Fluid biomarkers in Alzheimer’s disease

This content is intended for health care professionals only for educational and informational purposes and does not substitute for sound medical judgment or clinical decision making in the context of medical treatment

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Contents

PET, positron emission tomography

Measures of biomarker accuracies

Sensitivity is the proportion of people with disease X who have a positive test. **Specificity** is the proportion of people without disease X who have a negative test. Intrinsic power of the test: the ability to detect true-positive and true-negative results at a given cutoff and are not influenced by the disease prevalence.
Overall accuracy refers to the proportion of correctly classified patients among all patients.

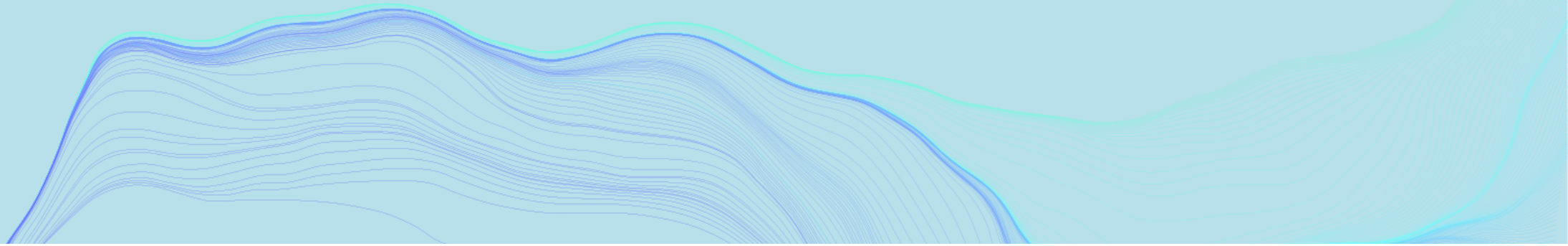
Receiver operating characteristic AUC is interpreted as the probability that a randomly chosen individual with a disease is rated or ranked as more likely to have the disease than a randomly chosen individual without the disease.
A value of 0.5 means the test has no better accuracy than random guessing, while a value of 1 reflects a perfectly accurate test. AUC is not impacted by cut-off values.

Positive predictive value (PPV) is the proportion of true-positive tests out of all positive test results, and **negative predictive value (NPV)** is the proportion of true-negative tests out of all negative tests.
Directly dependent on the prevalence rates of the disease within the specific context of use and patient population.

Hampel H, et al. Neuron. 2023 Jun 5:S0896-6273(23)00390-2. doi: 10.1016/j.neuron.2023.05.017. Epub ahead of print.

Learning Zone

Understanding AD fluid biomarkers



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NIA-AA research framework: 2018

BACKGROUND

In 2018, the NIA-AA updated and unified the 2011 guidelines:

- **Objective:** to update the scheme for defining and staging the disease across its entire spectrum with which the research community can communicate findings in a common manner
- This ‘research framework’ was intended for observational and interventional research use, not clinical care

FOCUS

- The research framework defines AD by its underlying pathophysiologic processes
- It regards AD as a **disease continuum** and focuses on diagnosis of AD with biomarkers in living persons, regardless of their symptoms

BIOMARKER CLASSIFICATION

- **The AT(N) classification** – the 2018 research framework identified three groups of biomarkers:
  - **A**: aggregated Aβ or associated pathological state
  - **T**: aggregated tau or associated pathological state
  - **N**: neurodegeneration or neuronal injury
- Each category can be quantified using a CSF and/or imaging biomarker:
  - **CSF biomarkers** are measures of protein concentrations in CSF from the lumbar sac that reflect the rates of production and clearance at a given point in time
  - **Imaging measures** represent the magnitude of the neuropathological load or damage accumulated over time

Aβ, amyloid beta; AD, Alzheimer’s disease; CSF, cerebrospinal fluid; NIA-AA, National Institute on Aging–Alzheimer's Association

1. Jack Jr CR, et al. Alzheimers Dement 2018;14:535–562

NIA-AA research framework AT(N) biomarker criteria for the identification of individuals with AD pathologic change

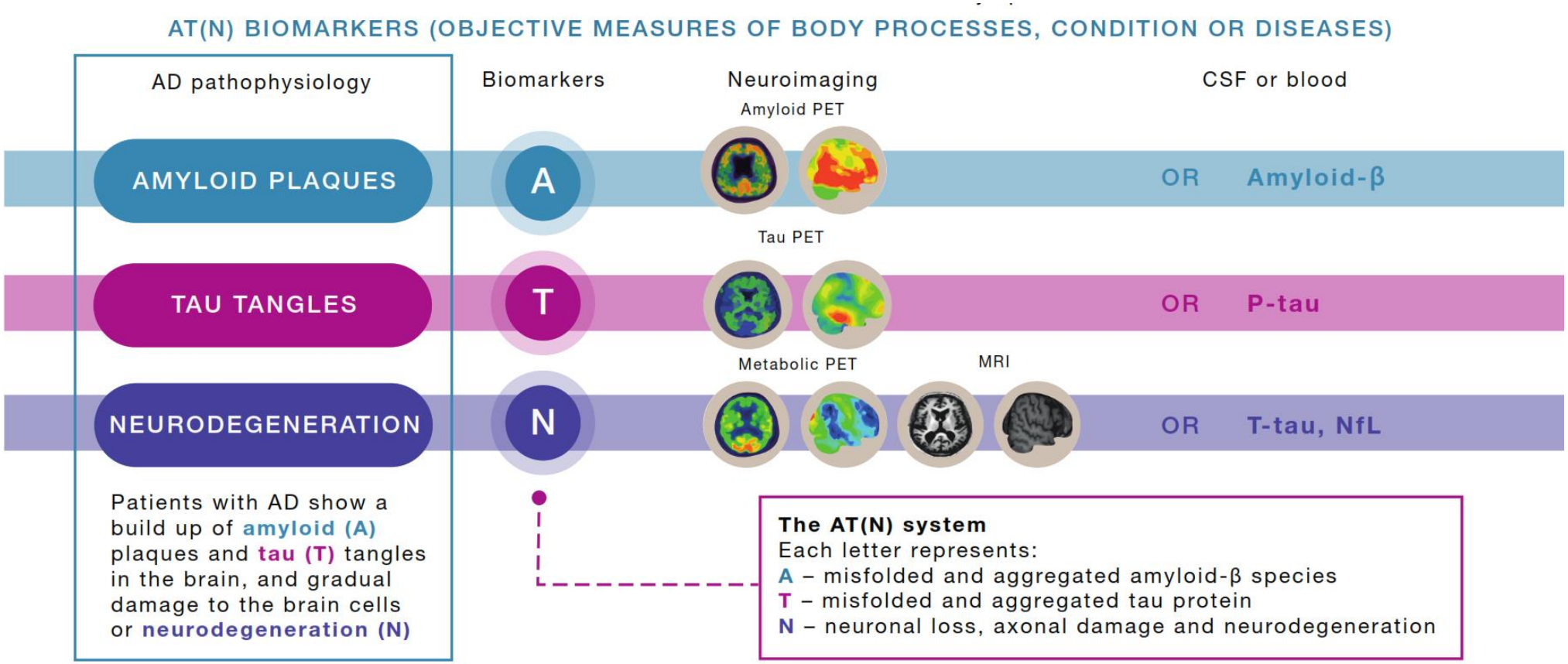

Figure used with permission from Jack CR Jr, et al. Alzheimers Dement 2018;14:535–562 (CC-BY 4.0; https://creativecommons.org/licenses/by-nc-nd/4.0/)

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging and Alzheimer's Association; p-tau, phosphorylated-tau; PET, positron emission tomography; t-tau, total-tau

Jack CR Jr, et al. Alzheimers Dement 2018;14:535–562

NIA-AA research framework defines Alzheimer's disease as a pathologic change irrespective of clinical syndrome

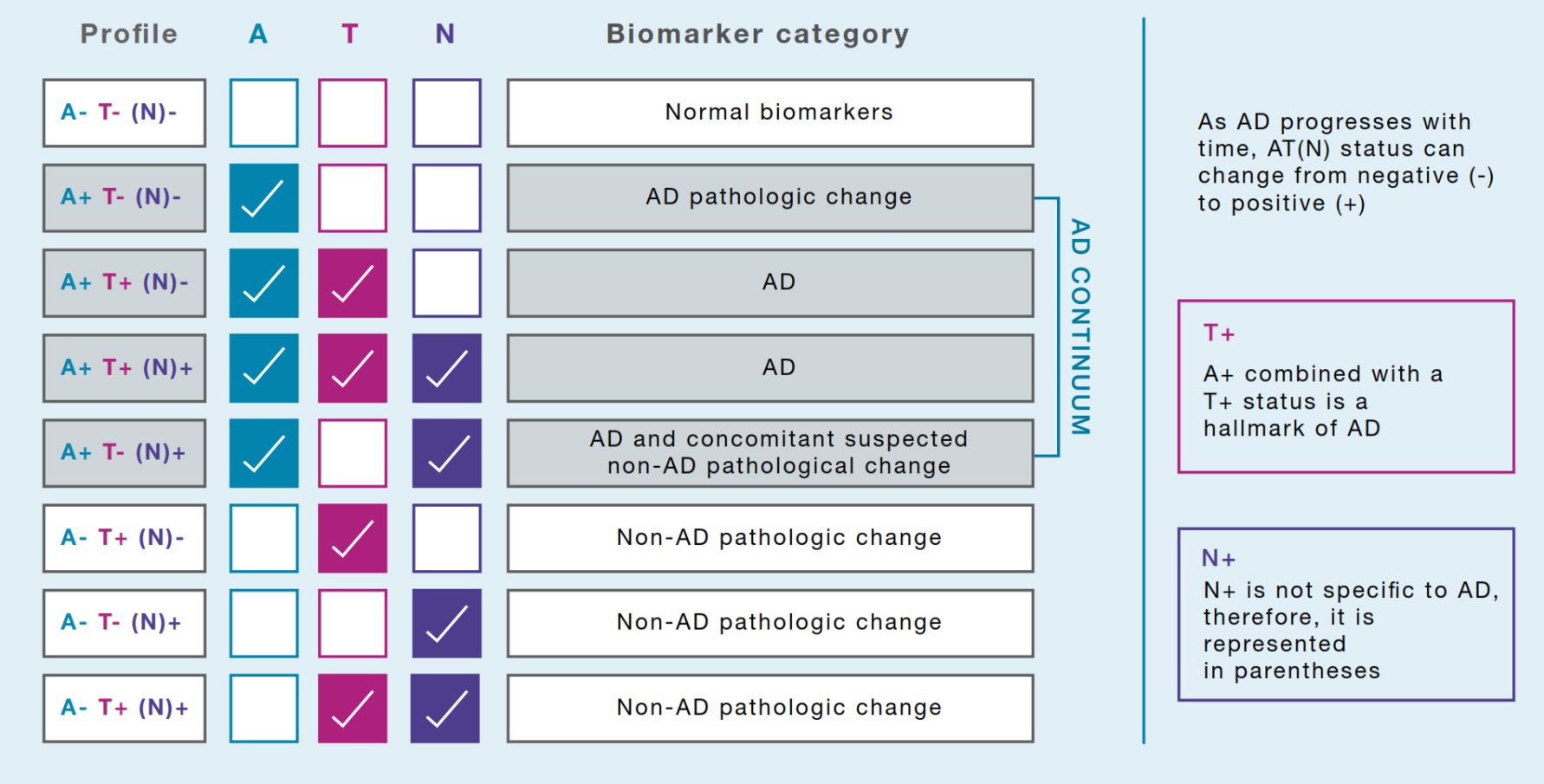

Table reprinted with permission from Jack CR Jr, et al. Alzheimers Dement 2018;14:535–562 (CC-BY 4.0: http://creativecommons.org/licenses/by/4.0)
AD, Alzheimer's disease; NIA-AA, National Institute on Aging—Alzheimer's Association
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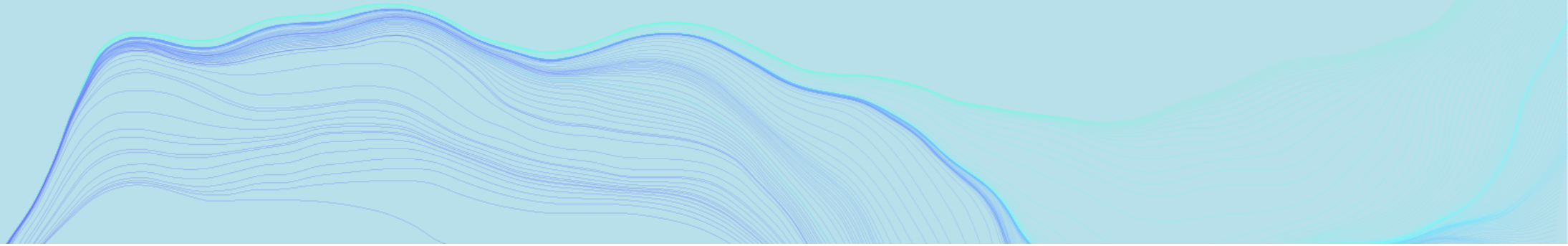
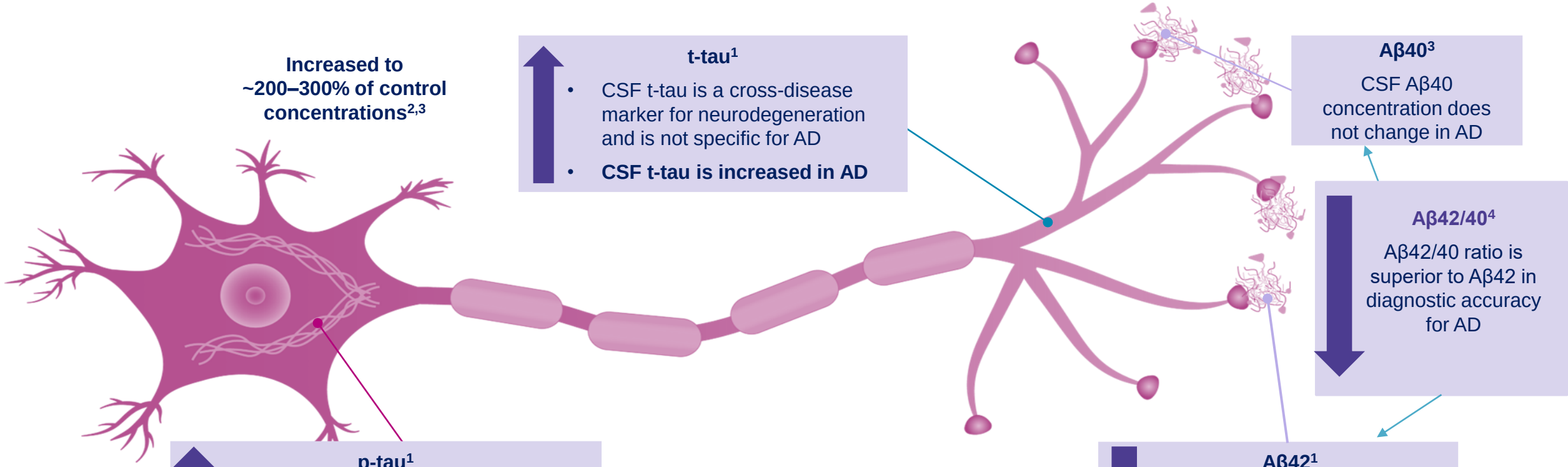
Learning Zone

