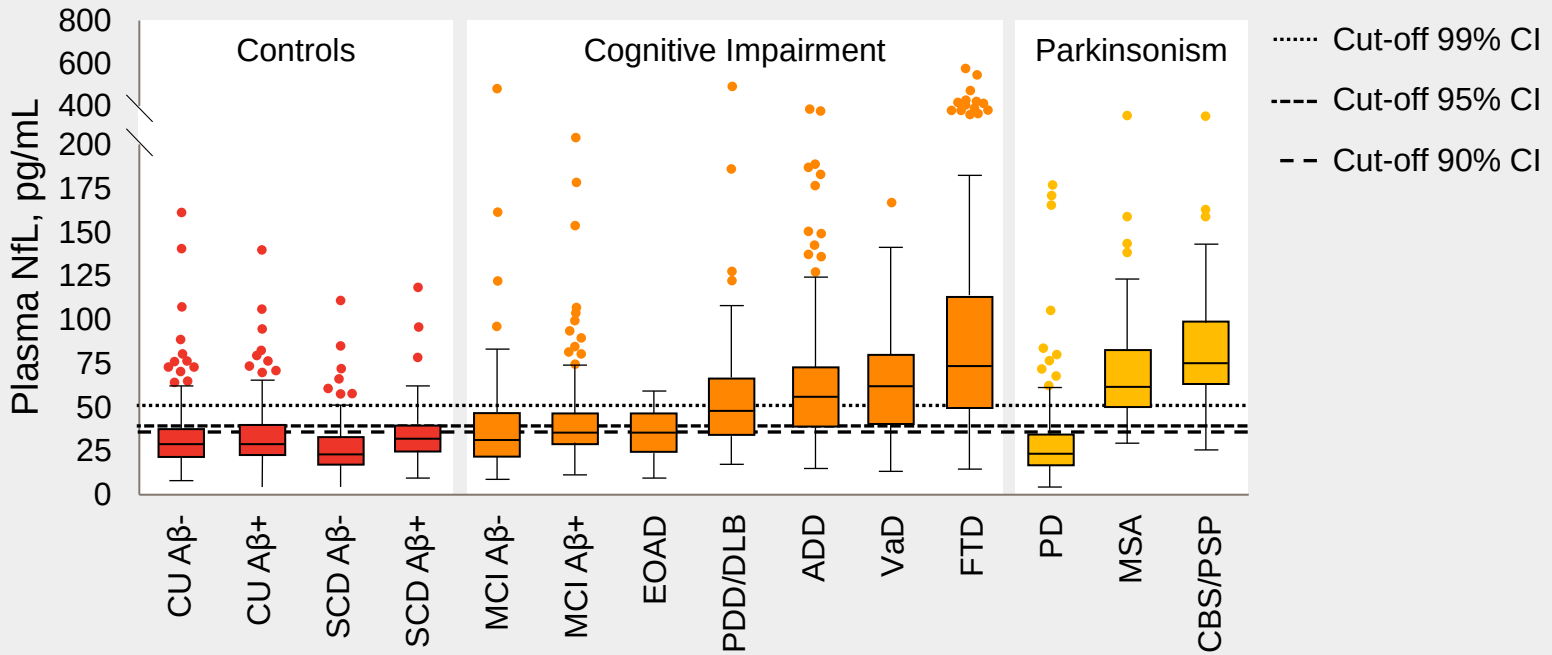
Not specific to AD[1]

Increase due to both central nervous system and peripheral neuronal injury[2-4]

Cannot be used to rule out a neurodegenerative disease[1,4]

Probably of most interest in the differential diagnosis of atypical PD disorders and FTD[1,4]

Plasma NfL concentrations for different diagnostic and control groups[1,*]



Modified from: Ashton NJ, et al. *Nat Commun*. 2021[1]

*Analysis from samples from the Lund cohort. This cohort consisted of 1464 participants enrolled as part of the prospective and longitudinal Swedish BioFINDER study (clinical trial no. NCT01208675).
Aβ=Amyloid-Beta; AD=Alzheimer's Disease; ADD=Alzheimer's Disease Dementia; CBS=Corticobasal Syndrome; CI=Confidence Interval; CU=Cognitively Unimpaired; DLB=Dementia with Lewy Bodies; EOAD=Early-onset Alzheimer's Disease; FTD=Frontotemporal Dementia; MCI=Mild Cognitive Impairment; MSA=Multiple System Atrophy; NfL=Neurofilament Light Chain; PD=Parkinson's Disease; PDD=Parkinson's Disease Dementia; PSP=Progressive Supranuclear Palsy; SCD=Subjective Cognitive Decline; VaD=Vascular Dementia.

1. Ashton NJ, et al. A Multicentre Validation Study of the Diagnostic Value of Plasma Neurofilament Light. *Nat Commun*. 2021;12(1):3400. 2. Ashton NJ, et al. Increased Plasma Neurofilament Light Chain Concentration Correlates With Severity of Post-Mortem Neurofibrillary Tangle Pathology and Neurodegeneration. *Acta Neuropathol Commun*. 2019;7(1):5. 3. Ferreira-Atuesta C, et al. The Evolution of Neurofilament Light Chain in Multiple Sclerosis. *Front Neurosci*. 2021;15:642384. 4. Barro C, et al. Blood Neurofilament Light: A Critical Review of Its Application to Neurologic Disease. *Ann Clin Transl Neurol*. 2020;7(12):2508-2523.

