Early Alzheimer's Treatment:

Is there a role for blood-based biomarkers?

DATE: May 15, 2026 PRESENTED BY: Andrew Natonson, MD, Director OHSU Alzheimer's Amyloid Clinic

Disclosures:

- No financial disclosures

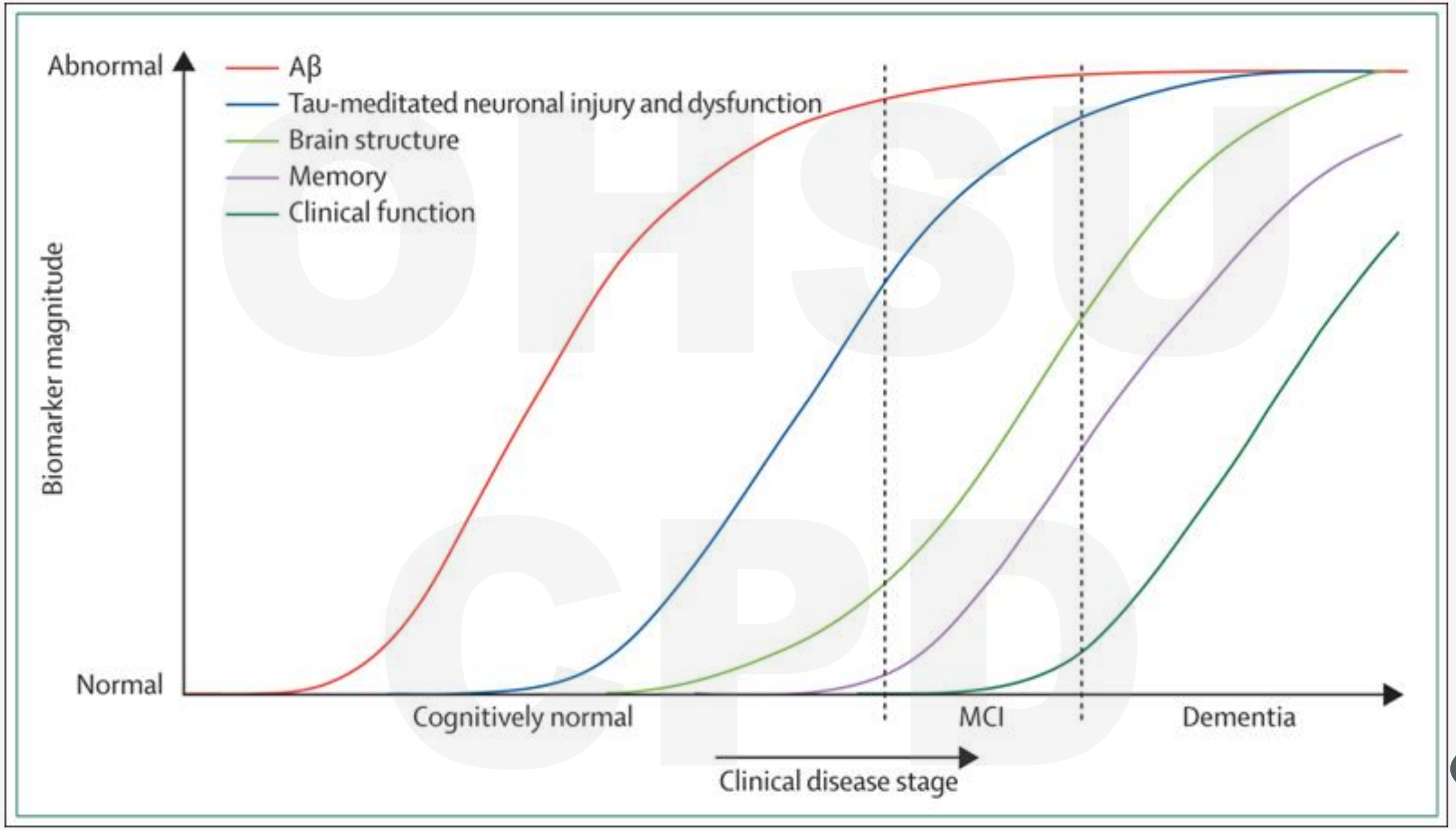
Alzheimer's Disease: The Dementia Revolution

Then (clinical)	Now (biological)
Based on symptoms alone	NIA-AA 2024 framework AT(N) model
Biology only verified post-mortem	Alzheimer's pathology is present regardless of clinical symptoms

NIAA 2024 Framework of AD

- **AT(N)**, continuum from pre-clinical, to MCI, to dementia
- Amyloid testing: amyloid PET +, serum Aβ42/40 ratio, serum p-tau^{217}, serum p-tau^{181} , low CSF $A\beta_{42}$
- Tau testing: high CSF p- tau, tau PET scan
- Neurodegeneration: Structural MRI, FDG-PET, CSF total tau, serum NfL

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	



Alzheimer's disease begins 20 years or more before memory loss and other symptoms develop