CSF biomarkers in AD



CSF biomarkers in AD



Increased to ~200–300% of control concentrations[2,3]

t-tau[1]

- CSF t-tau is a cross-disease marker for neurodegeneration and is not specific for AD
- **CSF t-tau is increased in AD**

Aβ40[3]

CSF Aβ40 concentration does not change in AD

Aβ42/40[4]

Aβ42/40 ratio is superior to Aβ42 in diagnostic accuracy for AD

Increased to ~200% of control concentrations[2,3]

p-tau[1]

- CSF p-tau measures the amount of tau that is phosphorylated, a variant of tau found in tangles
- **CSF p-tau is increased in AD**

Reduced to ~50% of control concentrations[2,3]

Aβ42[1]

CSF Aβ42 is decreased in AD, reflecting the increased aggregation and deposition of amyloid plaques in the brain

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated-tau; t-tau, total-tau

1. Blennow K, Zetterberg H. J Intern Med 2018;284:643–663; 2. Blennow K, et al. Alzheimers Dement 2015;11:58–69; 3. Olsson B, et al. Lancet Neurol 2016;15:673–684; 4. Hansson O, et al. Alzheimers Res Ther 2019;11:34

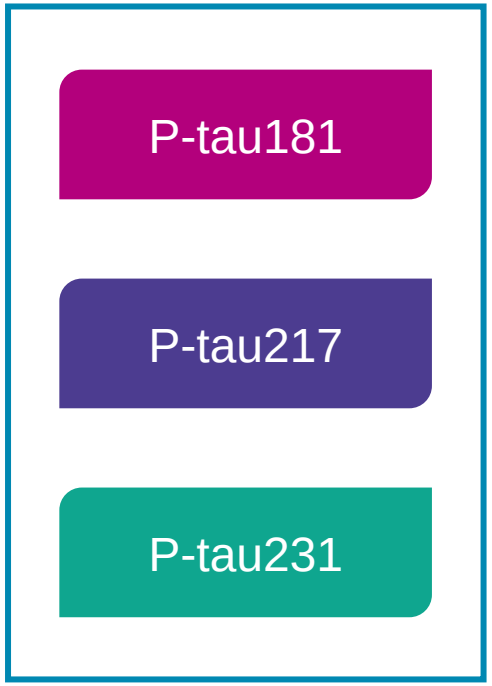
Core CSF biomarkers in AD

AD pathophysiology		Biomarker	Change in CSF concentrations compared with controls	Note
Amyloid plaque	↓	• Aβ42	• Decreased to ~50%[1,2]	A combination of biomarkers has been used to reduce methodological variance and increase diagnostic accuracy, such as p-tau/Aβ42 ratio and Aβ42/Aβ40[4,5]
	↓	• Aβ42/Aβ40	• Decreased to ~50%[3]	
Tau tangles	↑	• p-tau	• Increased to ~200%[1,2]	
Neurodegeneration	↑	• t-tau	• Increased to 250–300%[1,2]	

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated-tau; t-tau, total-tau

1. Blennow K, et al. Alzheimers Dement 2015;11:58–69; 2. Olsson B, et al. Lancet Neurol 2016;15:673–684; 3. Ovod V, et al. Alzheimers Dement. 2017;13(8):841–849; 4. Hansson O, et al. Alzheimers Dement 2018;14:1470–1481; 5. Hansson O, et al. Alzheimers Dement 2018;14:1313–1333

CSF biomarkers: p-tau pathology markers



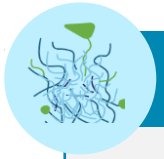
- **CSF p-tau biomarkers**, such as **p-tau181**, **p-tau217** and **p-tau231**, are increased in the early stages of AD (including preclinical AD and MCI), in response to emerging Aβ pathology[1–3]
  - One study observed that p-tau181 and p-tau217 were **highly specific for amyloid plaque pathology**[4]
  - Studies suggest that p-tau231 increases earliest, followed by p-tau217, then p-tau181[5]
- Studies have identified several p-tau isoform biomarkers that could accurately differentiate Aβ+ from Aβ− cognitively unimpaired individuals[1,2]
  - p-tau231 has also been shown to more accurately differentiate Aβ+ CU individuals from Aβ− CU individuals than CSF p-tau181 and CSF t-tau[1]

CSF p-tau biomarkers may be useful for identifying individuals in the very early stages of AD[1]

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; CU, cognitively unimpaired; GAP-43, growth-associated protein 43; GFAP, glial fibrillary activation protein; MCI, mild cognitive impairment; MCP-1, monocyte chemoattractant protein 1; NfL, neurofilament light chain; p-tau, phosphorylated tau; SNAP-25, synaptosomal-associated protein 25; sTREM2, soluble triggering receptor expressed on myeloid cells-2; t-tau, total tau; YKL-40, chitinase-3-like protein 1

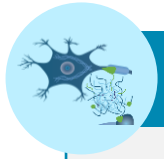
1.Suárez-Calvet M, et al. EMBO Mol Med 2020;12:e12921; 2. Karikari TK, et al. Alzheimers Dement 2021;17:755–767; 3.; Nabizadeh F, et al. Ann Indian acad Neurol 2022;25:845–851; 4. Barthélemy NR, et al. J Exp Med 2020;217:e20200861; 5. Hampel H, et al. Neuron 2023; S0896-6273(23)00390-2 [E-pub ahead of print]

The use of CSF biomarker ratios



Aβ42/40 ratio

- The concentration of Aβ42 in the CSF depends on the physiologic amyloid status and on the total amount of Aβ peptides[1]
- By normalizing to the concentration of Aβ40, the ratio adjusts for potential differences in Aβ production and provides a better index of underlying amyloid-related pathology[1,2]



Tau/Aβ42 ratios

- Tau/Aβ42 ratios combine measures of two pathological processes into a single diagnostic biomarker[3]
- The addition of t-tau or p-tau may also reduce the random error or variance observed with Aβ42 measurements alone[3]

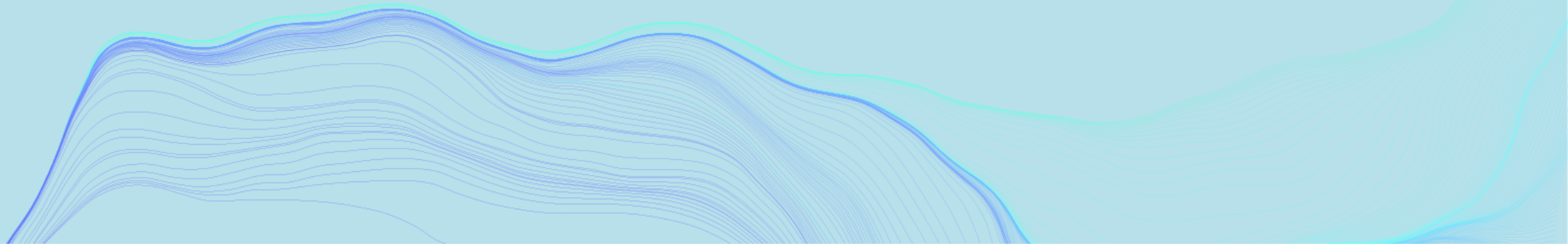
- CSF Aβ42/40, t-tau/Aβ42, and p-tau/Aβ42 ratios have been found:
  - To be more reliable than Aβ42 alone, and have stronger concordance with amyloid-PET[1–3]
  - To be less prone to methodological errors[1,2]
- Aβ42/40 cutoffs are almost identical, regardless of the type of assay used[1]

Aβ, amyloid beta; CSF, cerebrospinal fluid; PET, positive emission tomography; p-tau, phosphorylated-tau; t-tau, total-tau

1. Lewczuk P, et al. J Alzheimers Dis 2017;55:813–822; 2. Hansson O, et al. Alzheimers Res Ther 2019;11:34; 3. Hansson O, et al. Alzheimers Dement 2018;14:1470–1481; 4. Hansson O, et al. Alzheimers Dement 2018;14:1313–1333

Learning Zone

Emerging CSF biomarkers

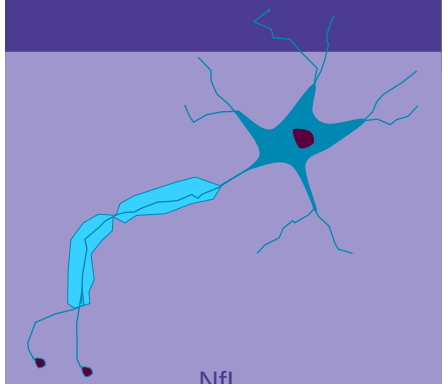


Summary of emerging CSF biomarkers

Emerging fluid biomarkers may complement core biomarkers for the diagnosis and prognosis of AD

Neurodegeneration

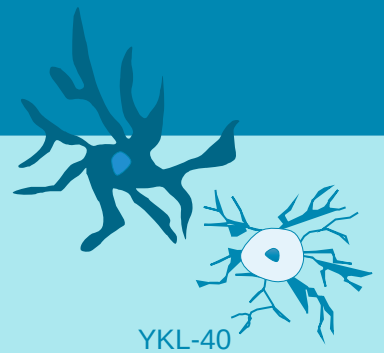
- Axon damage
- Membrane disruption
- Disruption of signaling



NfL

Neuroinflammation

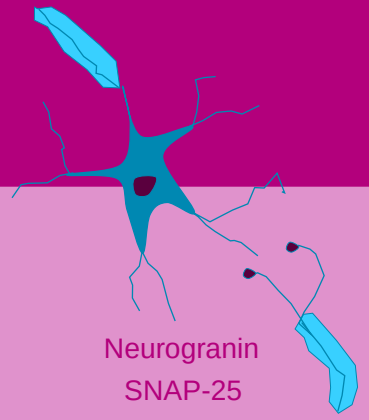
- Astrogliosis
- Microgliosis



YKL-40
GFAP
MCP-1
sTREM2

Synaptic dysfunction

- Disruption of synapse

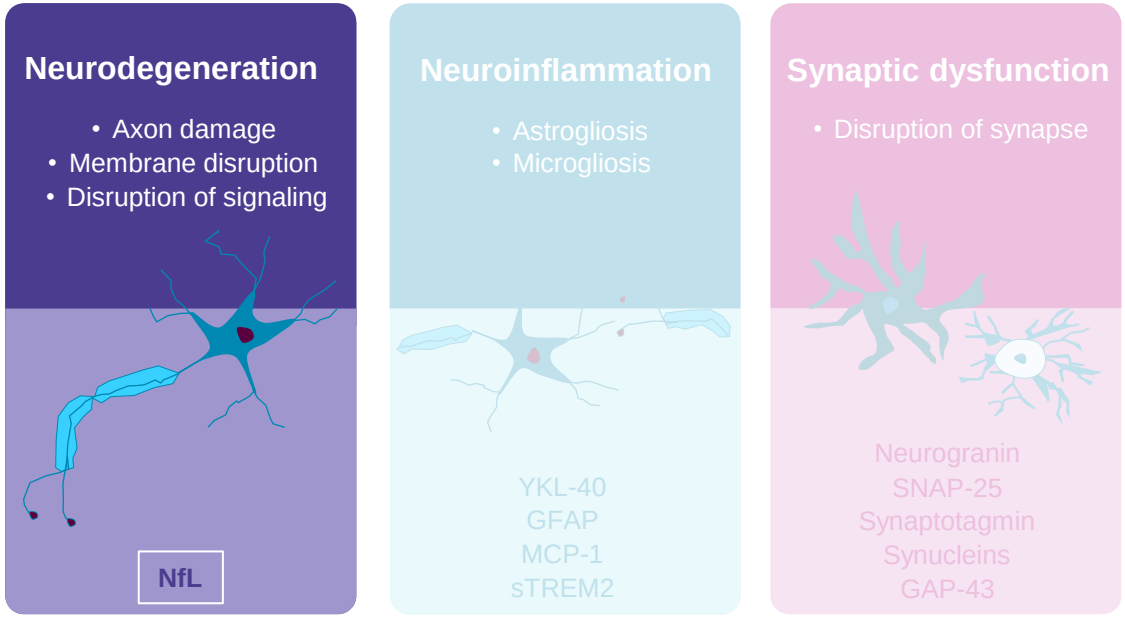


Neurogranin
SNAP-25
Synaptotagmin
Synucleins
GAP-43

AD, Alzheimer's disease; CSF, cerebrospinal fluid; GAP-43, growth-associated protein 43; GFAP, glial fibrillary activation protein; MCP-1, monocyte chemoattractant protein 1; NfL, neurofilament light chain; p-tau, phosphorylated tau; SNAP-25, synaptosomal-associated protein 25; sTREM2, soluble triggering receptor expressed on myeloid cells-2; YKL-40, chitinase-3-like protein 1

