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# Alzheimer’s disease: How plasma p-tau rewrites diagnosis

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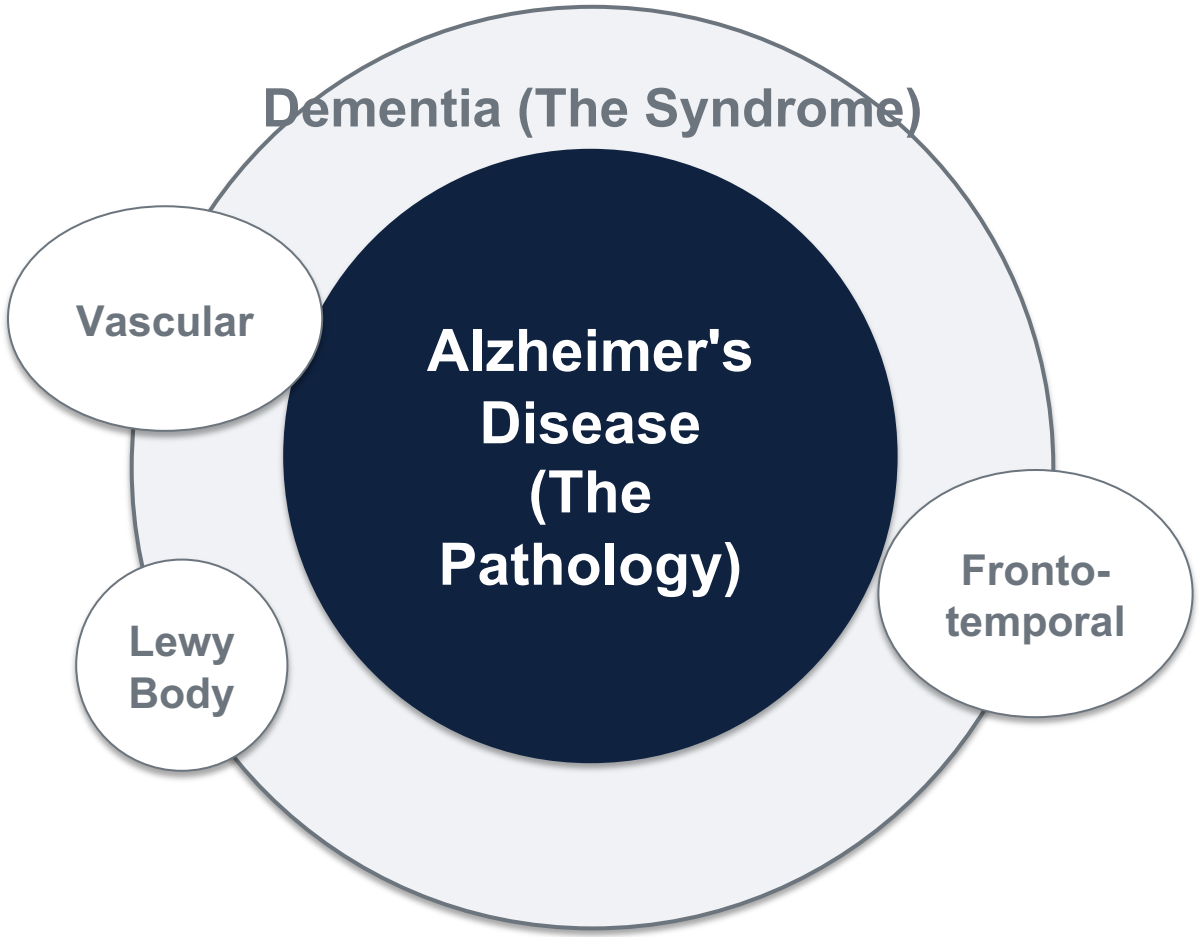
# Dementia is a Clinical Syndrome; Alzheimer's is its Leading Biological Cause

**Not every dementia is Alzheimer's Disease (AD).**

Mild cognitive impairment or dementia can stem from various underlying biological and medical conditions, such as vascular injuries, Lewy bodies, or frontotemporal degeneration.