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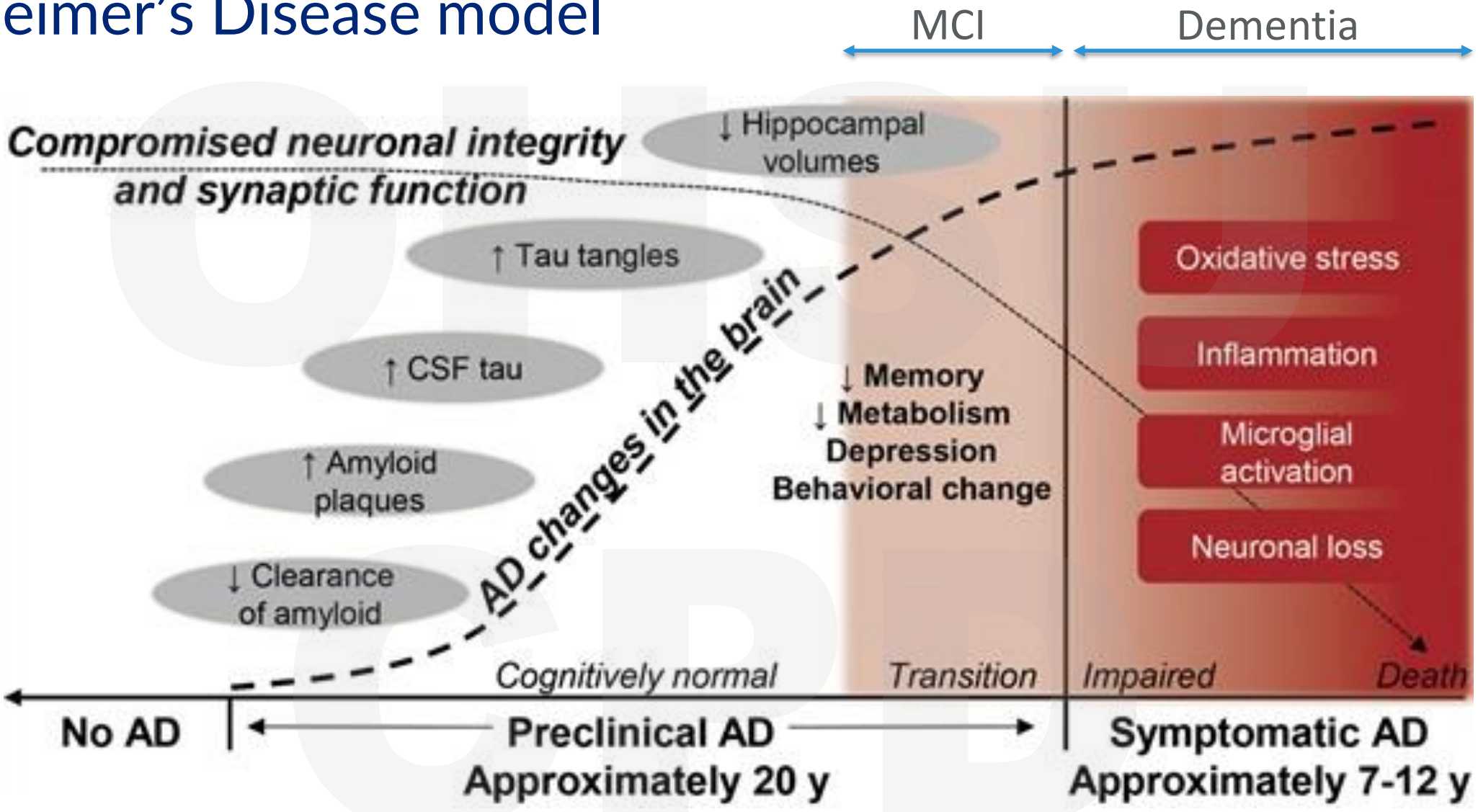
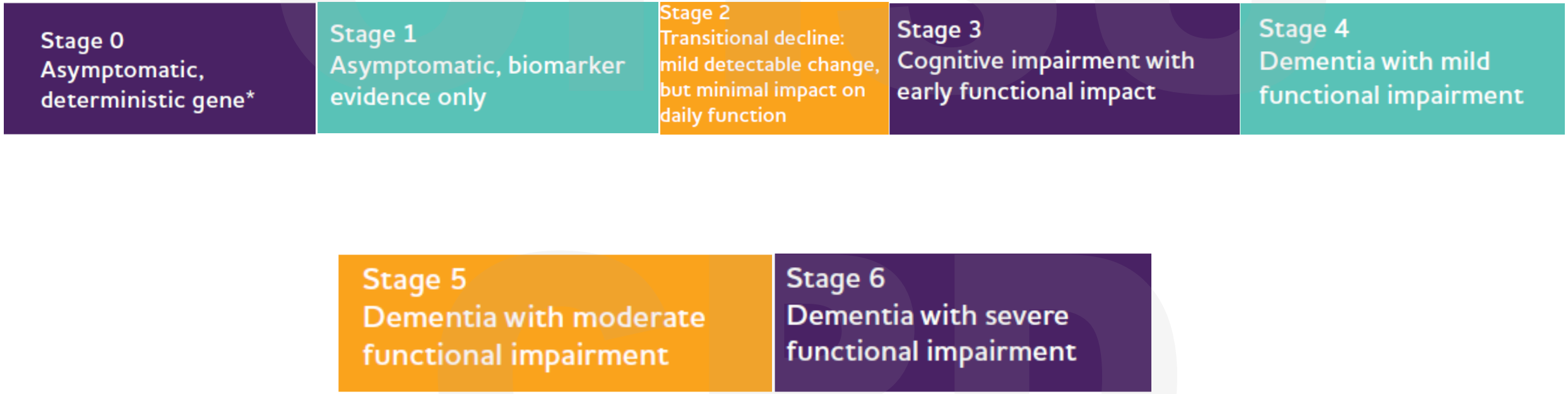
Alzheimer's Disease model



Modified from Continuum 2024

Alzheimer's Stages



Alzheimers Dement 2026;22. https://doi.org/10.1002/alz.71345.