Blood Biomarkers For Tau

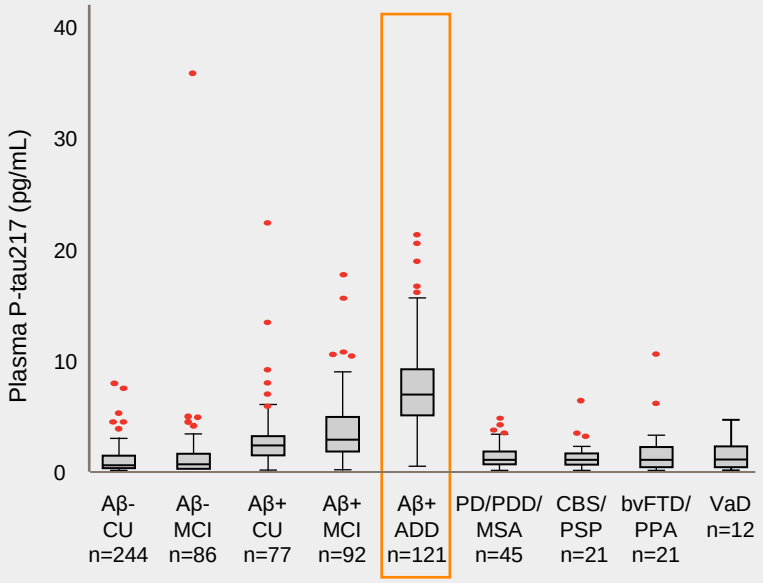
Focusing on plasma phosphorylated-tau

Lilly

Discriminative Accuracy of Plasma P-tau217 and P-tau181 for AD vs. Other Neurodegenerative Disorders

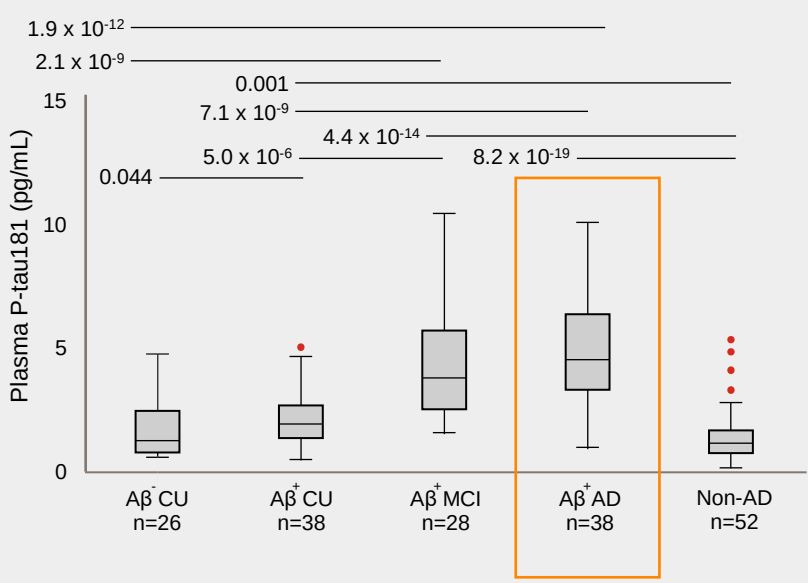
Levels of P-tau isoforms in plasma across diagnostic groups

Plasma P-tau217[1]



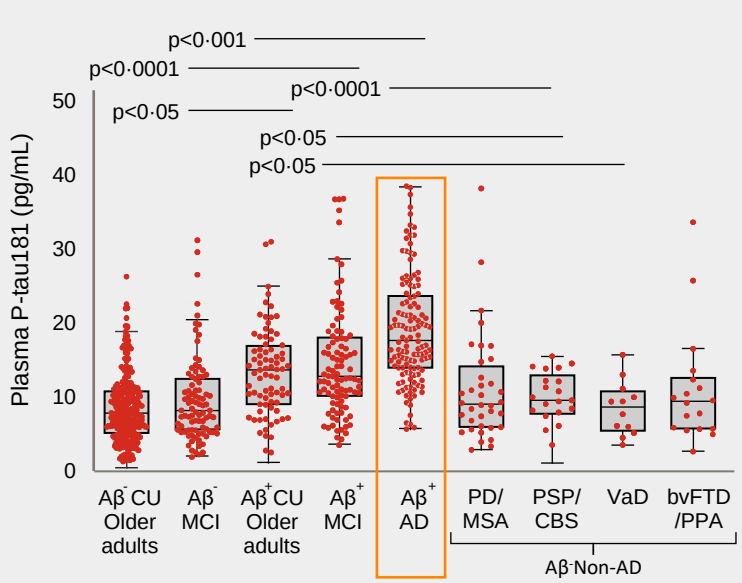
Modified from: Palmqvist S, et al. *JAMA*. 2020[1]

Plasma P-tau181[2]



Modified from: Janelidze, et al. *Nat Med*. 2020[2]

Plasma P-tau181[3]



Modified from: Karikari TK, et al. *Lancet Neurol*. 2020[3]