**AD accounts for an estimated 60% to 80% of all dementia cases.**



THE ASTANA TIMES
BRINGING KAZAKHSTAN TO THE WORLD

## Alzheimer's in Kazakhstan: What Explains Rising Diagnosis

BY NAGIMA ABUOVA *in* EDITOR'S PICKS, NATION *on* 31 MARCH 2026

ASTANA — With more than 55 million people living with dementia globally, Kazakhstan is seeing an upward trajectory in Alzheimer's disease incidence. Experts say the increase reflects demographic ageing, improved recognition of cognitive decline and more systematic case registration.

Photo credit: shutterstock

"It was once believed that Alzheimer's disease or dementia was becoming younger, but in fact, it turned out that we simply began to detect it better. Doctors have become more aware of cognitive decline and pay more attention to identifying these disorders. (…) Most likely, this reflects better detection rather than the disease truly becoming younger," candidate of medical sciences and psychotherapist Zhibek Zholdasova told The Astana Times.

# The Global Burden and the Prevention Window

## 315 Million

Cognitively unimpaired individuals who are biomarker-positive. This represents a massive three-fold population in the "preclinical" window.

## 101 Million

Estimated global prevalence of individuals with cognitive impairment due to Alzheimer's pathology (MCI and dementia).

## 14 Modifiable Factors

Controlling risk factors like hypertension, hearing loss, and air pollution could theoretically account for 45% of all dementia cases, driving down age-incidence in high-income countries.

*Synthesized from The Lancet Series on Alzheimer's Disease 2025*

# Etiology of Alzheimer's Disease

| Dimension | Sporadic AD | Familial AD |
|---|---|---|
| **Frequency** | Most common (>95%) | Very rare (Under 5% of all cases) |
| **Etiology** | Multifactorial (complex interaction of age, genetics, and environment) | Hereditary; Autosomal dominant type of inheritance |
| **Genetic Drivers** | APOE ε4 (major risk factor, but not deterministic) | Deterministic mutations in genes for Presenilin 1 (PSEN1), Presenilin 2 (PSEN2), and Amyloid Precursor Protein (APP) |
| **Age of Onset** | Typically late-onset (older age) | Usually develops at a younger age (early-onset) |
| **Modifiable & Environmental Factors** | Lifestyle, diet, education, vascular health, pollution. | Minimal impact due to deterministic genes. |

# The Amyloid Hypothesis: Imbalance in Aβ production and clearance drives plaque accumulation.

### ❖ Step 1

Amyloid Precursor Protein (APP) is cleaved by β-secretase and γ-secretase at the cell membrane.

### ❖ Step 2

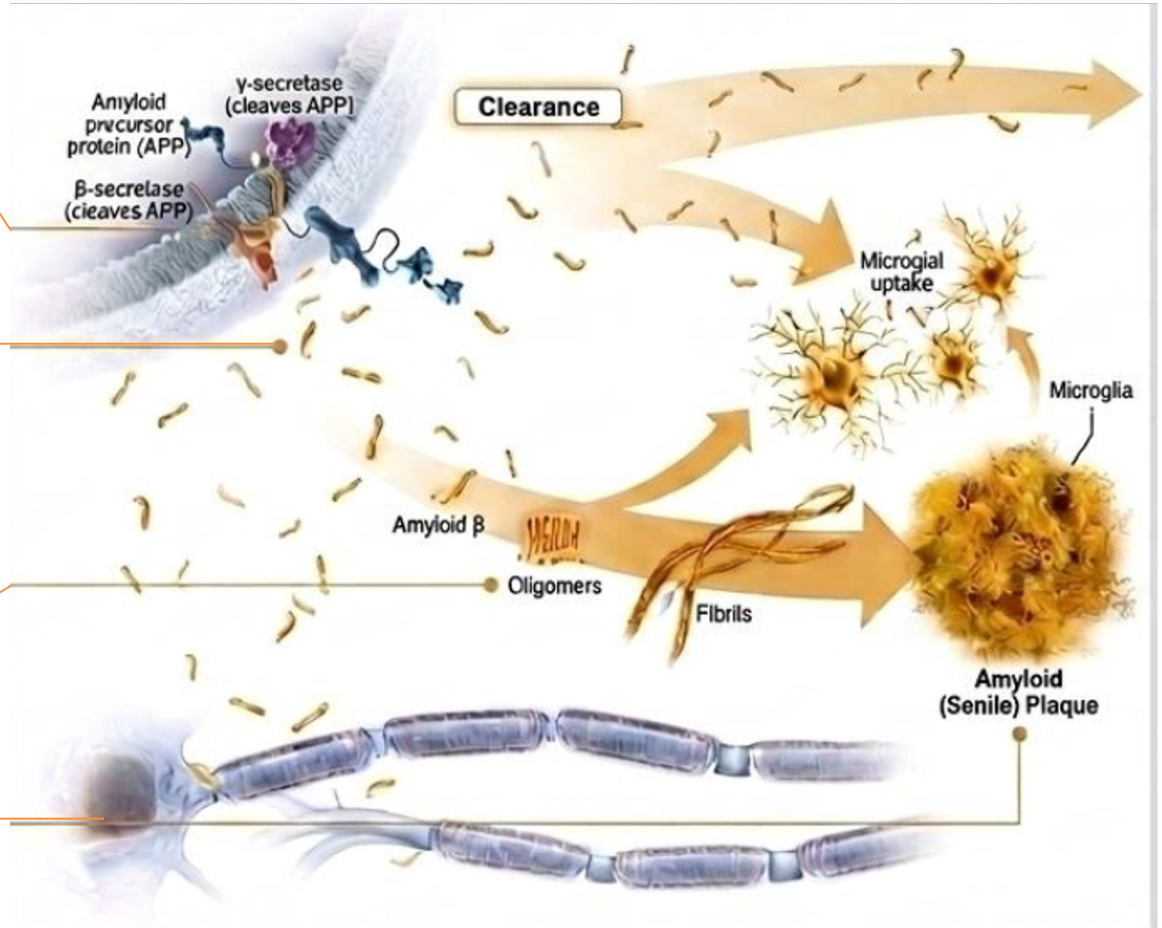
This cleavage produces Amyloid β (Aβ) peptides. Oxidative stress, impaired energy metabolism, hypoxic/ischemic insults, disrupted lipid homeostasis, and chronic neuroinflammation may affect BACE1 expression, endosomal processing, or APP trafficking.