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Alzheimer's Stages

Biological Staging by Positron Emission Tomography (PET)

	Amyloid PET	Tau PET Medial Temporal Lobe Uptake	Tau PET Moderate Neocortical Uptake	Tau PET High Neocortical Uptake	AT_2 Notation
A	+	—	—	—	$A+T_2^-$
B	+	+	—	—	$A+T_{2MTL}^+$
C	+	+	+	—	$A+T_{2MOD}^+$
D	+	+	+	+	$A+T_{2HIGH}^+$

Alzheimers Dement 2026;22. https://doi.org/10.1002/alz.71345.

Integrated Biological and Clinical Staging

	Stage 0	Clinical Stage 1	Clinical Stage 2	Clinical Stage 3	Clinical Stages 4-6
Initial biological stage (A)	NA	1A	2A	3A	4-6A
Early biological stage (B)	NA	1B	2B	3B	4-6B
Intermediate biological stage (C)	NA	1C	2C	3C	4-6C
Advanced biological stage (D)	NA	1D	2D	3D	4-6D

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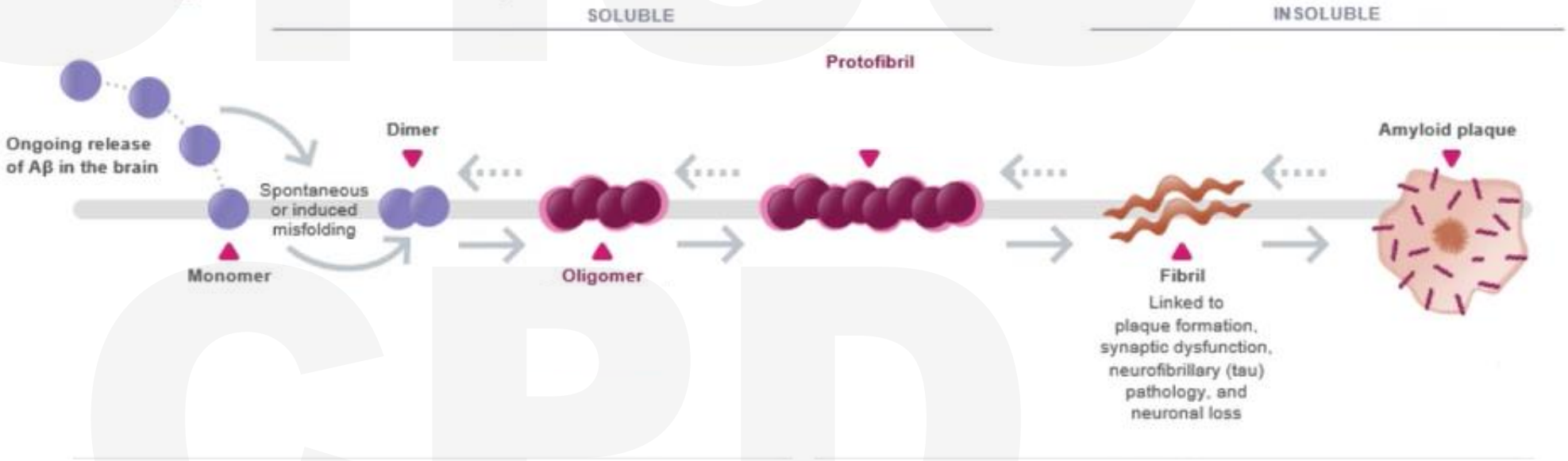
Alzheimer's disease: amyloid



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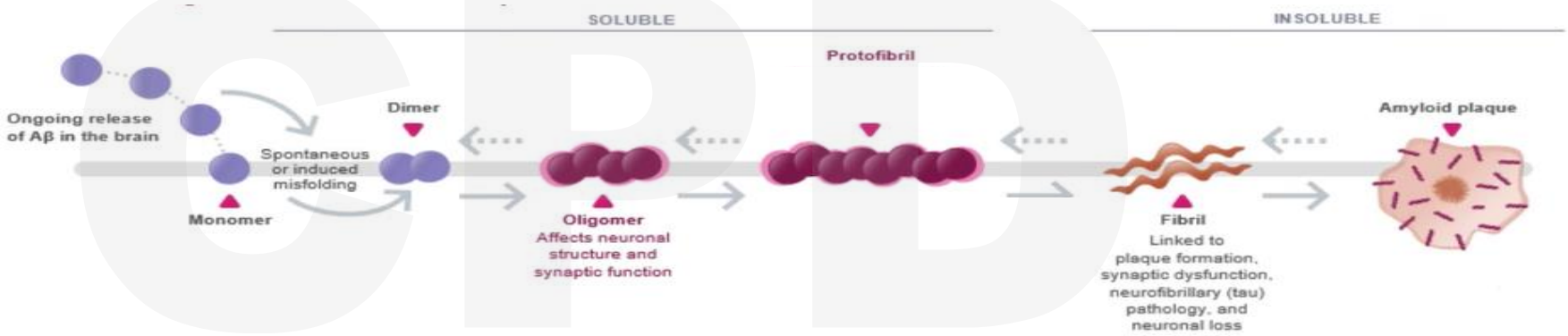
Alzheimer's disease Mabs:

- Aducanumab targets plaques, no clear clinical impact; Donanemab clears faster and more specific binding (TRAILBLAZER-ALZ4)
- Lecanemab targets soluble aggregates (oligomers and *protofibrils*) and plaques CLARITY-AD2 trial + results 2023
- Donanemab, targets amyloid plaques, TRAILBLAZER-ALZ2 + 2023



All of these therapies require positive biomarkers to get approval

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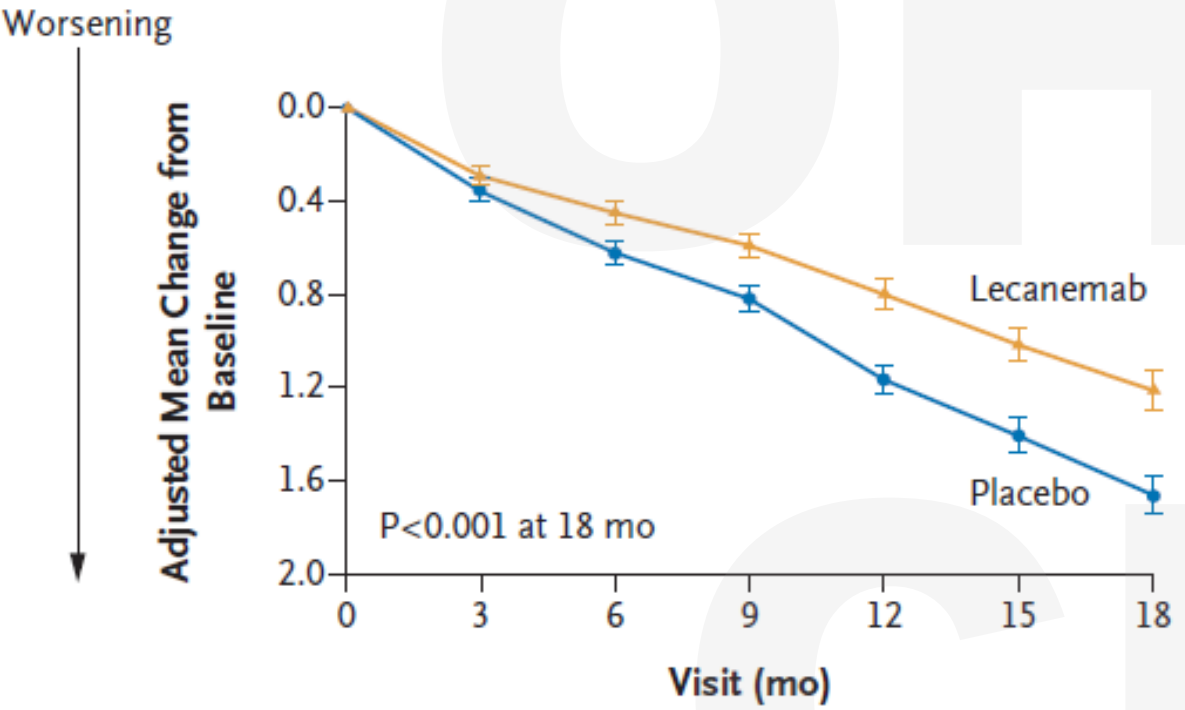
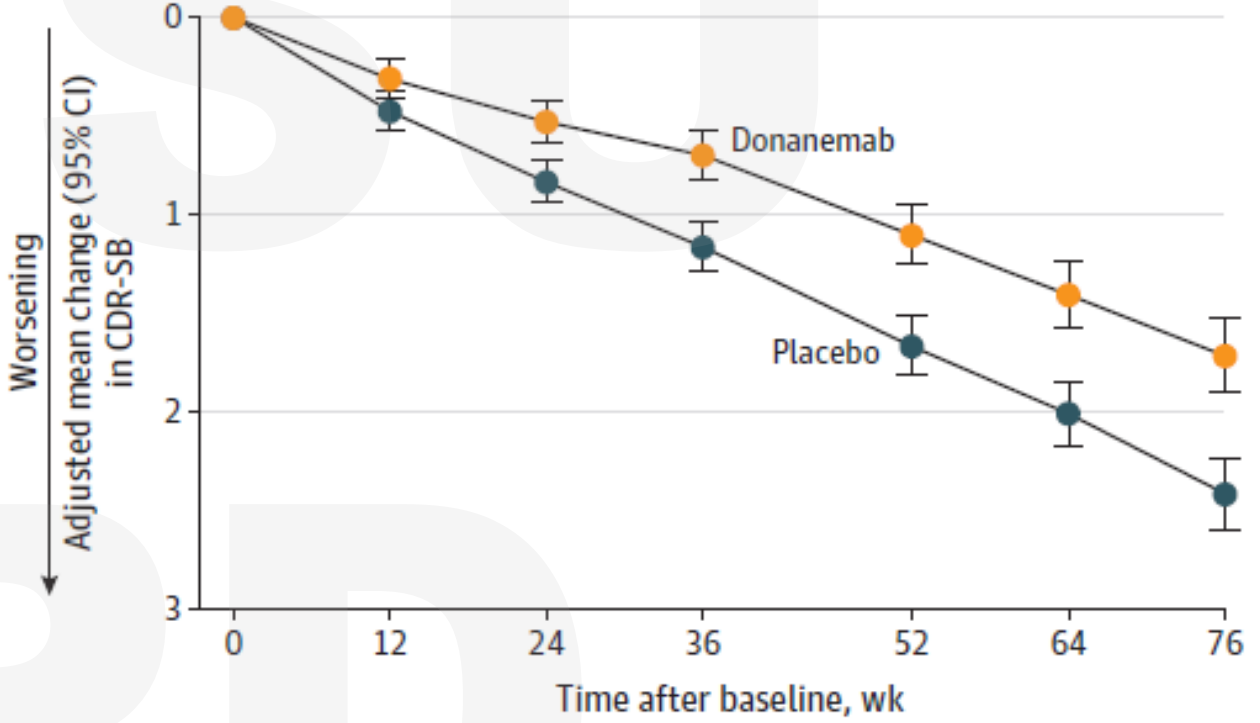
CDR-SB comparison