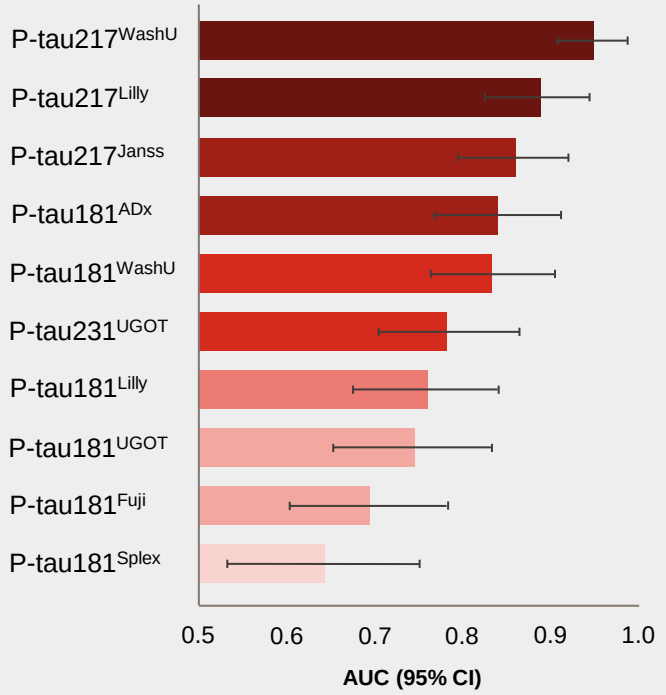
Also shown by Thijssen EH, et al. (*Lancet Neurol. 2021*)[4], among others.

Aβ=Amyloid-Beta; AD=Alzheimer's Disease; ADD=Alzheimer's Disease Dementia; bvFTD=Behavioral Variant Frontotemporal Dementia; CBS=Corticobasal Syndrome; CU=Cognitively Unimpaired; MCI=Mild Cognitive Impairment; MSA=Multiple Systems Atrophy; PD=Parkinson's Disease; PDD=Parkinson's Disease Dementia; PPA=Primary Progressive Aphasia; PSP=Progressive Supranuclear Palsy; P-tau=Phosphorylated tau; VaD=Vascular Dementia.

1. Palmqvist S, et al. Discriminative Accuracy of Plasma Phospho-Tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. *JAMA*. 2020;324(8):772-781. 2. Janelidze S, et al. Plasma P-tau181 in Alzheimer's Disease: Relationship to Other Biomarkers, Differential Diagnosis, Neuropathology and Longitudinal Progression to Alzheimer's Dementia. *Nat Med*. 2020;26(3):379-386. 3. Karikari TK, et al. Blood Phosphorylated Tau 181 as a Biomarker for Alzheimer's Disease: a Diagnostic Performance and Prediction Modelling Study Using Data from Four Prospective Cohorts. *Lancet Neurol*. 2020;19(5):422-433. 4. Thijssen EH, et al. Plasma Phosphorylated Tau 217 and Phosphorylated Tau 181 as Biomarkers in Alzheimer's Disease and Frontotemporal Lobar Degeneration: A Retrospective Diagnostic Performance Study. *Lancet Neurol*. 2021;20(9):739-752. Erratum in: *Lancet Neurol*. 2021;20(10):e6.

Head-to-Head Comparison of Plasma P-tau Assays

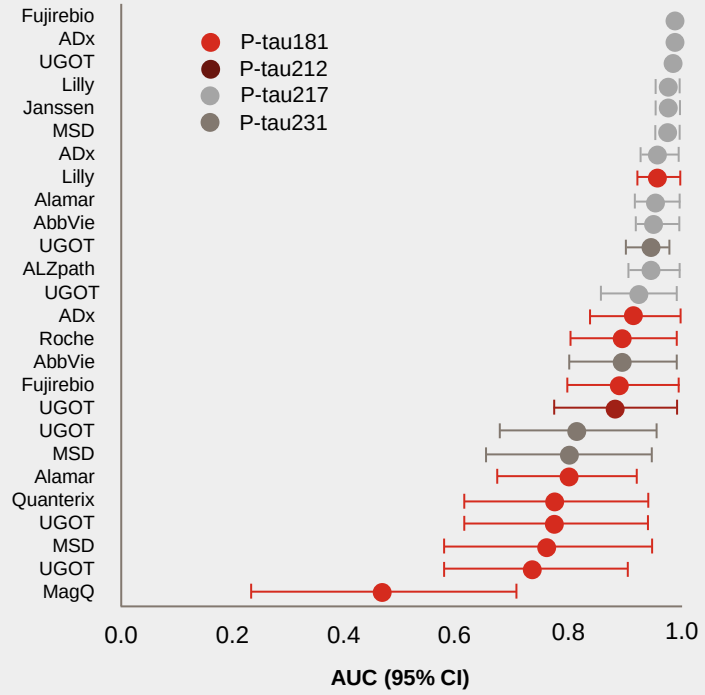
ROC curve analysis for abnormal CSF Aβ42/40 status in participants with MCI[1,*]



Modified from: Janelidze S, et al. *Brain.* 2023[1]

Global Biomarker Standardization Consortium plasma P-tau study[2,#]

ROC analysis for AD positivity according to CSF amyloid status



Modified from: Ashton N, et al. Presented at CTAD 2023[2]

P-tau217 is the top performer[1,2]

Both mass spectrometry and immunoassays perform well[1,2]

Works well on scalable/ fully automated platforms[1,2]