### ❖ Step 3

Aβ peptides aggregate into oligomers, then fibrils.

### ❖ Step 4

Fibrils accumulate externally as Amyloid (Senile) Plaques, triggering an inflammatory response and microglial uptake. This process initiates neuronal damage.




*Rubino et al. 2018, www.nature.com/articles/d42473-018-00068-2*

# Hyperphosphorylated tau destroys neuronal structural integrity from within.

❖ **Step 1**

Inside a healthy neuron, tau proteins stabilize microtubules, which are essential for nutrient transport.

❖ **Step 2**

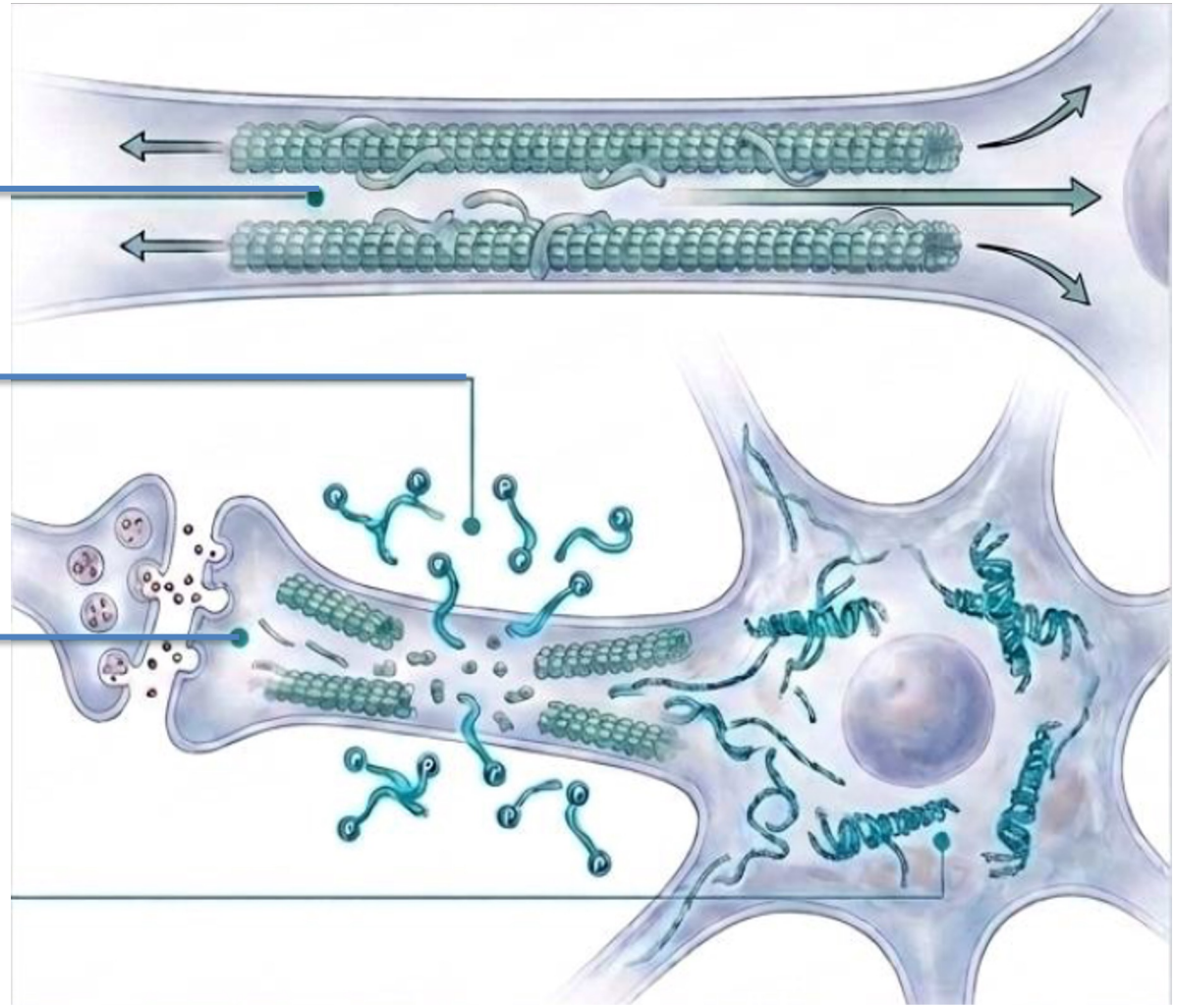
In AD, tau becomes hyperphosphorylated (ptau), detaching from microtubules.

❖ **Step 3**

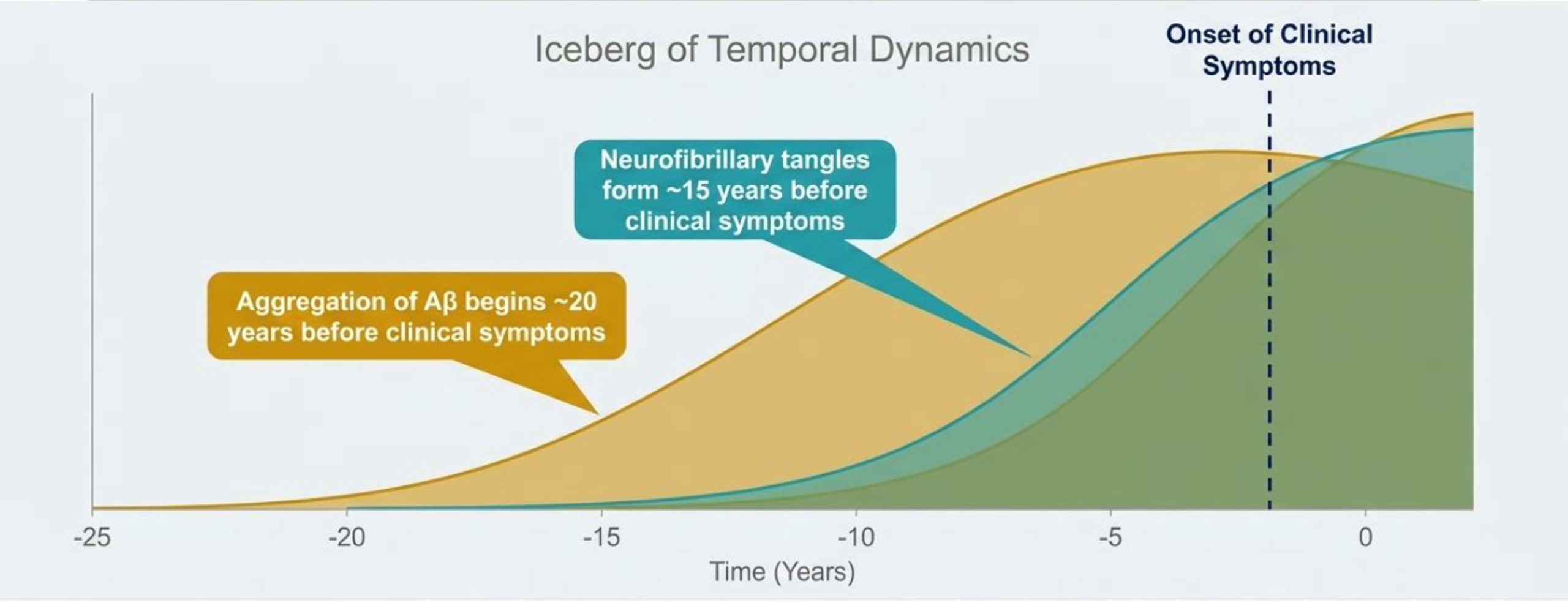
The destabilized microtubules collapse, impairing synaptic function and leading to neurodegeneration.