1. Dhiman K, et al. Cell Mol Life Sci 2019;76:1833–1863; Tible M, et al. Neurology 2020;95:e953-e961; 2. Nilsson J, et al. Alzheimers Dement 2023;19:1775–1784; 3. Zhang H, et al. Alz Res Therapy 2018;10:80;
4. Colom-Cadena M, et al. Alz Res Therapy 2020;12;21

Emerging CSF biomarkers: neurodegeneration



NfL elevation is a marker of axonal injury[1,2] that may be able to predict the onset of clinical symptoms[3]

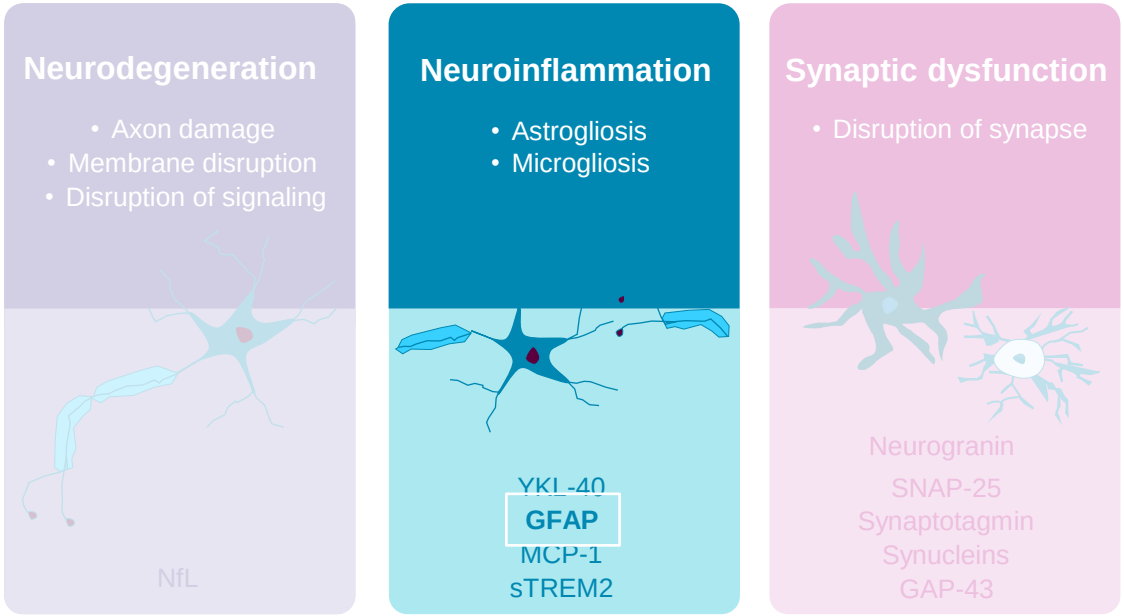
- CSF concentrations of NfL are known to be increased in individuals with neurodegenerative diseases, including AD, compared with controls[1–4]
- However, it is not specific for AD, and concentrations are increased in many neurological conditions[1,5]
- Individuals with high CSF NfL have been found to progress more rapidly to AD than those with lower levels[6]
- NfL may be a useful proximity marker and outcome measure for clinical trials of many neurodegenerative diseases[7]

CSF NfL is elevated in AD and could be used as a potential biomarker to study disease progression and severity along the AD continuum;[4,6,7] however, it is elevated in many other neurodegenerative conditions and is therefore not specific for AD[4]

AD, Alzheimer's disease; CSF, cerebrospinal fluid; GAP-43, growth-associated protein 43; GFAP, glial fibrillary activation protein; MCP-1, monocyte chemoattractant protein 1; NfL, neurofilament light chain; p-tau, phosphorylated tau; SNAP-25, synaptosomal-associated protein 25; sTREM2, soluble triggering receptor expressed on myeloid cells-2; YKL-40, chitinase-3-like protein 1

1. Molinuevo JL, et al. Acta Neuropathol 2018;136:821–853; 2. Olsson B, et al. Lancet Neurol 2016;15:673–684; 3. Weston PSJ et al. Alzheimers Res Ther 2019;11:19; 4. Dhiman K, et al. Cell Mol Life Sci 2019;76:1833–1863; 5. Niikado M, et al. J Gerontol A Biol Sci Med Sci 2019;74:442–445; 6. Chen Y, et al. J Integr Neurosci 2021;20:861-870; 7. Zetterberg H, Schott JC. Nat Med 2019;25:201–203

Emerging CSF biomarkers: neuroinflammation (1/2)



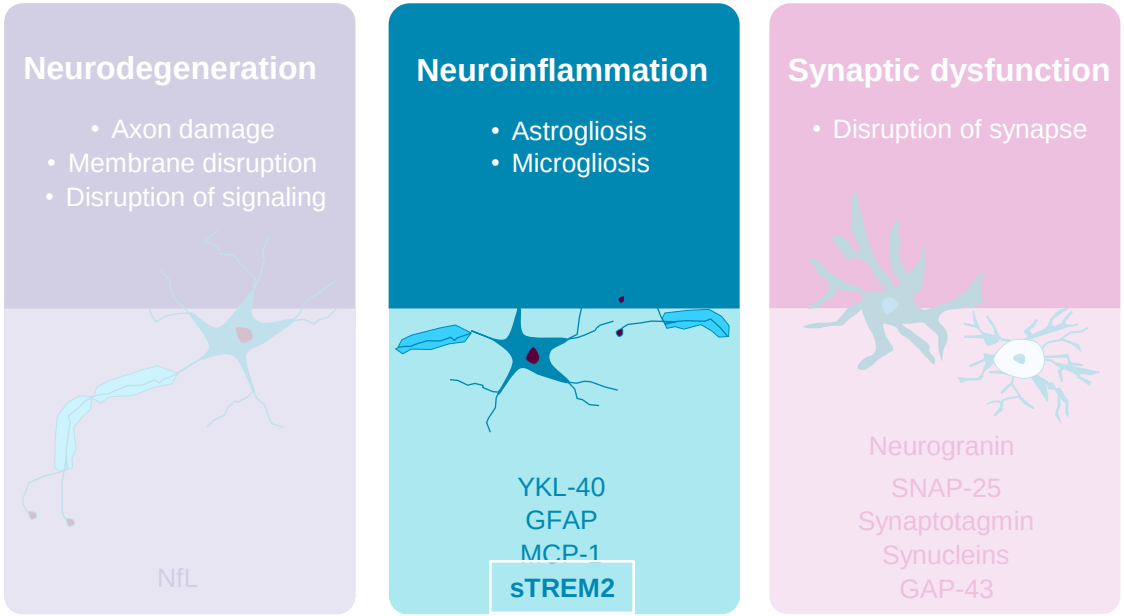
- **GFAP** is an astrocyte-specific biomarker that is involved in cell mobility and migration, proliferation and astrocyte transformation, vesicle transport and autophagy, and astrocyte-neuron interactions[1,2]
- Following CNS injury, GFAP and its breakdown products are released into biofluids, making them suitable biomarkers[3]
- GFAP is implicated in astrogliosis in AD, as well as other neurodegenerative disorders[2]
- Higher CSF GFAP levels are associated with cognitive decline among individuals with core AD pathology at the symptomatic pre- and early stages of dementia[4]

GFAP does not possess significant differential diagnostic utility, but does show potential as a biomarker for cognitive decline and disease monitoring in AD[2]

AD, Alzheimer's disease; CNS, central nervous system; CSF, cerebrospinal fluid; GAP-43, growth-associated protein 43; GFAP, glial fibrillary activation protein; MCP-1, monocyte chemoattractant protein 1; NfL, neurofilament light chain; p-tau, phosphorylated tau; SNAP-25, synaptosomal-associated protein 25; sTREM2, soluble triggering receptor expressed on myeloid cells-2; YKL-40, chitinase-3-like protein 1

1. Ortiz-Rodriguez A, Arevalo MA. Int J Mol Sci 2020;21:2479; 2. McGrowder DA, et al. Brain Sci 2021;11:215; 3. Hampel H, et al. Neuron 2023;S0896-6273(23)00390-2 [E-pub ahead of print]; 4. Teitsdottir UD, et al. Alzheimers Res Ther 2020;12;92;

Emerging CSF biomarkers: neuroinflammation (2/2)



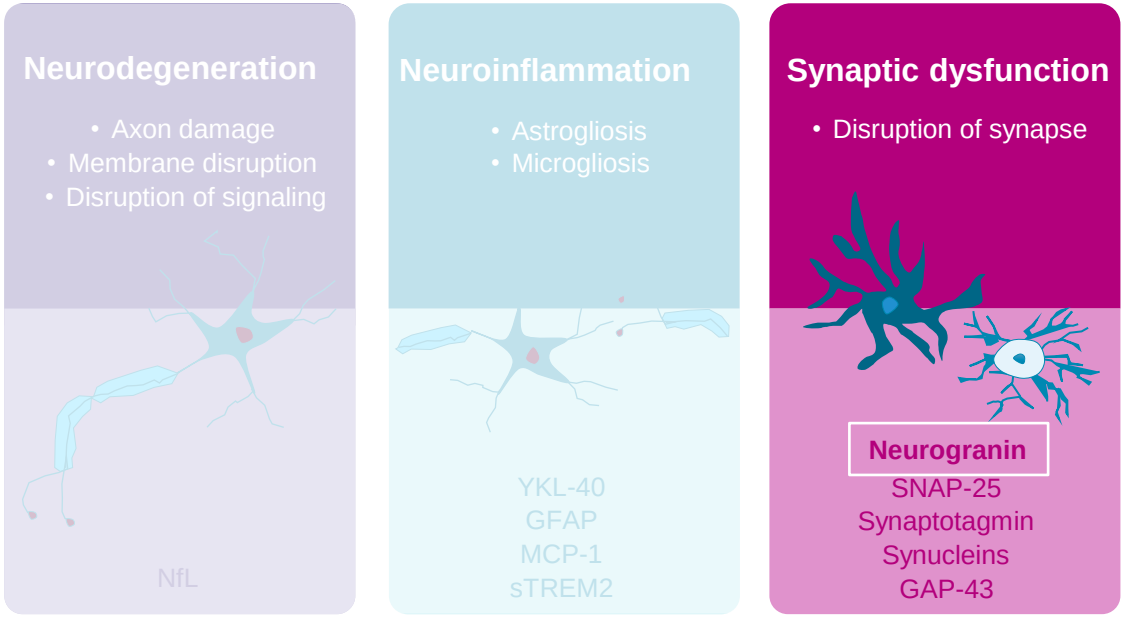
- CSF **sTREM2** could be utilized as a marker of neuroinflammation;[1] its levels are increased in early AD and correlate well with markers of neurodegeneration and tau pathology[2]
- sTREM2 is linked to microglial responses to neuronal injury; therefore, sTREM2 may offer complementary information to existing diagnostic methods[1]
- Greater levels of sTREM2 may be associated with reduced AD progression; however, further research is required to understand the mechanisms behind this[3]
- Levels of CSF sTREM2 may vary between different populations, suggesting race may influence AD-related inflammation[4]

sTREM2 could be used to identify individuals with early AD, or to monitor neuroinflammation along the AD continuum[2]

AD, Alzheimer's disease; CSF, cerebrospinal fluid; GAP-43, growth-associated protein 43; GFAP, glial fibrillary activation protein; MCP-1, monocyte chemoattractant protein 1; NfL, neurofilament light chain; p-tau, phosphorylated tau; SNAP-25, synaptosomal-associated protein 25; sTREM2, soluble triggering receptor expressed on myeloid cells-2; YKL-40, chitinase-3-like protein 1

1. Rauchmann BS, et al. Neurobiol Aging 2019;74:182–190; 2. Dhiman K, et al. Cell Mol Life Sci 2019;76:1833–1863; 3. Hu WT, et al. Nat Commun 2021;12:4001; 4. Schindler SE, et al. Neurol Genet 2021;7:e571

Emerging CSF biomarkers: synaptic dysfunction (1/2)



Neurogranin elevation is a marker of synaptic dysfunction[1]