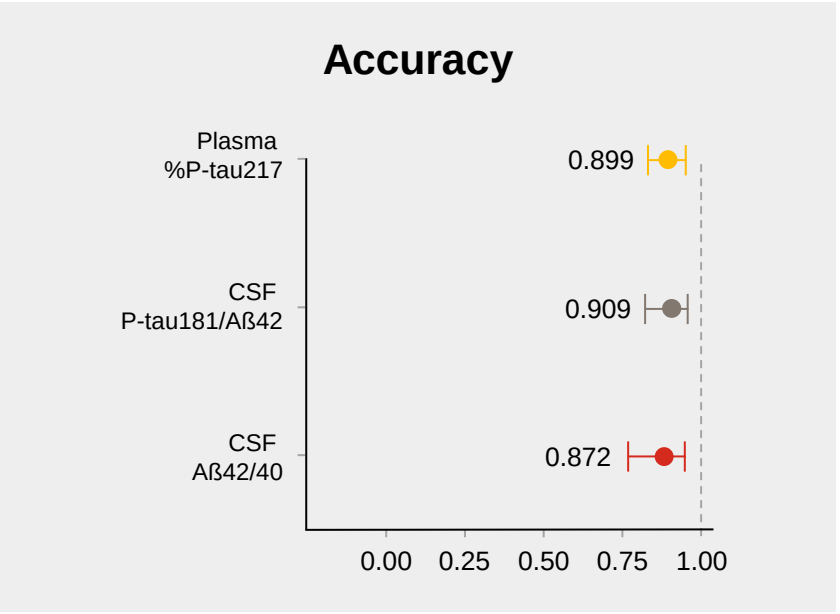
*ROC analysis of 135 participants for ROC differentiating MCI participants with abnormal CSF Aβ42/40 from those with normal CSF Aβ42/40. #Round-robin analysis of 40 plasma samples.
Aβ=Amyloid-Beta; AD=Alzheimer's Disease; AUC=Area Under the Curve; CI=Confidence Interval; CSF=Cerebrospinal Fluid; MCI=Mild Cognitive Impairment; P-tau=Phosphorylated tau; ROC=Receiver Operating Characteristic.

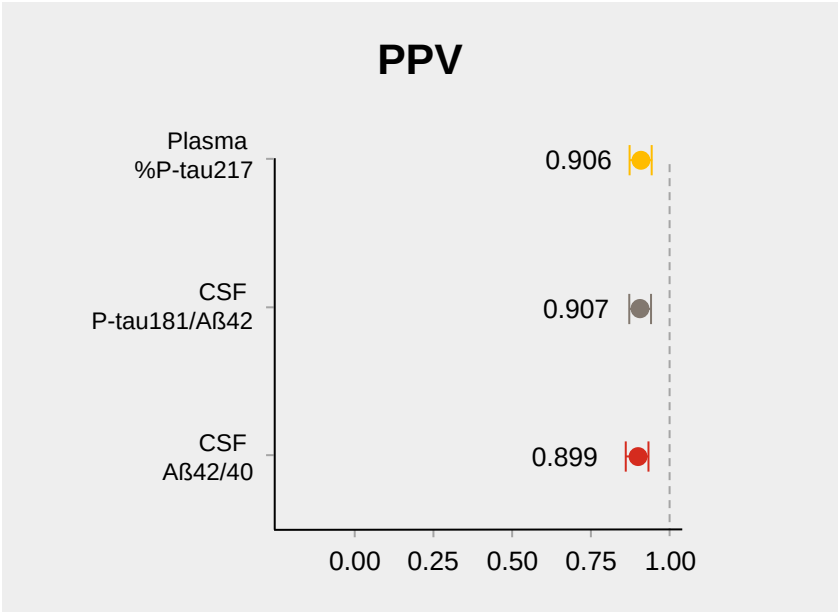
1. Janelidze S, et al. Head-to-Head Comparison of 10 Plasma Phospho-Tau Assays in Prodromal Alzheimer's Disease. *Brain.* 2023;146(4);1592-1601. 2. Ashton N, et al. The Alzheimer's Association Global Biomarker Standardisation Consortium (GBSC) Plasma Phospho-Tau Round Robin Study. Presented at CTAD 2023. Boston, MA, USA. October 24-27, 2023. Retrieved from AlzForum Conference Series Clinical Trials on Alzheimer's Disease (CTAD) 2023, Part 11: Plasma P-Tau-217 Assays Work Well, But No Home Run for Diagnosis. Available from: https://www.alzforum.org/news/conference-coverage/plasma-p-tau-217-assays-work-well-no-home-run-diagnosis. Accessed February 2025.

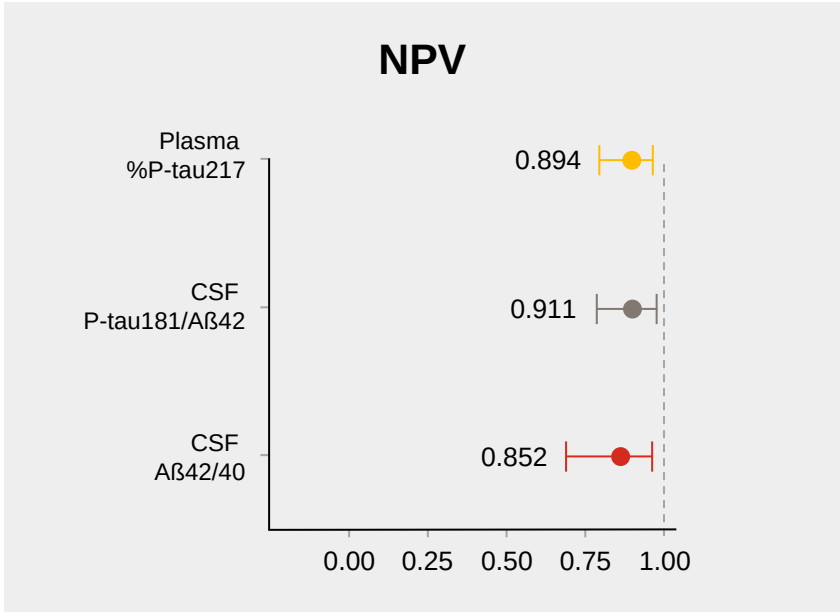
Comparison Between Plasma P-tau217 and CSF Biomarkers in Secondary Care