❖ **Step 4**

The detached tau proteins clump together inside the neuron to form Neurofibrillary Tangles (NFTs).

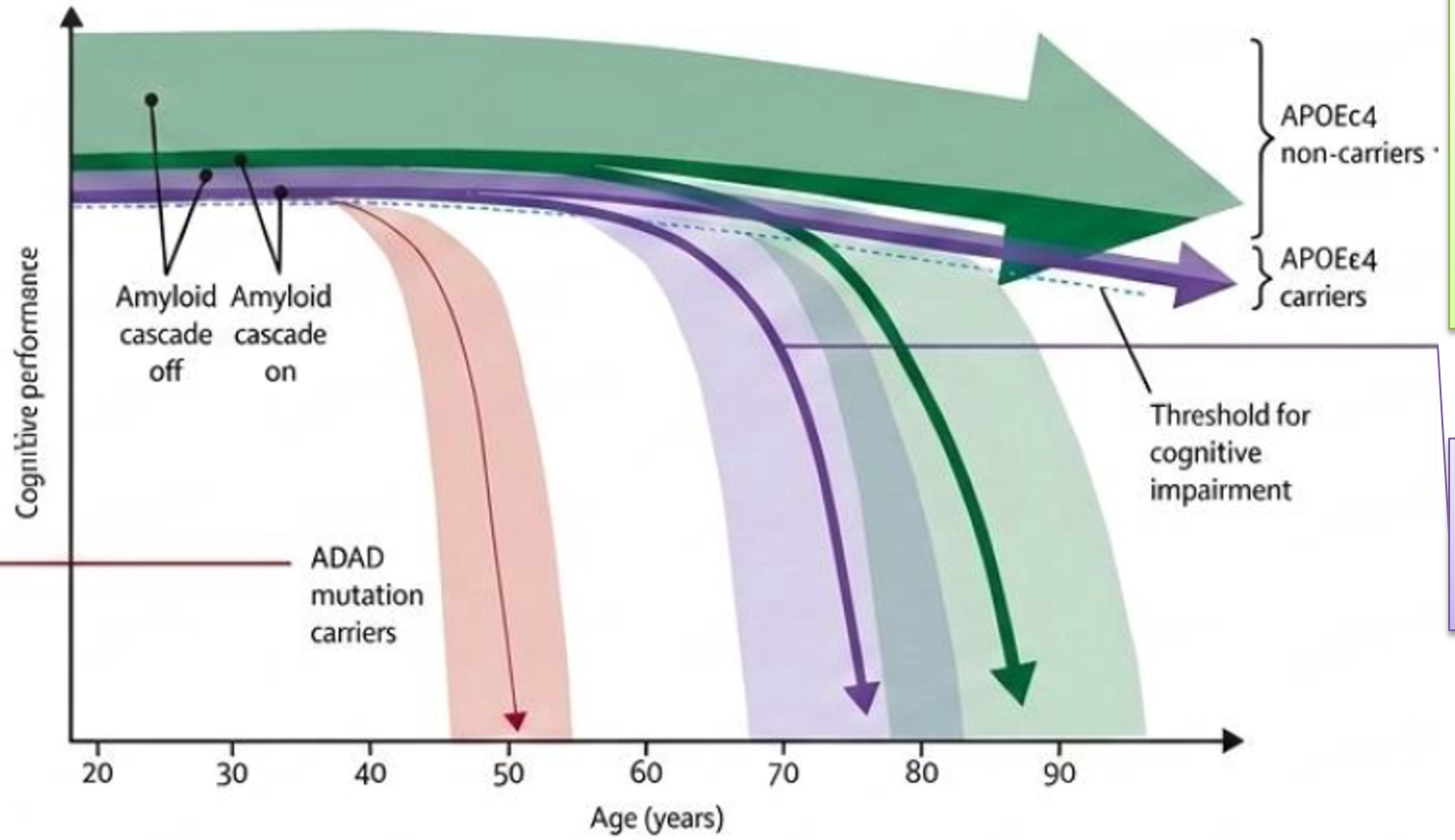


# Pathological changes silently precede cognitive symptoms by up to two decades




**Key Insight:** By the time mild cognitive impairment or dementia is clinically detectable, extensive, irreversible biological accumulation has already occurred.

# The Diverging Paths of Cognitive Ageing




Non-carriers, showing wide variability in crossing the cognitive impairment threshold

Autosomal Dominant (ADAD) mutation carriers

APOE ε4 carriers (high genetic risk)

Disease biology is patient-specific. Individuals enter the amyloid cascade at different times, and resilience against cognitive decline varies based on stochastic factors, such as non-APOE risk or protective genes, non-AD co-pathologies, lifestyle factors, frailty, and environmental exposures.

# Alzheimer's disease research timeline

1906 — Dr Alois Alzheimer first discovers AD[1]

1982 — Clinical criteria for 'probable AD dementia' published[3]

1984 — APP gene identified as risk factor[4]

1987 — Braak staging system for neurofibrillary tangles first published[5]

1991 — Acetylcholinesterase inhibitors first introduced as AD therapeutic drugs[6]

1993 — Memantine, a non-competitive NMDA receptor antagonist, approved for AD in the US and Europe[7]

2003 — Publication of amyloid-PET performed in living humans for the first time[8]

2004 — Preclinical AD characterized[9]

2011 — Accepted biomarker models of AD published[10,11]

2012-2013 — High-performance blood biomarkers for phosphorylated tau developed and validated in multiple cohort studies[12]

2020 — FDA accelerated approval of aducanumab (the first disease-modifying therapeutics for AD)[13]