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757



No. of participants							
Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

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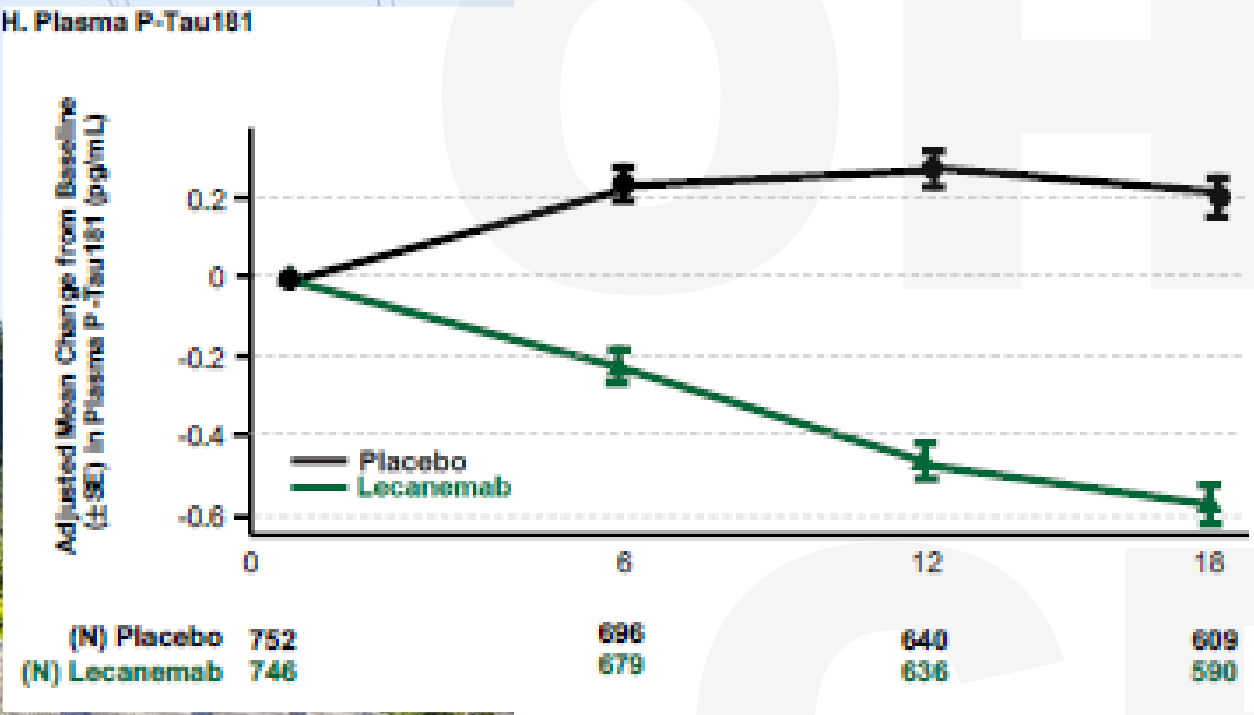
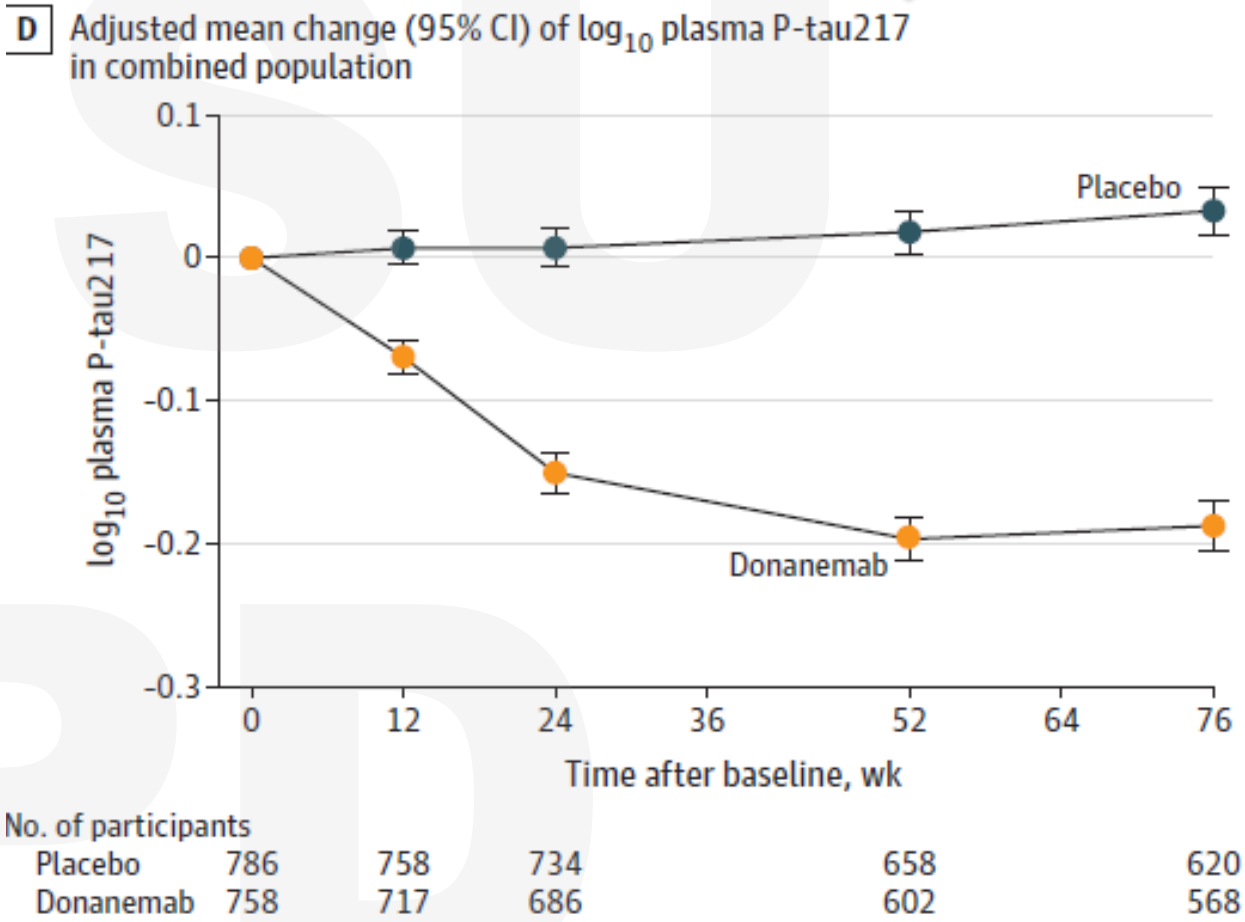
Anti-Amyloid Therapy (AAT) ⬇ tau