%P-tau217 vs CSF tests to predict amyloid-PET status in cognitively impaired patients[1,*]

Cutoff (predefined) set at a specificity of 90%[1]







1. Barthélemy NR, et al. *Nat Med.* 2024[1]

Use of high-performance blood tests in clinical practice can provide similar accuracy as CSF biomarkers[1]

*Analysis with 304 participants in secondary care as part of the BIOFINDER-2 cohort. P-tau217 was measured using %P-tau217: P-tau217/not-phosphorylated-tau217 ratio.
Aβ=Amyloid-Beta; CSF=Cerebrospinal Fluid; NPV=Negative Predictive Value; P-tau=Phosphorylated tau; PET=Positron Emission Tomography; PPV=Positive Predictive Value.
1. Barthélemy NR, et al. Highly Accurate Blood Test for Alzheimer's Disease Is Similar or Superior to Clinical Cerebrospinal Fluid Tests. *Nat Med.* 2024;30(4):1085-1095.

Comparison of Diagnostic Accuracy between High-performing Blood Test and Physicians[1]

Overview of clinical process

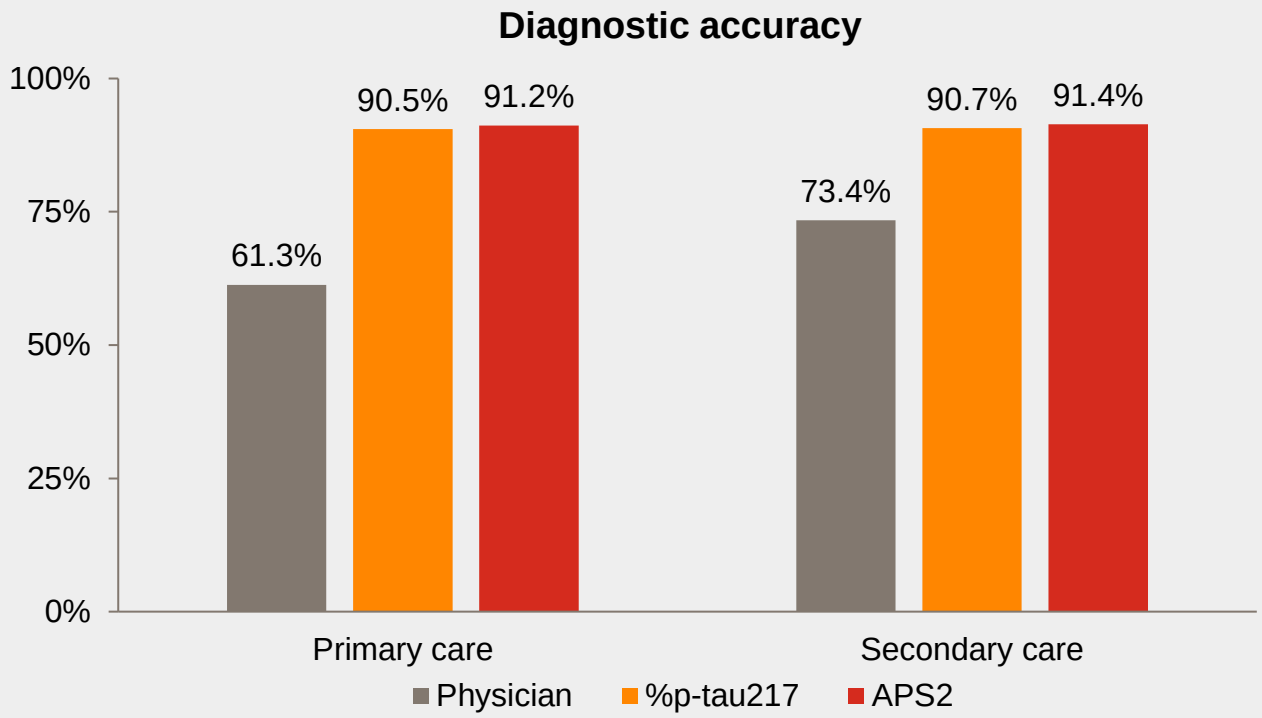
Standard clinical evaluation without AD biomarkers

PCP (primary care) or dementia specialists (secondary care) record the clinical diagnosis

Further evaluation including CSF/PET AD biomarkers

Clinical consensus diagnosis by dementia specialist and neuro-psychologist incl. CSF/PET, but not BBM, information (outcome)

Outcome: clinical biomarker-verified AD diagnosis*



Modified from Palmqvist S, et al. *JAMA*. 2024[1]

*Predefined blood test cutoffs were used. Plasma samples were sent bi-weekly for continuous and prospective analysis. %p-tau217 is a ratio of p-tau217 and non-p-tau217. APS2 or Amyloid Probability Score-2 is a predefined combination of plasma %p-tau217 and plasma Aβ42/40 ratio.

Aβ=Amyloid Beta; AD=Alzheimer's Disease; APS2=Amyloid Probability Score 2; BBM=Blood-based Biomarker; CSF=Cerebrospinal Fluid; p-tau=Phosphorylated Tau; PCP=Primary Care Physician; PET=Positron Emission Tomography.

1. Palmqvist S, et al. Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care. *JAMA*. 2024;332(15):1245–1257. Incl. Supplement.

Blood-Based Biomarkers in AD: What Needs to Be Done Before Clinical Implementation?