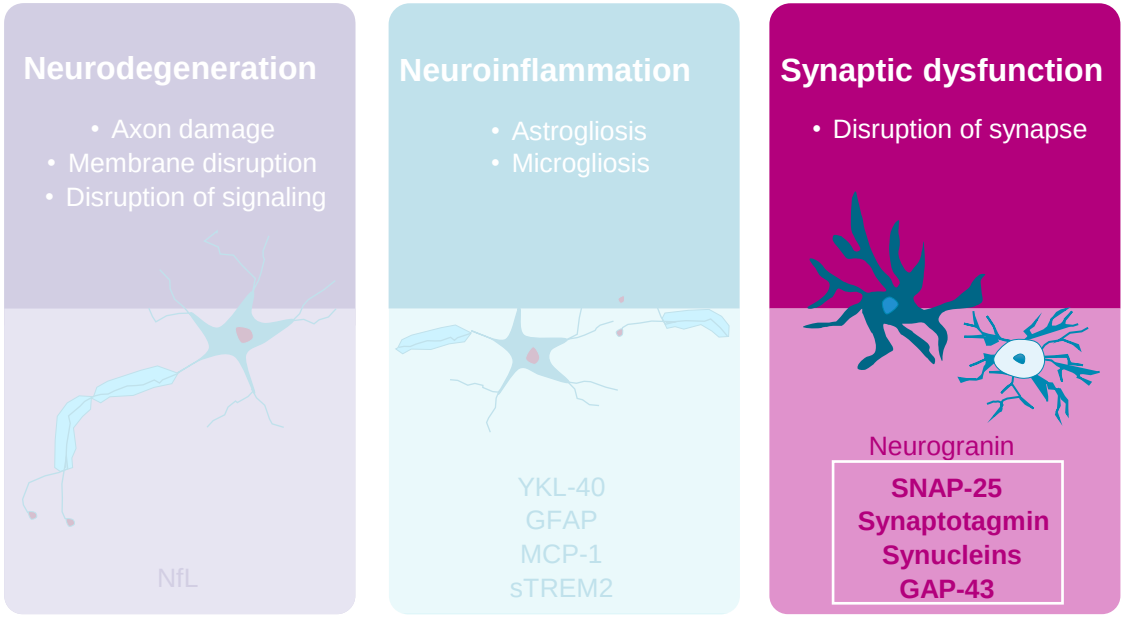
- CSF neurogranin is elevated in individuals with AD and other neurodegenerative disorders compared with healthy controls[1]
- CSF neurogranin has been positively correlated with levels of t-tau and p-tau, and thus might reflect synaptic injury in the very early stages of AD[1,2]
- CSF neurogranin also correlates with brain atrophy and amyloid load[3]

Measurement of synaptic proteins may be a useful marker of neurodegenerative diseases.[3] CSF neurogranin might be a useful biomarker for understanding the rate of cognitive decline along the AD continuum[3]

AD, Alzheimer's disease; CSF, cerebrospinal fluid; DLB, Lewy body dementia; FTD, frontotemporal dementia; GAP-43, growth-associated protein 43; GFAP, glial fibrillary activation protein; MCI, mild cognitive impairment; MCP-1, monocyte chemoattractant protein 1; NfL, neurofilament light chain; p-tau, phosphorylated-tau; SNAP-25, synaptosomal-associated protein 25; sTREM2, soluble triggering receptor expressed on myeloid cells-2; YKL-40, chitinase-3-like protein 1

1. Willemse EAJ, et al. Neurobiol againg 2021;108:99–109; 2. Wang L; Alzheimer's Disease Neuroimaging Initiative. Aging Clin Exp Res 2019;31:185–191; 3. Dhiman K, et al. Cell Mol Life Sci 2019;76:1833–1863

Emerging CSF biomarkers: synaptic dysfunction (2/2)



- Other CSF synaptic biomarkers, such as **SNAP-25, synaptotagmin, GAP-43, and β-synuclein** may support AD diagnoses and monitoring of disease progression / treatment response[1,2]
- SNAP-25 increases with disease severity and may offer **predictive value for individuals with MCI developing AD**[3]
- One study found that CSF SNAP-25 and SNAP-25/Aβ42 may complement the prognostic utility of CSF Aβ42, t-tau, and p-tau in predicting cognitive impairment progression[3]

Cognitive impairment in AD closely parallels the loss of synapses due to the toxic effects of Aβ, tau, and inflammation. Emerging biomarkers of synapse dysfunction reflect such synapse injury and loss in the brain due to disease[4]

Aβ, amyloid beta; AD, Alzheimer's disease; ADPD, International Conference on Alzheimer's and Parkinson's Diseases; CSF, cerebrospinal fluid; GAP-43, growth-associated protein 43; GFAP, glial fibrillary activation protein; MCI, mild cognitive impairment; MCP-1, monocyte chemoattractant protein 1; NfL, neurofilament light chain; p-tau, phosphorylated tau; SNAP-25, synaptosomal-associated protein 25; sTREM2, soluble triggering receptor expressed on myeloid cells-2; t-tau, total tau; YKL-40, Chitinase-3-like protein 1

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CSF MTBR-tau243 as a specific biomarker of tau tangle pathology

p-tau181, p-tau217 and p-tau231 are strongly associated with increasing burden of amyloid plaques and do not directly represent insoluble tau aggregates. Microtubule-binding region (MTBR)-tau species containing residue 243 (MTBR-tau243) has been found strongly associated with tau PET and disease progression, therefore considered a new CSF biomarker of tau aggregate pathology

- In this study in two large independent sporadic AD cohorts, p-tau217 was the CSF measure most strongly correlated with amyloid PET, whereas MTBR-tau243 was the CSF measure most strongly associated with tau PET
  - CSF MTBR-tau243 had the largest rate of increase in participants that are already positive for both amyloid and tau pathologies vs p-tau217, suggesting that CSF MTBR-tau243 best reflects disease progression in late stages
- CSF MTBR-tau243 was the individual biomarker that best predicted MMSE scores vs p-tau217, and prediction improved when p-tau205 was added

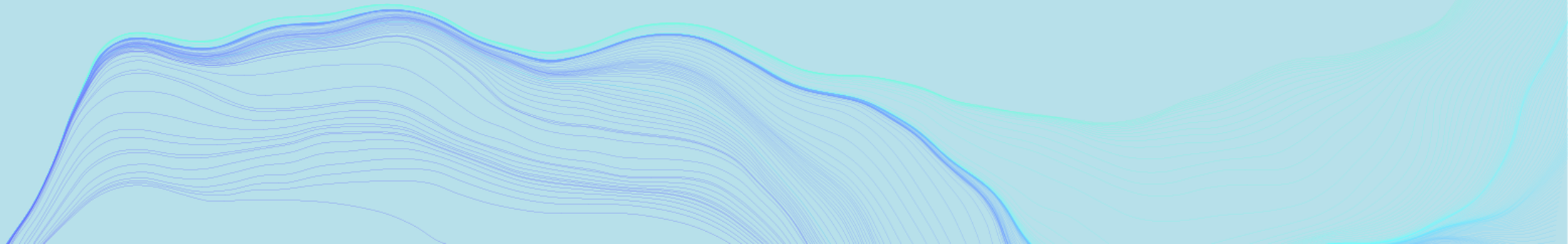
Data suggests that CSF MTBR-tau243 may be a viable alternative to tau PET for use as a pre-screening tool or a tau pathology endpoint surrogate for clinical trials, and as an accurate diagnostic measure of tau pathology

CSF, cerebrospinal fluid; MTBR, microtubule-binding region; PET, positron emission tomography, p-tau, phosphorylated tau

Horie K, et al. Nat Med. 2023. doi: 10.1038/s41591-023-02443-z. Epub ahead of print.

Learning Zone

CSF AD biomarker concordance with PET



Biomarkers of amyloid are concordant with each other

CSF Aβ42 and amyloid PET correlate closely and both have high diagnostic accuracy[1–4]

Concentrations of CSF Aβ42 decrease as more amyloid is deposited in the brain[5]

As amyloid becomes deposited in the brain, it can be visualized by amyloid PET[1–4]

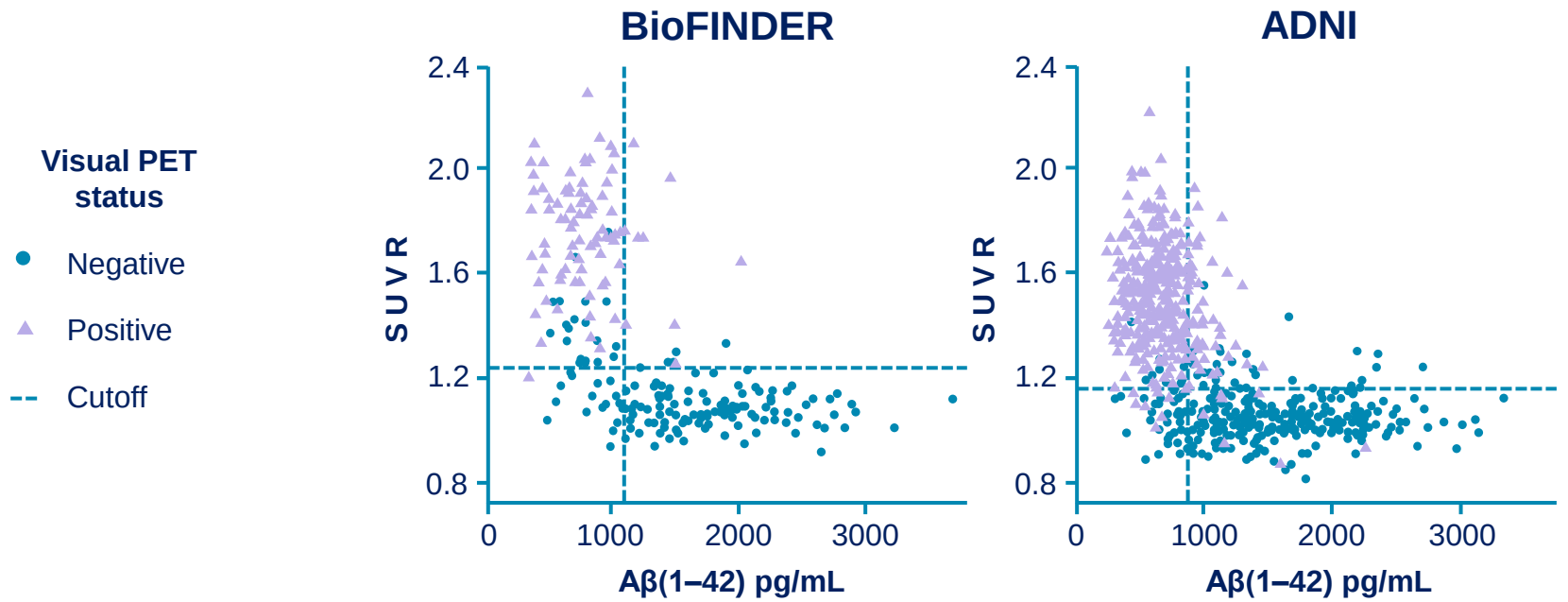
CSF and amyloid PET measure slightly different forms of Aβ,[6] which may explain why the results are sometimes discordant[1,2]

Aβ, amyloid beta; CSF, cerebrospinal fluid; PET, positron emission tomography

1. Bateman RJ, et al. N Engl J Med 2012;367:795–804; 2. Palmqvist S, et al. Brain 2016;139:1226–1236; 3. Martinez G, et al. Cochrane Database Syst Rev 2017;11:CD012216.pub2; 4. Hansson O, et al. Alzheimers Dement 2018;14:1470–1481; 5. Blennow K, et al. Alzheimers Dement 2015;11:58–69; 6. Fagan AM, et al. Ann Neurol 2009;65:176–183

CSF Aβ42 concordance with amyloid PET imaging

- Studies have established a strong inverse correlation between amyloid PET readings and low CSF Aβ42 levels, demonstrating that CSF Aβ is a robust marker of amyloid accumulation in the brain[1]
- One study found that CSF Aβ42 and PET were >90% concordant in a cohort of patients with MCI[2]



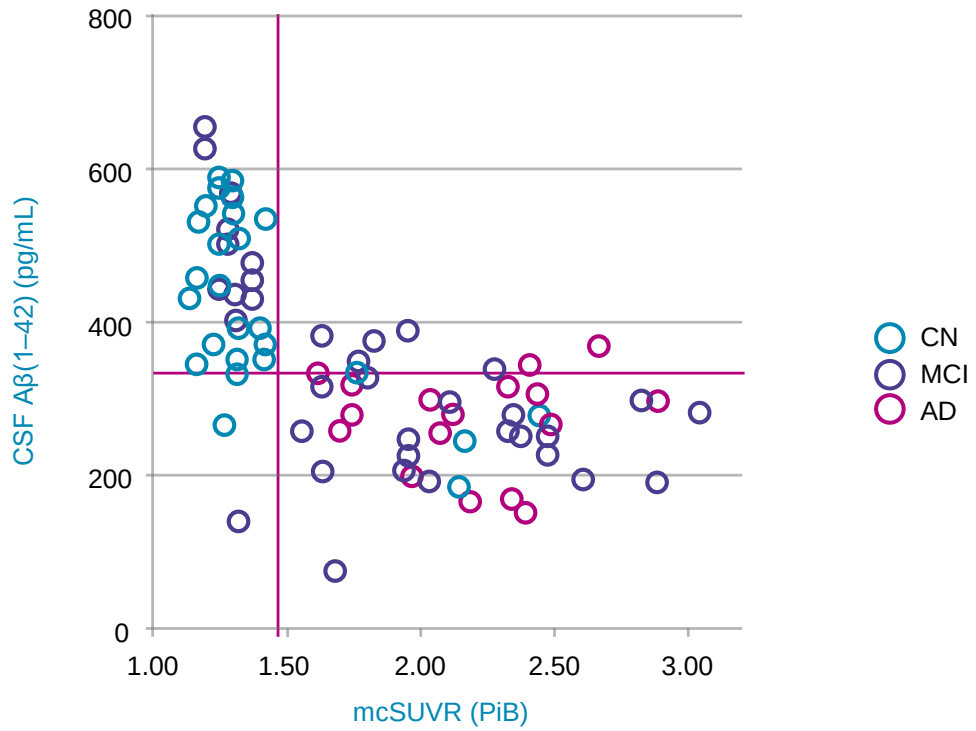
Using an SUVR classification cutoff and a predefined CSF biomarker cutoff, **high concordance was observed between CSF Aβ42 and Aβ PET** for both the BioFINDER (N=233) and ADNI (N=645) cohorts[2]