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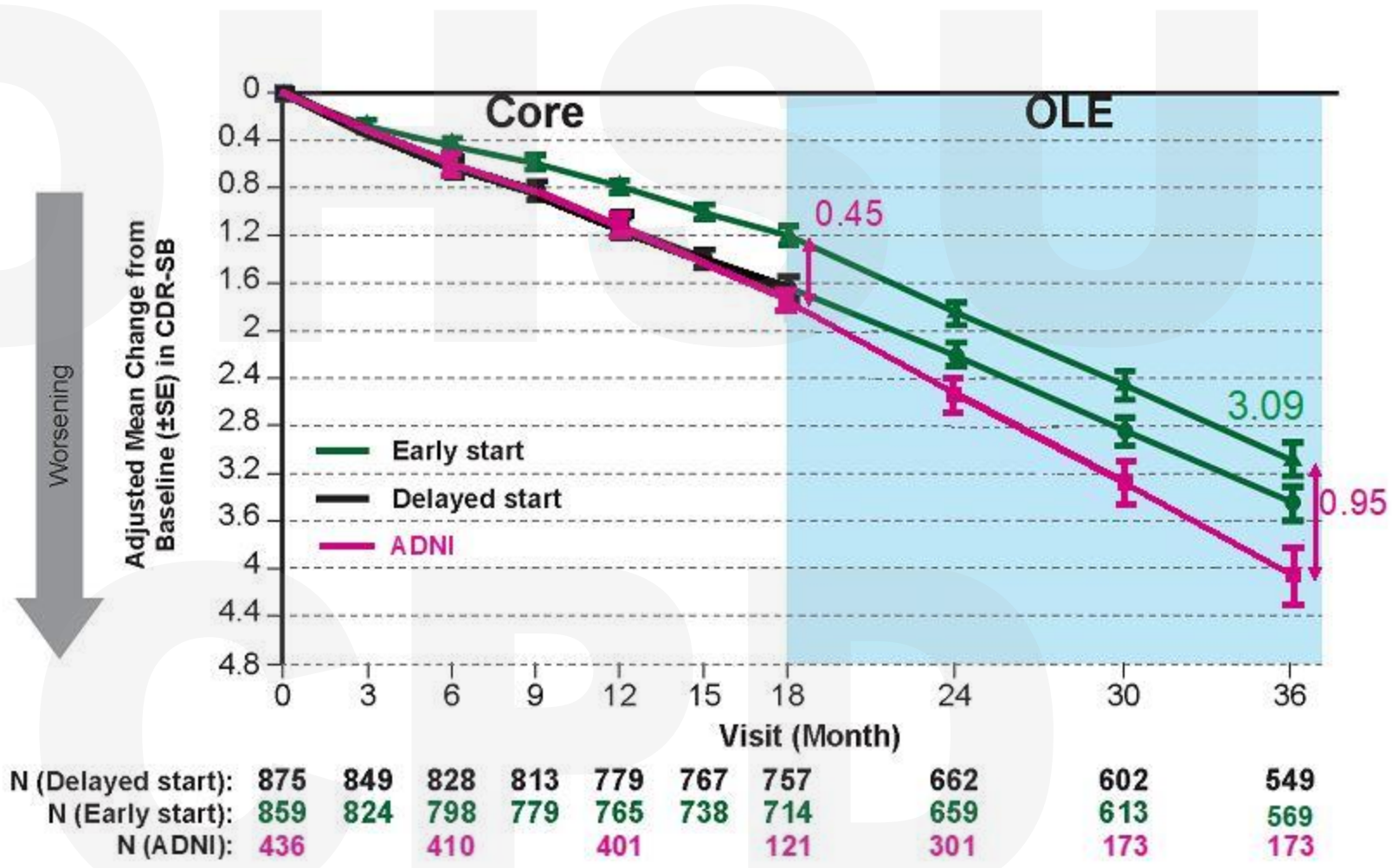
Lecanemab open label extension:



Data from AAIC 2024

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What about blood-based markers?