The Alzheimer's Association appropriate use recommendations for BBMs in AD:[1]

- **To determine** "clinical robustness in a real-world setting in prospective studies where
  (1) pre-defined cutoffs are used
  (2) samples are analyzed continuously over the study period"

- **To perform** "prospective studies in primary care settings, including representative and diverse populations with cognitive symptoms"

- **To evaluate** "BBMs in diverse (real-life) memory clinic populations prospectively using predefined cutoffs"

Perform the above using high-quality reference standard (CSF or PET)

AD=Alzheimer's Disease; BBM=Blood-Based Biomarker; CSF=Cerebrospinal Fluid; PET=Positron Emission Tomography.

1. Hansson O, et al. The Alzheimer's Association Appropriate Use Recommendations for Blood Biomarkers in Alzheimer's Disease. *Alzheimers Dement.* 2022;18(12):2669-2686.

Case – Blood-Based Biomarkers

80-year-old woman

Newly widowed, living alone, sees son bi-weekly

Cognitive symptoms (started 2-3 years ago):

- reduced initiative
- poorer memory
- trouble finding the right words
- increased anxiety, easily stressed

This case presentation discusses Dr. Sebastian Palmqvist's professional experience. Individual results might vary, and the experience discussed may not reflect the results seen in all patients.

Case - Work-up in Primary Care

MMSE 28/30 points

Routine blood tests did not find **any secondary causes**

CT scan

- Moderate to severe white matter lesions (Fazekas 2-3)
- Moderate hippocampal atrophy (MTA score 2)

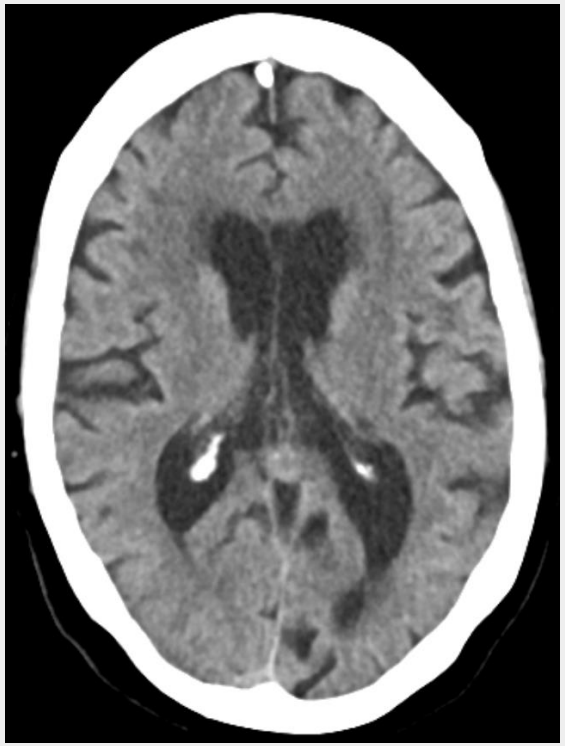
Assessment by PCP

- **Cognitive stage:** SCD (or possibly MCI)
- **Etiology:** Vascular pathology (8 out of 10 in certainty)

Plan

- Initiate cardiovascular treatment
- Follow-up in primary care

CT scan



CT=Computed Tomography; MCI=Mild Cognitive Impairment; MMSE=Mini-Mental State Examination; MTA=Medial Temporal Lobe Atrophy Score; PCP=Primary Care Physician; SCD=Subjective Cognitive Decline.
This case presentation discusses Dr. Sebastian Palmqvist's professional experience. Individual results might vary, and the experience discussed may not reflect the results seen in all patients.
Image provided by the speaker.

Case – Further Investigation at Our Memory Clinic

PrecivityAD2 test	**Positive**
APS2	**98**/100 (<18 negative, 18-37 intermediate)
%P-tau217	**4.52** (reference <2.4)
Aβ42/40	**0.096** (reference <0.089)
P-tau217 (Lumipulse)	**0.56** pg/mL (reference <0.27 pg/mL)* – not shown to the PCP

Re-evaluation by PCP

Cognitive stage
SCD (or possibly MCI)

Etiology
AD (9 out of 10 in certainty)

Plan

Initiate cardiovascular treatment

Refer to our memory clinic

*Locally determined cutoffs; cutoffs may vary from one laboratory to another.
Aβ=Amyloid-Beta; AD=Alzheimer's Disease; APS2=Amyloid Probability Score 2; MCI=Mild Cognitive Impairment; P-tau=Phosphorylated tau; PCP=Primary Care Physician; SCD=Subjective Cognitive Decline.
This case presentation discusses Dr. Sebastian Palmqvist's professional experience. Individual results might vary, and the experience discussed may not reflect the results seen in all patients.

Case – Further Investigation at Our Memory Clinic

In-depth ADL interview

Lack of initiative → not shopping for groceries in time → no food at home → son now responsible for grocery shopping

Procrastinates in addressing invoices and administrative tasks → son taking over these responsibilities

Additional cognitive testing

ADAS cog 10-word delayed recall: **2**/10 correct

RBANS 10-word delayed recall: **0**/10 correct

TMT A: **50** sec (normal for age)

TMT B: **Cannot complete**

BNT-15: **6**/15 correct namings (abnormal)

ADAS=Alzheimer's Disease Assessment Scale; ADL=Activities of Daily Living; BNT-15=Boston Naming Test 15; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; TMT=Trail Making Test.