Aβ, amyloid beta; ADNI, Alzheimer's Disease Neuroimaging Initiative; BioFINDER, Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably; CSF, cerebrospinal fluid; PET, positron emission tomography; SUVR, standardized uptake value ratio

1. Leuzy A et al. Brain 2016;139:2540–2553; 2. Hansson O, et al. Alzheimers Dement 2018;14:1470–1481

CSF Aβ42 concordance with PiB amyloid PET imaging in a Japanese population

Mean cortical PiB SUVR plotted against CSF Aβ1–42 for J-ADNI participants (n=81)



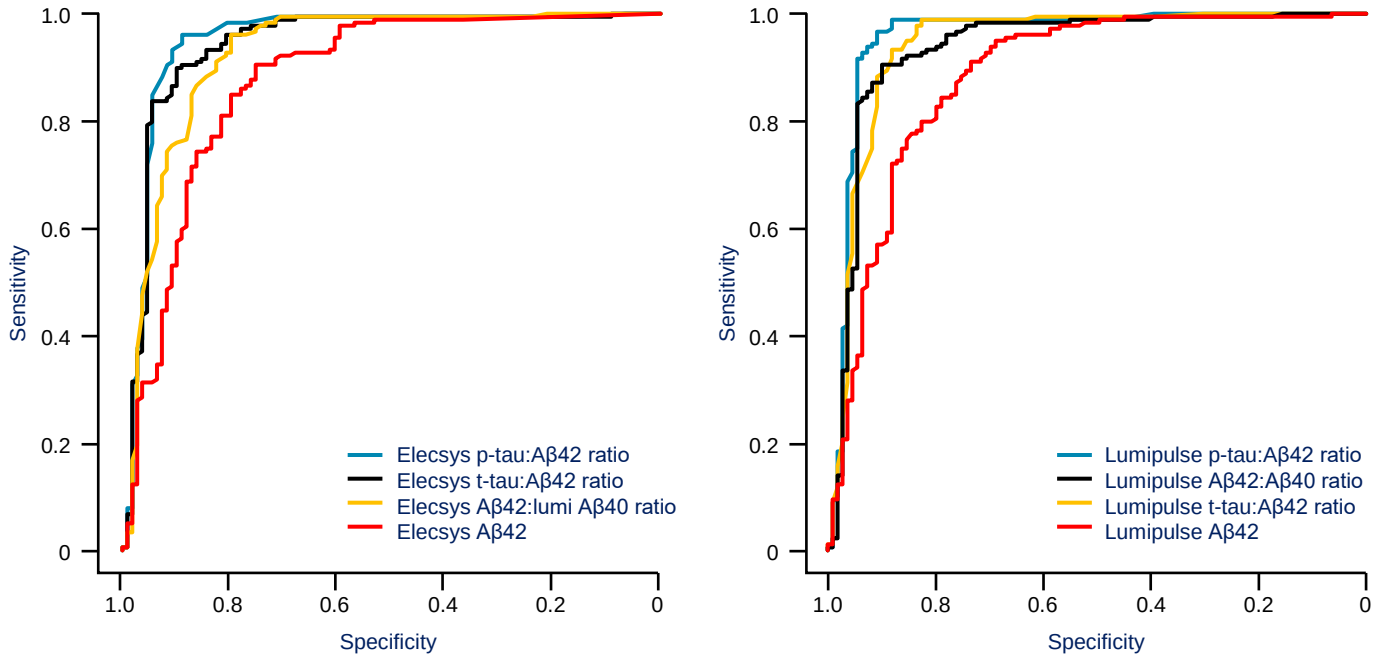
Good concordance was observed between CSF Aβ1–42 and Aβ PET in J-ADNI participants

AD, Alzheimer's disease, CN, cognitively normal, J-ADNI, Japanese Alzheimer's Disease Neuroimaging Initiative; MCI, mild cognitive impairment; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratios

Figure adapted from Iwatsubo T, et al. Alzheimers Dement 2018;14(8):1077–1087

Strong concordance between CSF biomarker ratios and amyloid PET

Receiver operating characteristic curves of Aβ42 alone and as ratio of Aβ40, p-tau, or t-tau to predict amyloid PET (N=288)



- The fully automated Elecsys® and Lumipulse® assays showed similar high concordance with amyloid PET (OPA: 90%–94%) when using biomarker ratios with either Aβ40, t-tau, or p-tau, and improved concordance compared with CSF Aβ42 alone (OPA: 84%–85%)
- The study was performed in a real-world memory clinic

The p-tau/Aβ42 ratio resulted in the highest AUCs and OPA for both analyzers compared with t-tau/Aβ42, Aβ42/Aβ42, or Aβ42 alone

Aβ, amyloid beta; AUC, area under the curve; CI, confidence interval; CSF, cerebrospinal fluid; OPA, overall percentage agreement; PET, positron emission tomography; p-tau, phosphorylated-tau; t-tau, total-tau

Willemse EAJ et al, Alzheimer's Dement 2021;13:e12182

Concordance of CSF biomarker ratios with amyloid PET

Biomarker ratios p-tau/Aβ42, Aβ42/40, and t-tau/Aβ42 on two automated platforms have shown similar optimal concordance with amyloid PET in different memory clinic cohorts[1,2]

Biomarker	Method	Sensitivity (95% CI)	Specificity (95% CI)	OPA (95% CI)
Aβ42	Elecsys®	91 (77–95)%	75 (69–89)%	85 (80–90)%
	Lumipulse®	91 (75–98)%	73 (65–91)%	84 (79–89)%
Aβ42/40	Elecsys®	96 (86–99)%	80 (73–91)%	90 (86–93)%
	Lumipulse®	99 (89–100)%	83 (79–94)%	92 (89–96)%
p-tau/Aβ42	Elecsys®	96 (90–98)%	89 (84–96)%	93 (90–96)%
	Lumipulse®	97 (91–100)%	91 (85–97)%	94 (92–97)%
t-tau/Aβ42	Elecsys®	89 (83–98)%	90 (81–97)%	90 (86–94)%
	Lumipulse®	91 (83–96)%	90 (84–97)%	90 (87–94)%

- In a study of participants from across the AD spectrum, the p-tau/Aβ42 ratio had the highest overall agreement for PET positivity compared to Aβ42, Aβ42/40, and t-tau/Aβ42[1]
- The biomarker outcomes from either platform reflected amyloid pathology, as long as the platform-specific cut-points were applied[1]
- Both platforms are currently being used in a clinical setting

CSF biomarker ratios are better predictors of PET amyloid positivity than CSF Aβ42 alone[1]

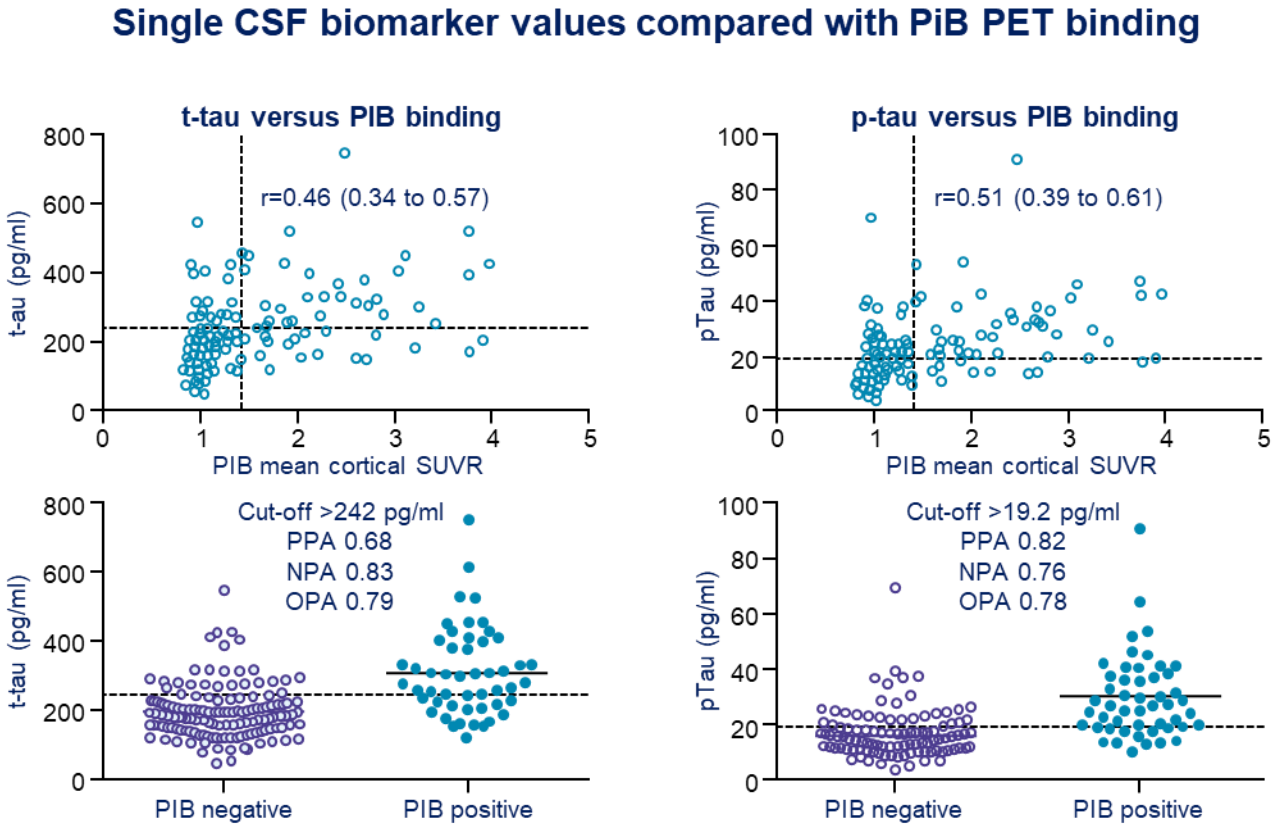
Table adapted from Willemse EAJ, et al. Alzheimers Dement 2021;13:e12182 (CC-BY 4.0: https://creativecommons.org/licenses/by-nc-nd/4.0/)

Aβ, amyloid beta; AD, Alzheimer's disease; CI, confidence interval; CSF, cerebrospinal fluid; OPA, overall percentage agreement; PET, positive emission tomography; p-tau, phosphorylated tau; t-tau, total tau

1. Willemse EAJ, et al. Alzheimers Dement 2021;13:e12182; 2. Campbell MR, et al. Alzheimers Dement 2021;13:e12190

CSF tau correlation with amyloid PET imaging

- Studies have established a correlation between CSF tau biomarkers (and their ratios) and amyloid PET [1–6]
- **Increases in CSF tau are correlated with amyloid deposition, but CSF Aβ42 decreases before tau increases**[1,2]
- Excellent correlation with amyloid PET, and comparable sensitivity and specificity using different platforms has also been observed with CSF tau biomarkers and their ratios[3–5]



Amyloid binding was positively correlated with t-tau (r=0.46, P<0.0001), and p-tau (r=0.51, P<0.0001)

Figures used with permission from: Schindler SE, et al. Alzheimers Dementia 2018;14:1460–1469 (CC-BY 4.0: https://creativecommons.org/licenses/by/4.0/)

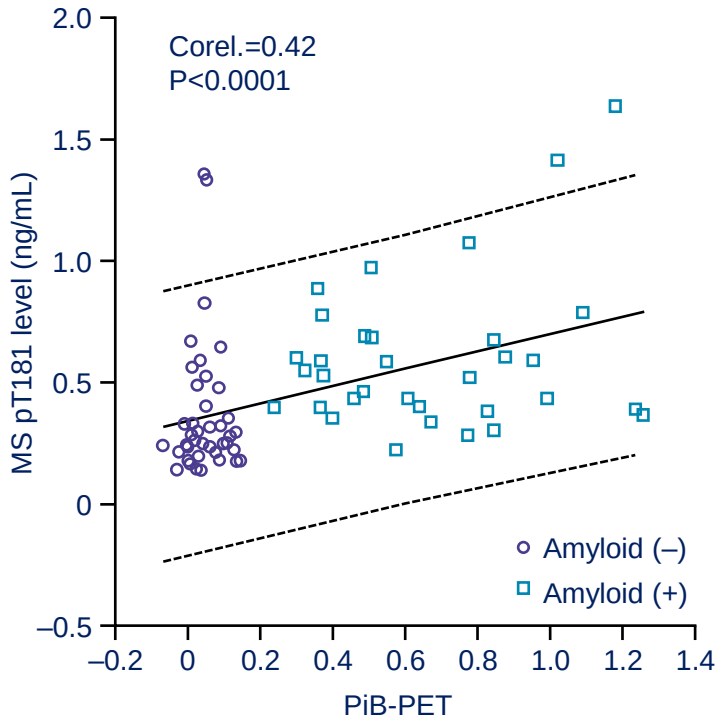
Aβ, amyloid beta; CSF, cerebrospinal fluid; NPA, negative percentage agreement; OPA, overall percentage agreement; PET, positive emission tomography; PiB, Pittsburgh compound B; PPA, positive percentage agreement; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio; t-tau, total tau