- All available data regarding outcomes and appropriate use of AAT have focused on PET or CSF biomarkers
- Two BBM were FDA approved in 2025
- Starting February 11th, 2026, CMS has updated their registry to include BBMs as possible confirmation of Amyloid

What about blood-based markers?

Aβ 42/40 ratio - The Original BBM

- Normalizes the amount of abnormal Aβ 42 to normal Aβ40
- Falls in preclinical patients, c/w PET data

Brain 144, 434–449.

- Accurately? (82-97%) differentiates MCI/AD patients from cognitively unimpaired patients

Mol Neurodegener 16, 30.

- Compared to PET, AUC 0.76 – good but not great

Exp Brain Res 236, 1241–1250.

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What about blood-based markers?

pTau181

- In patients with MCI, higher results seen in patients more likely to progress to dementia (3.8 vs 2.9 pg/mL)
- Low results had <20% chance of progression over 3 years
- Can be dependent on renal function or heart failure (false positives)

Alz Res Therapy **14**, 149 (2022)

- Very high negative predictive value (97%)

Journal of Neurology, Neurosurgery & Psychiatry 2023; **94** 420-427

What about blood-based markers?

pTau217 – the most accurate to date, accuracy increases when combined with Aβ42

- Positive correlation with brain atrophy, CSF biomarkers, and cognition in healthy community cohort

Brain Communications, Volume 7, Issue 5, 2025

- In a memory clinic, accuracy between 92-96% compared to CSF

Alz Res Therapy **17**, 150 (2025)

The Blood Biomarker Revolution (FDA Cleared 2025)

The Best Overall

pTau217

(Fujirebio Lumipulse, Cleared May 2025). Measures p-tau217/Ab42 ratio.

Performance: AUC 0.90-0.97.

Utility: Highly sensitive marker of Alzheimer's pathology; rises directly in response to amyloid.

Correlates with AMYLOID, not tau status

The Rule-Out Champion

pTau181

(Roche Elecsys, Cleared Oct 2025).

Performance: 97.9% Negative Predictive Value (NPV).

Utility: FDA-cleared for primary care. If negative, redirect workup away from AD.

The Differentiator

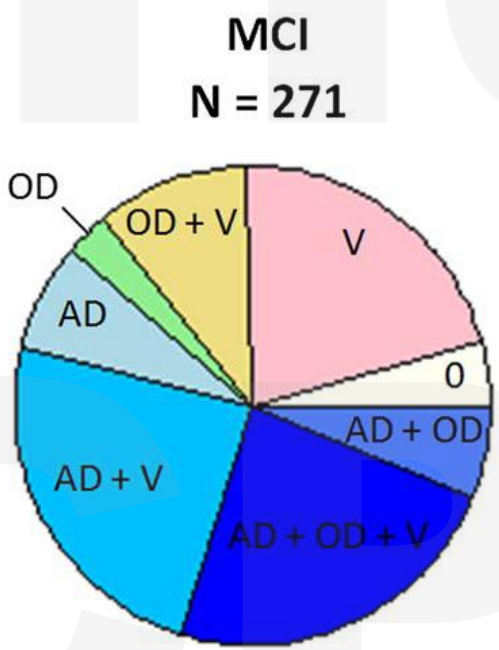
NfL (Neurofilament Light)

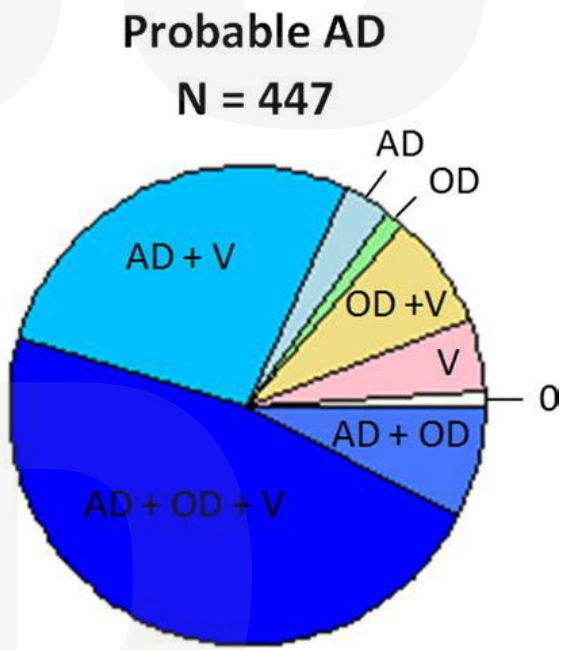
Performance: Non-specific marker of axonal damage.

Utility: Crucial for spotting FTD, where levels are significantly higher than in AD.