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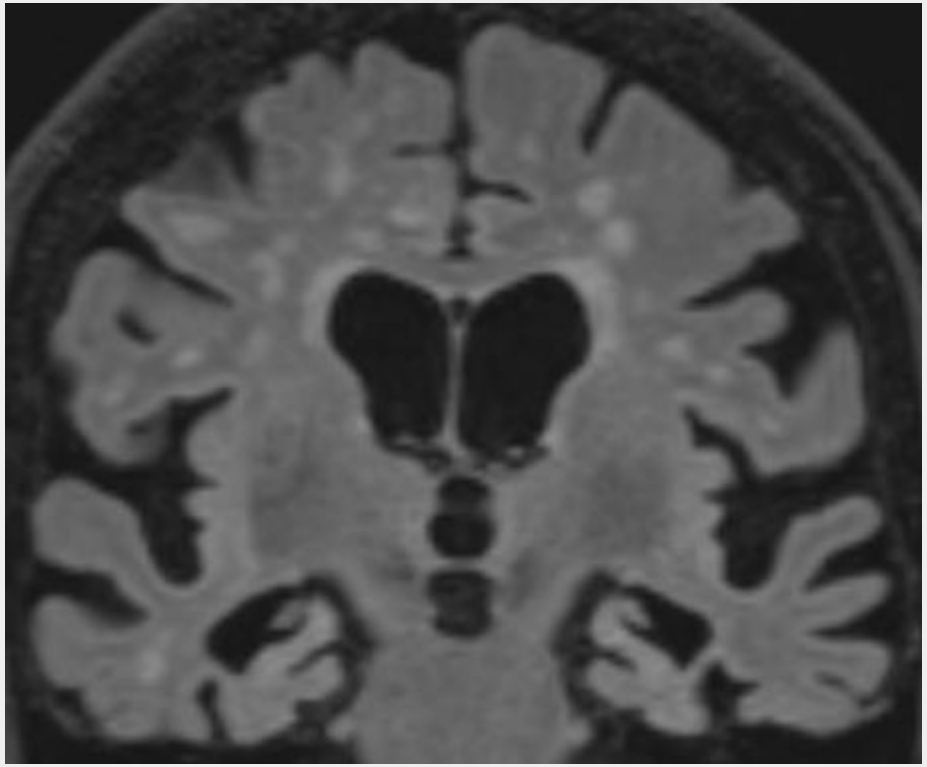
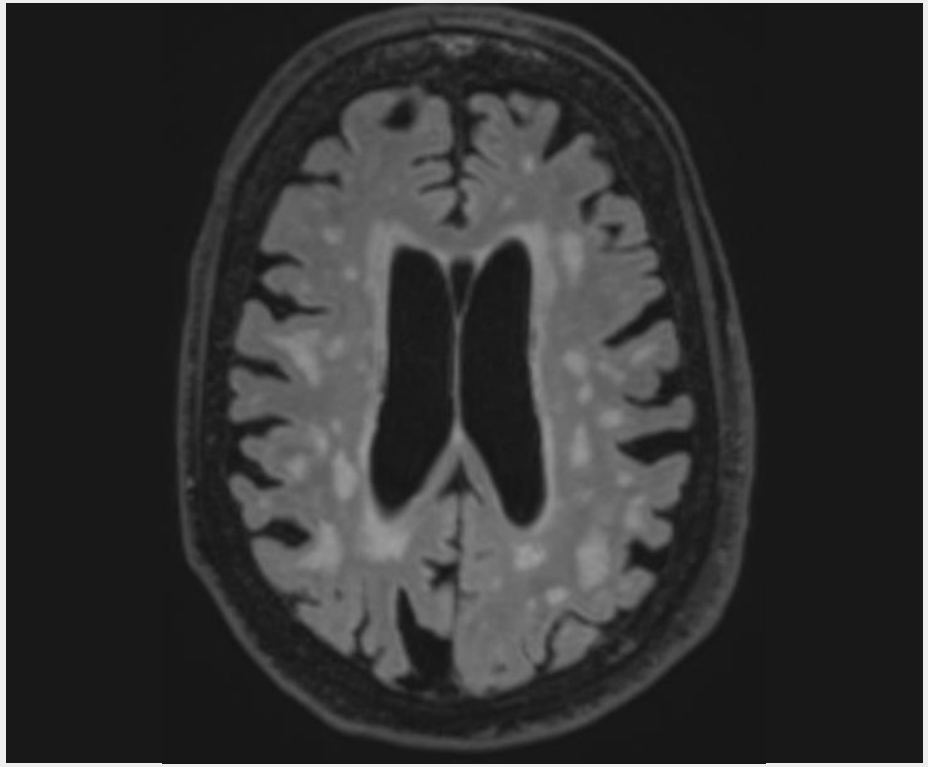
Case – MRI

MRI frontal view



MRI transversal view



MRI=Magnetic Resonance Imaging.
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Images provided by the speaker.