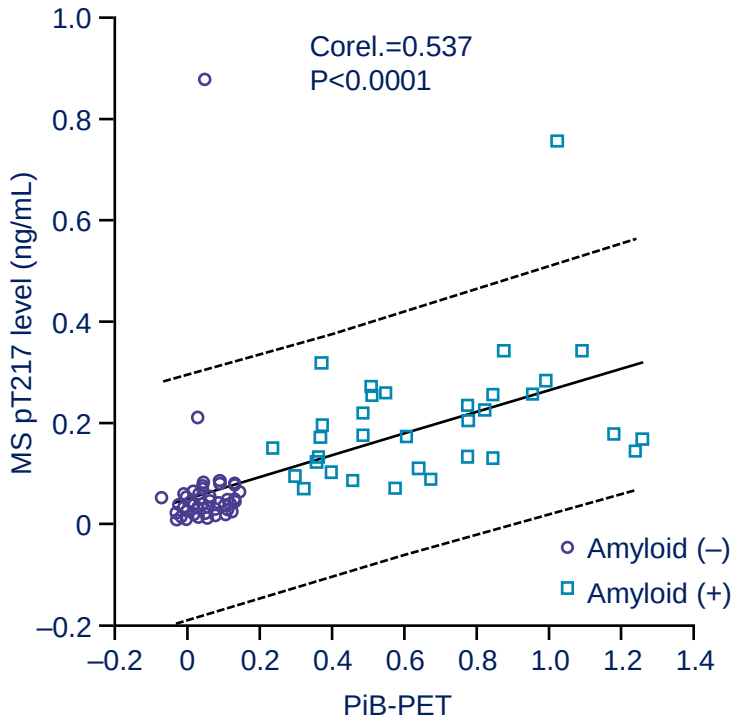
1. Schindler SE, et al. Alzheimers Dementia 2018;14:1460–1469; 2. Hansson O, et al. Alzheimers Dementia 2018;14:1470–1481; 3. Campbell MR, et al. Alzheimers Dement 2021;13:e12190; 4. Willemse EAJ, et al. Alzheimers Dement 2021;13:e12182; 5. Keshavan A, et al. Alzheimers Dement 2021;13:e12131; 6. Barthélemy NR, et al. Alz Res Ther 2020;12:26

CSF p-tau isoforms correlation with amyloid PET

- In a cohort of amyloid-positive and amyloid-negative patients (N=51), **CSF p-tau181 (P<0.001) and CSF p-tau217 (P<0.0001) were both significantly correlated with PiB-PET data** (Figures)
- The **p-tau181/p-tau217 ratio was significantly correlated with PiB-PET**, showing an even better coefficient than with p-tau217 levels alone

CSF p-tau correlation with PiB PET binding





Figures used with permission from Barthélemy NR, et al. Alz Res Ther 2020;12:26 (CC-BY 4.0: https://creativecommons.org/licenses/by/4.0/)
CSF, cerebrospinal fluid; MS, mass spectrometry; PET, positive emission tomography; PiB, Pittsburgh compound B; p-tau, phosphorylated tau; t-tau, total tau
Barthélemy NR, et al. Alz Res Ther 2020;12:26

CSF and PET amyloid biomarkers are not always concordant (1/2)

Although both Aβ markers detect the same neuropathological characteristic, a proportion of subjects within the AD spectrum show discordance between CSF Aβ42 and amyloid-PET status, with either abnormal CSF Aβ42 and normal amyloid PET, or vice versa[1]

Stage of disease course

- CSF Aβ can become abnormal prior to amyloid PET
  - Abnormal amyloid metabolism can be detected at a very early stage in the disease course before it is detectable by PET imaging[1]
- Individuals with discordance of CSF ratios may be in a transitional or borderline stage of disease[2,3]

Inter-individual variability

- Evidence suggests there may be two pathways (‘CSF-first’ vs ‘PET-first’) towards established amyloid pathology, characterized by different genetic profiles and rates of Aβ accumulation[4]

Aβ, amyloid beta; AD, Alzheimer’s disease; CSF, cerebrospinal fluid; PET, positive emission tomography; PiB, Pittsburgh compound B

1. Niemantsverdriet E, et al. J Alzheimers Dis 2017;60:561–576; 2. Schindler SE, et al. Alzheimers Dement 2018;14:1460–1469; 3. Campbell MR, et al. Alzheimers Dement (Amst) 2021;13:e12190; 4. Sala A, et al. Mol Psych 2021;26:5864–5874

CSF and PET amyloid biomarkers are not always concordant (2/2)

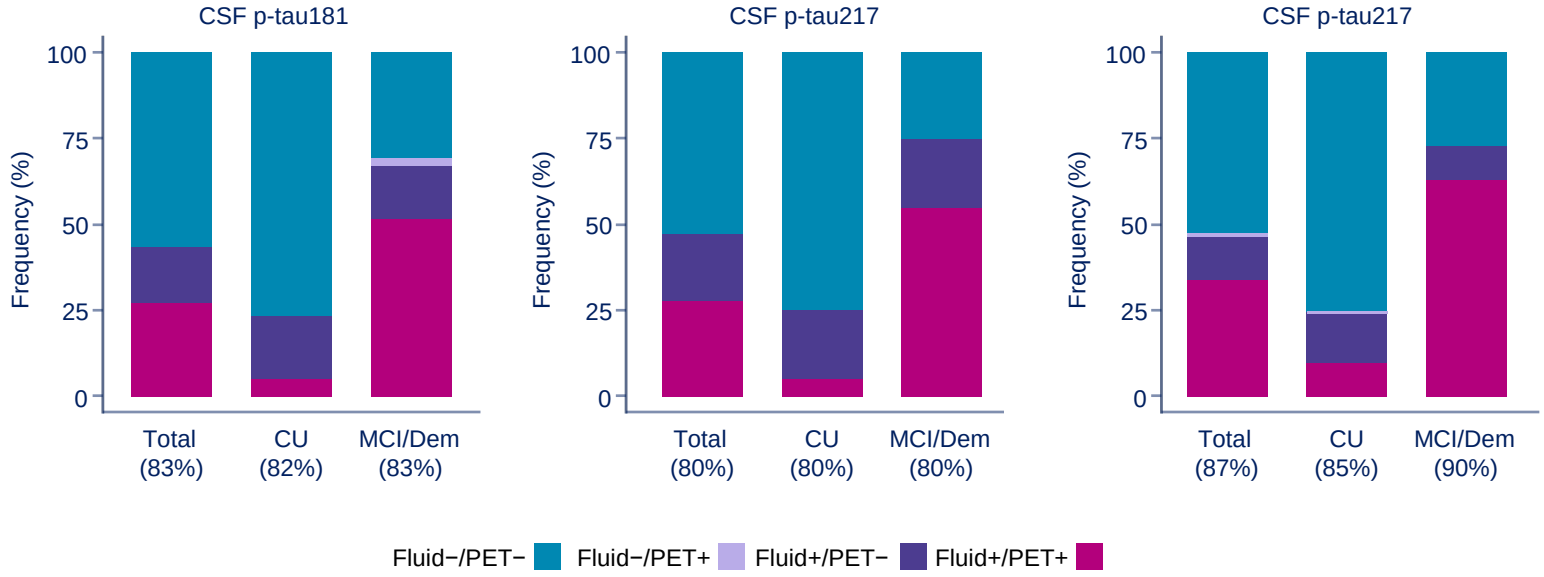
Errors in CSF handling and processing	CSF Aβ42 is prone to aggregation.[1] If samples are not taken in polypropylene tubes or are not handled properly then CSF Aβ42 may be artificially low.[2]
Cut-offs used during analysis	CSF Aβ42 cutoffs are often selected to maximize the discriminability between controls and AD dementia patients and may be determined independent of amyloid PET imaging[1]
Inter-reader variability	There may be variability in the visual/clinical interpretation of PET scans as positive and negative,[3] compared with quantitative analysis

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positive emission tomography

1. Niemantsverdriet E, et al. J Alzheimers Dis 2017;60:561–576; 2. Bjerke M, et al. Int J Alzheimers Dis 2010;2010:986310; 3. Major CK, Okhravi HR. Cureus 2021;13:e13481

CSF tau concordance with tau PET imaging

Concordance between tau PET and CSF p-tau181 and CSF p-tau217 in the BioFINDER-2 study



Total concordance between tau PET SUVR and CSF p-tau181 and CSF p-tau217 ranged from 80% to 87%

Figure used with permission from Ossenkoppele R, et al. EMBO Mol Med 2021;9;13:e14398 (CY-BY 4.0; https://creativecommons.org/licenses/by/4.0/)

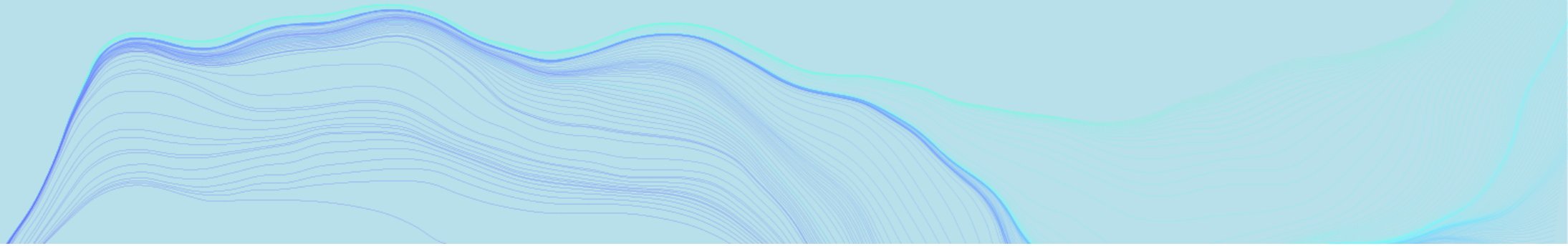
*Temporal meta-ROI includes the weighted average of entorhinal, amygdala, parahippocampal, fusiform and inferior and middle temporal cortex

CSF, cerebrospinal fluid; CU, cognitively unimpaired; dem, dementia; MCI, mild cognitive impairment; PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standard uptake reference value

Ossenkoppele R, et al. EMBO Mol Med 2021;13:e14398

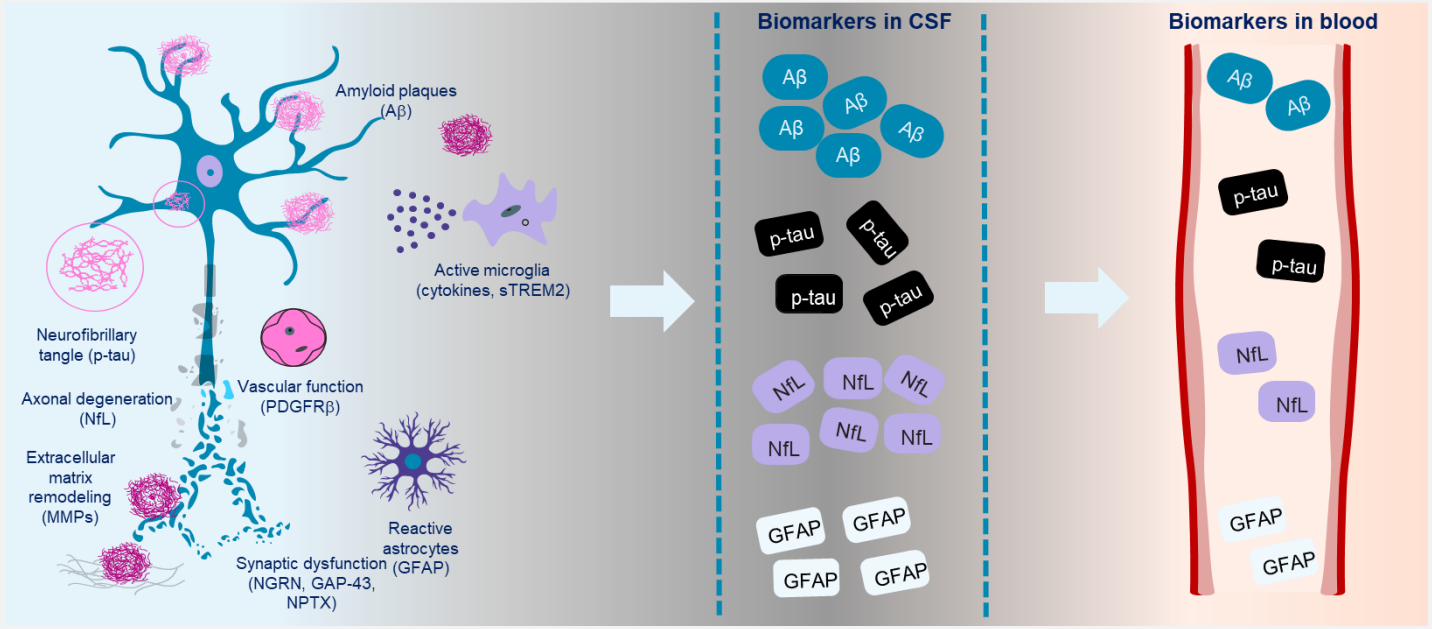
Learning Zone

Advances in blood-based biomarkers



Eisai hhc human health care

Blood-based biomarkers in AD



- Amyloid beta (Aβ)
  - Aβ42/40 ratio
- P-tau isoforms
  - p-tau217 and p-tau181
- NfL
- GFAP

- While CSF biomarkers and PET are approved for clinical use, access to both can be limited. In addition, lumbar punctures to collect CSF can be perceived as invasive or risky and PET scans are costly to perform[2]
- BBBMs have the potential to transform clinical care by enabling widespread, affordable access to biomarker testing[2]