Neurodegeneration (N)

Caveat: co-pathology is the norm





Acta Neuropathol (2017) 134:171–186

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Caveat: co-pathology is the norm

- Co-pathology was not monitored with biomarkers in AAT clinical trials. Parkinsonism and severe CVD were excluded.
  - Some co-pathology likely snuck in
  - Ongoing studies looking for patients with biomarkers of Lewy Body & AD for AAT now

Caveat: Co-morbidities may impact serum levels

- Knowns:
  - Impaired renal function
  - High BMI
  - Diabetes
  - Impaired liver function
  - TBI
  - Stroke

Alzheimers Dement. 2022 Sep 24;19(4):1403–1414
Alzheimers Dement. 2025 Jan; 21(1)

Caveat: Possible ethnic/racial differences

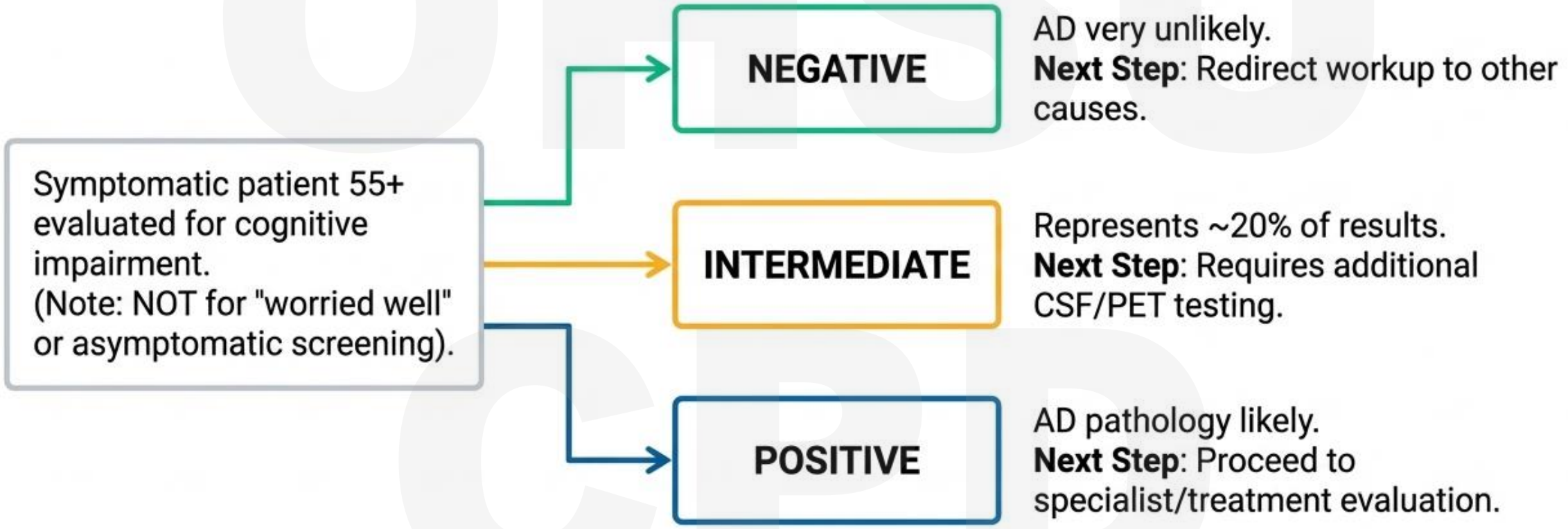
- There are known racial/ethnic differences in presentation of AD
- Minorities are under-represented in all dementia research, particularly AAT
- Conflicting data on biomarkers currently

Journal of Alzheimer's Disease. 2025;103(1):81-91

BBM – current use/limitations

- Payers are still not consistent with coverage
  - Typical patients will not pay more than $800
  - Financial assistance available
- Some payers may still require CSF/PET before approving AAT

The Triage Algorithm: Interpreting Blood Tests



Rule: Blood tests are triage tools. A negative result is highly reliable; positives require confirmatory testing.

Skin Biopsy for α-Synuclein (DLB)— NOW AVAILABLE

Syn-One Test (CND Life Sciences) — NIH "Top Promising Medical Finding 2024"

Sensitivity	**93-100%**	across synucleinopathies (PD, DLB, MSA, PAF)
Specificity	**>95%**	zero false positives in non-synucleinopathy controls
Coverage	**Medicare**	participating provider; commercial coverage expanding

Source: Gibbons CH, et al. JAMA. 2024;331(15):1298-1306

Future:

- Recruitment is complete for AHEAD: can lecanemab prevent AD in patients with biomarkers but no symptoms? Stay tuned

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- Recruitment is complete for AHEAD: can lecanemab prevent AD in patients with biomarkers but no symptoms? Stay tuned
- Lecanemab may soon be available as a SC pen injector (FDA scheduled to vote May 24th, 2026)
- If patients are interested in being in research, please have them email ADResearch@OHSU.edu

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Summary:

- Blood based biomarkers for Alzheimer's disease are now widely available (Quest labs, Labcorp, others)
- Blood based biomarkers have a role in triage of memory patients
- Intermediate results should prompt confirmatory testing
- Positive results can potentially be used to support AAT for early Alzheimer's disease with Medicare, but not commercial payers currently
- New biomarkers for other dementias are emerging; don't forget about possible co-pathology

Questions?

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Thank You