Case – CSF analysis (Fujirebio)

CSF Aβ42/40	**0.052** (reference <0.072)
CSF P-tau	**85 ng/L** (reference <50)*
CSF Aβ42/P-tau181	**6.4** (reference >15)*

Assessment by me

Cognitive stage: mild dementia (yes, despite an MMSE of 28)

Etiology: AD and vascular pathology (both are likely causing symptoms)

Plan

Initiated ChEI and shortly after that memantine

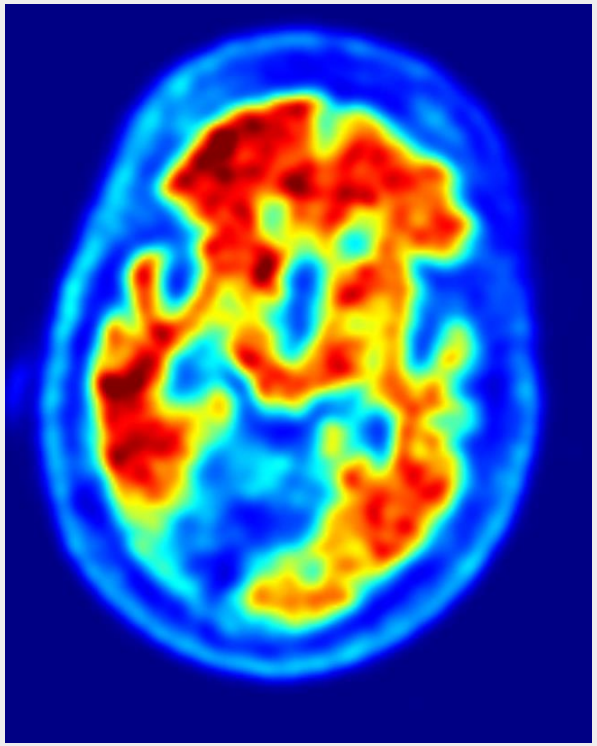
Initiated contacts with home care services and a nurse that delivered medication (was not taken correct)

6 months later
MMSE 24/30

*Locally determined cutoffs; cutoffs may vary from one laboratory to another.
Aβ=Amyloid-Beta; AD=Alzheimer's Disease; ChEI=Cholinesterase Inhibitors; CSF=Cerebrospinal Fluid; MMSE=Mini-Mental State Examination; P-Tau=Phosphorylated tau.
This case presentation discusses Dr. Sebastian Palmqvist's professional experience. Individual results might vary, and the experience discussed may not reflect the results seen in all patients.

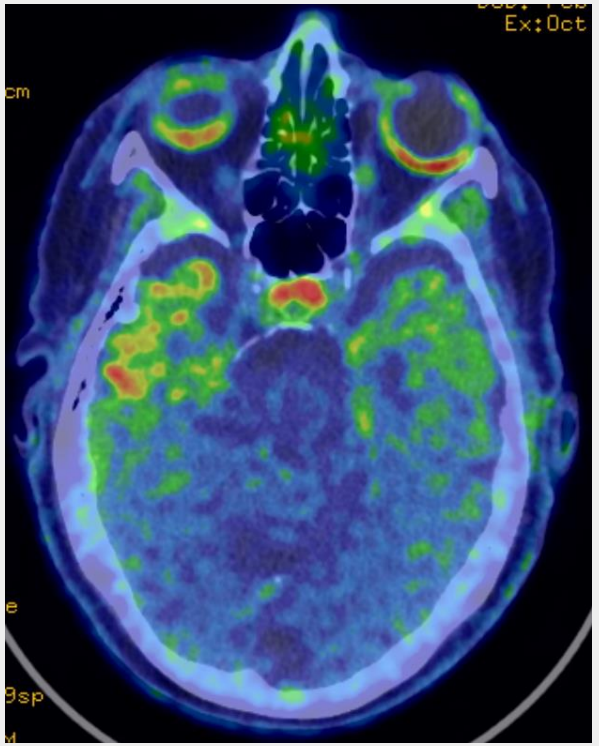
Case – Biomarker PET

Amyloid PET: positive



Radioligand: 18F-flutemetamol

Tau PET: increased uptake in the temporal lobes



Radioligand: 18F-RO948

PET=Positron Emission Tomography.

This case presentation discusses Dr. Sebastian Palmqvist's professional experience. Individual results might vary, and the experience discussed may not reflect the results seen in all patients.

Images provided by the speaker.

Takeaways

- BBMs (especially plasma P-tau217) are accurate for detecting AD pathology in individuals with cognitive symptoms.[1-3]
- Accuracy differs depending on the assay (many are now planned to be used in clinical practice).[1]
- Positive for AD pathology ≠ AD pathology causing the symptoms (clinical evaluation needed).[3,4]
- BBMs have the potential to aid in the diagnosis and selection of patients for referral.[2,3]
- Guidelines are needed (especially for use in primary care).[2,5,6]

AD=Alzheimer's Disease; BBM=Blood-Based Biomarker; P-tau=Phosphorylated tau.

1. Janelidze S, et al. Head-to-Head Comparison of 10 Plasma Phospho-Tau Assays in Prodromal Alzheimer's Disease. *Brain.* 2023;146(4);1592-1601. 2. Hampel H, et al. Blood-Based Biomarkers for Alzheimer's Disease: Current State and Future Use in a Transformed Global Healthcare Landscape. *Neuron.* 2023;111(18):2781-2799. 3. Hansson O, et al. Blood Biomarkers for Alzheimer's Disease in Clinical Practice and Trials. *Nat Aging.* 2023;3(5):506-519. 4. Brum WS, et al. A Two-Step Workflow Based on Plasma T-Tau217 to Screen for Amyloid β Positivity with Further Confirmatory Testing Only in Uncertain Cases. *Nat Aging.* 2023;3(9):1079-1090. 5. Hansson O, et al. The Alzheimer's Association Appropriate Use Recommendations for Blood Biomarkers in Alzheimer's Disease. *Alzheimers Dement.* 2022;18(12):2669-2686. 6. Hampel H, et al. Designing the Next-Generation Clinical Care Pathway for Alzheimer's Disease. *Nat Aging.* 2022;2(8):692-703.