Image used with permission from Teunissen CE, et al. Lancet Neurol 2022;21:66–77

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; GAP-43, growth-associated protein 43; GFAP, glial fibrillary activation protein; MMP, matrix metalloproteinase; NfL, neurofilament light chain; NGRN, neurogranin; NPTX, neuronal pentraxin; PDGFRβ, platelet-derived growth factor receptor beta; p-tau, phosphorylated-tau; sTREM2, soluble triggering receptor expressed on myeloid cells-2; t-tau, total-tau

1. Teunissen CE, et al. Lancet Neurol 2022;21:66–77; 2. Hampel H, et al. Neuron 2023:S0896-6273(23)00390-2

Interpreting core AD biomarkers measured in the blood

Biomarkers	Change in AD	Interpretation
Aβ42/40 ratio	• Ratio is on average **10–15% lower** in **amyloid-positive** than **amyloid-negative** older individuals[1]	• **Low ratio** associated with brain amyloidosis[1] • Magnitude of decrease is **less marked in plasma** vs CSF (~50%)[1,2]
p-tau	• Concentrations are dependent on disease stage (**42–77% increase in cognitively unimpaired amyloid-positive older** individuals)[3] • Mean **increase** in **p-tau181, p-tau217,** and **p-tau231** is **~200–400%** of control levels in amyloid-positive individuals with MCI due to AD or AD dementia[3]	• Plasma p-tau **increases with higher brain tau** pathology load assessed by tau PET[4,5] • Increased p-tau is found in the **early stages** of the AD continuum[4]

An important distinction between plasma p-tau isoforms and Aβ42/40 as biomarkers is their effect size. The average differences in concentrations of p-tau and Aβ42/40 between amyloid-positive and -negative groups are higher with p-tau, with concentrations of p-tau dependent on disease stage[3]

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PET, positron emission tomography; p-tau, phosphorylated tau

1. Ovod V, et al. Alzheimers Dement. 2017;13(8): 841–849; 2. Blennow K, Zetterberg H. J Intern Med 2018;284:643–663; 3. Hampel H, et al. Neuron. 2023;111:2781–2799; 4. Janelidze S, et al. Nat Med 2020;26:379–386; 5. Karikari TK, et al. Lancet Neurol 2020;19:422–433

Blood-based biomarkers: Aβ42/40

- Plasma and CSF Aβ, and PET imaging are **highly correlated with each other.**[1] **Plasma Aβ42/40** has shown **high correspondence** with **amyloid PET status**[2,3]

- **Plasma Aβ42/40 assays have been found to predict Aβ status in all stages of AD**[4,5]
  Their accuracy can be further increased by analyzing *APOE* genotype[4,5]

- Plasma **Aβ42/Aβ40 + p-tau217/nptau-217 ratio,** in a prospective BioFINDER-primary care study, identified AD pathology and correctly diagnosed AD in up to 87% of cases compared with PCPs using standard assessment tools (54% of cases)[6]

- Findings suggest that **plasma Aβ42/40** could be used as a prior **screening tool** for those **at risk of AD dementia**[2]; plasma Aβ42/40 demonstrates utility in predicting conversion of individuals to AD[7]

Aβ42/40 assays are either immunoassay-based or mass spectrometry (MS) based; MS-based assays have generally demonstrated higher performance[8]

Aβ, amyloid beta; AD, Alzheimer's disease; APOE, apopoliprotein E; CSF, cerebrospinal fluid; np-tau, non-phosphorylated tau; PCP, primary care physician; PET, positive emission tomography; p-tau, phosphorylated tau

1. Nakamura A et al. Nature 2018;554:249–254; 2. Schindler SE et al. Neurology 2019;93:e1647–e1659; 3. Li Y, et al. Neurology. 2022;98(7):e688–e699; 4. Palmqvist S, et al. JAMA Neurol. 2019;76:1060–1069; 5. Hu Y, et al. JAMA Network Open 2022;5:e228392; 6. PrecivityAD2™. Palmqvist S, et al. AAIC 2023 (Abstract 4-29-FRS-A); 7. Cullen NC, et al. Nat Commun. 2021;12(1):3555; 8. Hampel H, et al. Neuron 2023;111:2781–2799

Blood-based biomarkers: p-tau

- P-tau isoforms, including **p-tau181**, **p-tau217**, and **p-tau231,** have been successfully translated in blood[1–6]
- Serum/plasma p-tau181 **is increased in AD**[1] and has been found to increase stepwise between Braak stages[2]
- Blood p-tau181 and p-tau217 could serve as a **predictor of AD progression**[1,2,7]
- Some studies demonstrate that **p-tau217 is superior to p-tau181 across different reference standards** (CSF biomarkers, amyloid PET, tau PET, neuropathological findings, and clinical diagnosis), with higher clinical performance correlated with a bigger effect size for p-tau217.[8–10] The **p-tau217/np-tau217 ratio** has also demonstrated clinical performance in a primary care setting[11]
- Unlike NfL, plasma p-tau181 and p-tau231 **can differentiate AD from other neurodegenerative disorders (e.g., frontotemporal dementia)**[1,3,4]

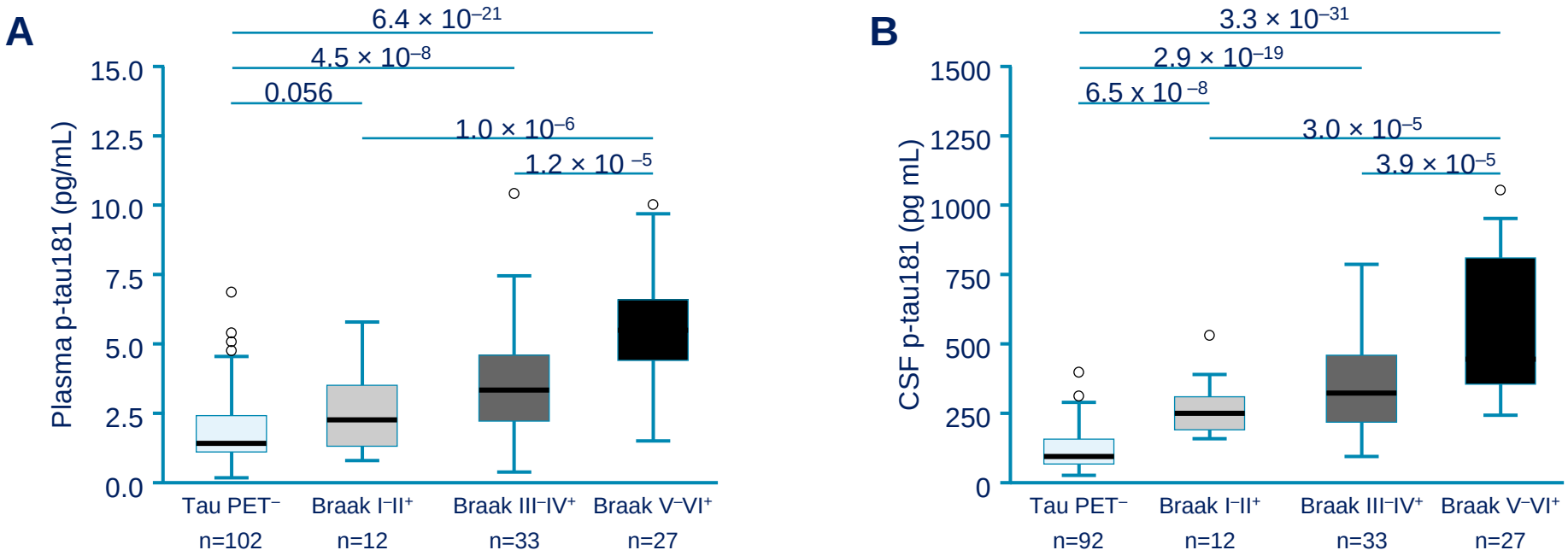
Ultrasensitive assays, such as Meso Scale Discovery (MSD) assays and single-molecule array (Simoa) platform, are able to detect and measure different phosphorylated forms of tau in the blood, including p-tau181 and p-tau217[1,3,4]

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; MCI, mild cognitive impairment; NfL, neurofilament light chain; PET, positive emission tomography; p-tau, phosphorylated tau

1. Karikari TK, et al. Lancet Neurol 2020;19:422–433; 2. Janelidze S, et al. Nat Med 2020;26:379–386; 3. Thijssen EH, et al. Nat Med 2020;26:387–397; 4. Ashton NJ, et al. Acta Neuropathol 2021;141:709–724; 5. Palmqvist S, et al. JAMA 2020;324:772–781; 6. Barthélemy JR, et al. J Exp Med 2020;217:e20200861; 7. Palmquist S, et al. Nat Med 2021;27:1034–1042; 8. Brickman AM, et al. Alzheimers dement 2021;17:1353–1364; 9. Mielke M, et al. Nat Med 2022;28:1398–1405; 10. Therriault J, et al. Alzheimer dement. 2023. doi: 10.1002/alz.13026. Online ahead of print. 11. Palmqvist S, et al. AAIC 2023 (Abstract 4-29-FRS-A)

Blood/plasma biomarkers: p-tau181

Plasma **p-tau181 increases stepwise between Braak stages**



Plasma (A) and CSF (B) concentrations of p-tau181 in individuals without significantly elevated tau-PET measurements in any Braak ROI (tau PET−), and those with significantly elevated measurements in one or more of these ROIs, including (1) Braak I–II (but not III–VI), (2) Braak III–IV (but not V–VI) or (3) Braak V–VI. Tau data were binarized based on the SUVR cutoff of 1.3

Figures used with permission from: Janelidze S, et al. Nat Med 2020;26:379–386

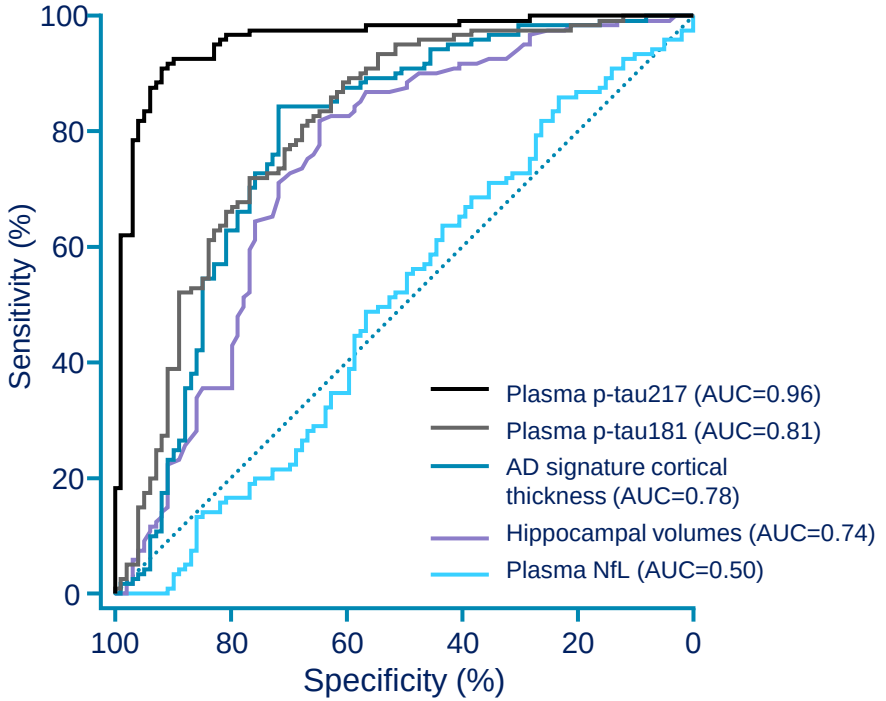
AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positive emission tomography; p-tau, phosphorylated tau; ROI, region of interest; SUVR, standardized uptake value ratio

Janelidze S, et al. Nat Med 2020;26:379–386

Blood/plasma biomarkers: p-tau217 (1/2)

- Plasma p-tau217 levels are increased in symptomatic AD and can differentiate AD from non-AD diseases with an accuracy similar to CSF p-tau and tau PET[1,2]
- Studies have shown that plasma p-tau217 can accurately **predict Aβ pathology in both symptomatic and asymptomatic phases of AD**[1,2]
- Some studies have shown that p-tau217 may be a better marker of AD pathology than p-tau181 (see figure)[1,3,4]
  - p-tau217 may be a better marker for the differential diagnosis of AD syndromes vs FTLD syndromes, compared with p-tau181[4]

Comparison of plasma p-tau217 vs other plasma and MRI biomarkers[1]



Plasma p-tau217 might be useful to support the differential diagnosis of individuals with cognitive impairment, particularly where clinics have limited access to CSF or PET testing[1]

Figure used with permission from: Palmqvist S, et al. JAMA 2020;324:772–781

Aβ, amyloid beta; AD, Alzheimer's disease; AUC, area under the curve; CSF, cerebrospinal fluid; CU, cognitively unimpaired; FTLD, fronto-temporal lobar degeneration; MRI, magnetic resonance imaging; NfL, neurofilament light chain; p-tau, phosphorylated tau; PET, positive emission tomography

1. Palmqvist S, et al. JAMA 2020;324:772–781; 2. Barthélemy JR, et al. J Exp Med 2020;217:e20200861; 3. Mielke M, et al. Nat Med 2022;28:1398–1405; 4. Thijssen EH, et al. Lancet Neurol 2021;20:739–752

Blood/plasma biomarkers: p-tau217 (2/2)

- Studies have shown that **plasma p-tau217 can discriminate AD from other neurodegenerative diseases** and cognitively unimpaired individuals[1,2]
- Plasma **p-tau217 levels are increased in AD but not in neurodegenerative diseases characterized by other types of cerebral tau pathology**, such as progressive supranuclear palsy or corticobasal syndrome[1]

Levels of plasma p-tau217 for AD and other neurodegenerative diseases[1]

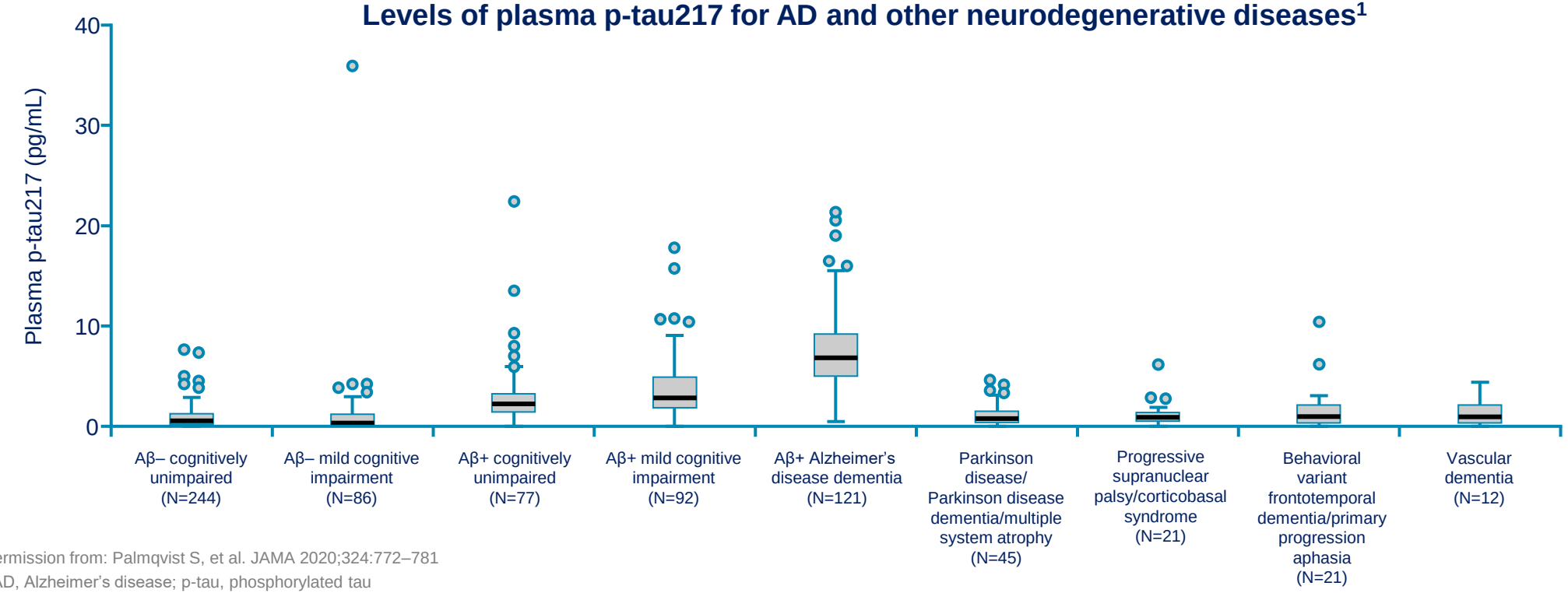


Figure used with permission from: Palmqvist S, et al. JAMA 2020;324:772–781

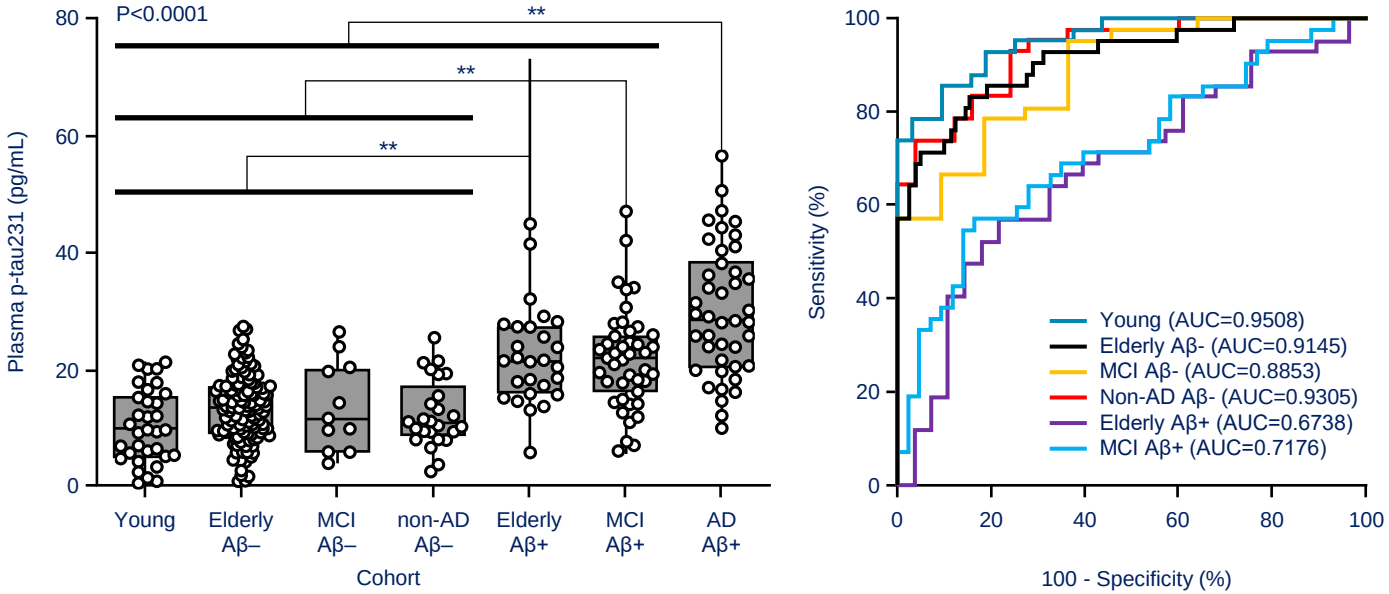
Aβ, amyloid beta; AD, Alzheimer's disease; p-tau, phosphorylated tau

1. Palmqvist S, et al. JAMA 2020;324:772–781; 2. Barthélemy JR, et al. J Exp Med 2020;217:e20200861

Blood/plasma biomarkers: p-tau231

- Plasma p-tau231 has been shown to accurately distinguish AD from non-AD neurodegenerative disorders (AUC=0.93)
  - In the TRIAD validation cohort* plasma p-tau231 was significantly increased in AD dementia and MCI Aβ+ groups compared with Aβ– groups (P<0.0001) (Figure)
- Plasma p-tau231 appears to be closely related to CSF and PET biomarkers
  - Plasma p-tau231 was strongly associated with both Aβ (r = 0.6234; P<0.0001) and tau PET (r=0.5233; P<0.0001), and was highly correlated with CSF Aβ1–42 (r=–0.4044; P<0.0001)

In the TRIAD validation cohort, plasma p-tau231 concentration was significantly increased in AD dementia and had high sensitivity/specificity in differentiating between Aβ+ and Aβ– groups



Plasma p-tau231 demonstrates excellent clinical utility as a rapid screening test for AD, but may serve as a staging biomarker of emerging AD pathology

Figure used with permission from Ashton NJ, et al. Acta Neuropathol 2021;141:709–724 (CC-BY 4.0: https://creativecommons.org/licenses/by/4.0/)

*Young adults, n=32; CU elderly adults, n=159; MCI, n=54; AD, n=42; non-AD, n=26

Aβ, amyloid beta; AD, Alzheimer's disease; AUC, area under the curve; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PET, positron emission tomography; p-tau, phosphorylated tau; TRIAD, Translational Biomarkers of Aging and Dementia

Ashton NJ, et al. Acta Neuropathol 2021;141:709–724

Performance of plasma-based p-tau assays

- The highest performing plasma-based p-tau assays have performance metrics that are comparable to Aβ PET and CSF testing
- A head-to-head comparison in individuals with MCI (N=135) of 10 assays found that an MS-based p-tau 217 assay had significantly better performance than p-tau immunoassays in detecting abnormal Aβ status (AUC=0.947; Pdiff <0.015) and progression to AD (AUC=0.932; Pdiff <0.027)
- These data indicate that some assays may be suitable for use in clinical trials whereas others may require improvement

ROC curve analysis for MCI participants with abnormal CSF Aβ42/40 vs those with normal CSF Aβ42/40

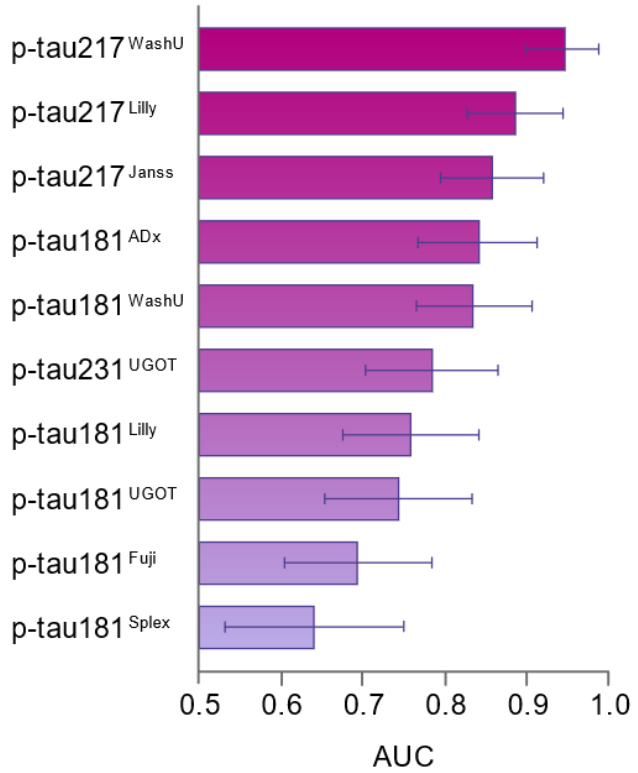


Figure used with permission from Janelidze S, et al. Brain 2023;146:1592–1601

Aβ, amyloid beta; AD, Alzheimer's disease; ADx, ADxNeurosciences; AUC, area under the curve; CSF, cerebrospinal fluid; Fuji, Fujirebio; Janss, Janssen Research and Development; Lilly, Lilly Research Laboratories; MCI, mild cognitive impairment; MS, mass spectrometry; PET, positron emission tomography; p-tau; curve phosphorylated tau; ROC, receiver operating characteristic; Splex, Splex immunoassay from Mesoscale Discovery; UGOT, University of Gothenburg; WashU, Washington University

Janelidze S, et al. Brain 2023;146:1592–1601

Blood/plasma biomarkers: NfL

Serum/plasma NfL correlates strongly with CSF NfL and may be a **reliable biomarker of neurodegeneration in AD and other neurodegenerative diseases**[1]

- Serum NfL is higher than plasma NfL; however, the majority of studies investigating NfL as a blood-based biomarker have utilized plasma to quantify NfL[2]

Cross-sectional studies have shown that **blood-based NfL increases with rising symptom severity across the clinical AD spectrum**[2,3]

- One study (N=196) found that serum NfL peaked in patients converting from presymptomatic to symptomatic AD and was associated with cortical thinning and cognitive changes[4]

Plasma NfL levels have also been shown **to correlate with future atrophy, hypometabolism and cognitive decline in AD**[5]

- One study (N=1583) found that blood-based NfL changed throughout the course of AD and reflected the intensity of neuronal injury[6]

Blood-based NfL may be a useful tool for **monitoring the effects of neurodegeneration** in AD and other neurodegenerative diseases;[6] however, it is **not specific to AD** and cannot be used to distinguish between AD vs non-AD dementia[4]

NfL is usually measured using ultrasensitive enzyme-linked immunosorbent assays on a single-molecule array (Simoa) platform[6]

AD, Alzheimer's disease; CSF, cerebrospinal fluid; NfL, neurofilament light chain

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Blood/plasma biomarkers: GFAP

Studies have shown that plasma GFAP increases along the AD continuum, and levels are increased among individuals with preclinical AD and even higher in symptomatic stages[1]

Plasma GFAP has been found to be associated with positive amyloid PET status,[2,3] and may outperform CSF GFAP in indicating amyloid-beta pathology[3]

- A panel including GFAP, plasma Aβ42/40, age, and APOE status resulted in a positive predictive value of 93%, with a sensitivity of 82%[2]
- One study found that plasma GFAP could predict amyloid PET positivity with greater performance (AUC 0.76) than CSF GFAP (AUC 0.69) in cognitively unimpaired individuals (N=288)[4]

Plasma **GFAP levels were found to be increased in cognitively normal older adults with high brain Aβ load** (n=33) indicating that it may serve as an early blood-based biomarker to identify individuals at risk of AD[5]

- In a longitudinal study (N=1327), **serum GFAP was associated with clinical AD up to 8 years prior to developing AD**[6]

Plasma GFAP is associated with AD-type pathology and can accurately predict clinical progression to AD dementia, suggesting it is an accurate biomarker for AD diagnosis and progression[3,7]

GFAP is usually measured using ultrasensitive enzyme-linked immunosorbent assays on a single-molecule array (Simoa) platform[1]

Aβ, amyloid beta; AD, Alzheimer's disease; APOE, apolipoprotein E; AUC, area under the curve; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; MCI, mild cognitive impairment; PET, positron emission tomography

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