2021–2022 — Positive results of the Phase 3 randomized clinical trial of donanemab in early symptomatic AD are published[14]

2023 — FDA converted accelerated approval of lecanemab to traditional approval[15]

**The path to the amyloid hypothesis took nearly 80 years.**

**1906** — Clinical Observation
Alois Alzheimer first describes the defining neuropathological hallmarks of the disease: senile plaques and neurofibrillary tangles.

**1984** — Molecular Decoding: Amyloid
Beta-amyloid is discovered as the primary component of senile plaques, leading to the formulation of the Amyloid Hypothesis.

**1985** — Molecular Decoding: Tau
Hyperphosphorylated tau is identified as the main component of neurofibrillary tangles (NFTs).

**Abbreviations:** APP,amyloid precursor protein; FDA,US Food and Drug Administration; NMDA, N-methyl-D-aspartate; PET, positron emission tomography

**Sources:** 1)Hippius & Neundörfer. Dialogues Clin Neurosci 2003;5(1):101–108; 2)Bartus et al. Science 1982;217(4558):408–414; 3)McKhann et al. Neurology 1984;34(7):939–944; 4)Kang et al. Nature 1987;325(6106):733–736; 5) Braak & Braak. Acta Neuropathol 1991;82(4):239–259; 6)Marucci et al. Neuropharmacology 2021;190:108352; 7)Thomas et al. Clin Interv Aging 2009;4:367–377; 8)Klunk et al. Ann Neurol 2004;55(3):306–319; 9)Sperling et al. Alzheimers Dement 2011;7(3):280–292; 10)Bateman et al. N Engl J Med 2012;367(9):795–804;11) Jack et al. Lancet Neurol 2013;12(2):207–216; 12)Karikari et al. Nat Rev Neurol 2022;18(7):400–418; 13)FDA 2021. https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease. Accessed Nov 2023; 14)Sims et al. JAMA 2023;330(6):512–527; 15)FDA 2023. https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval. Accessed Nov 2023

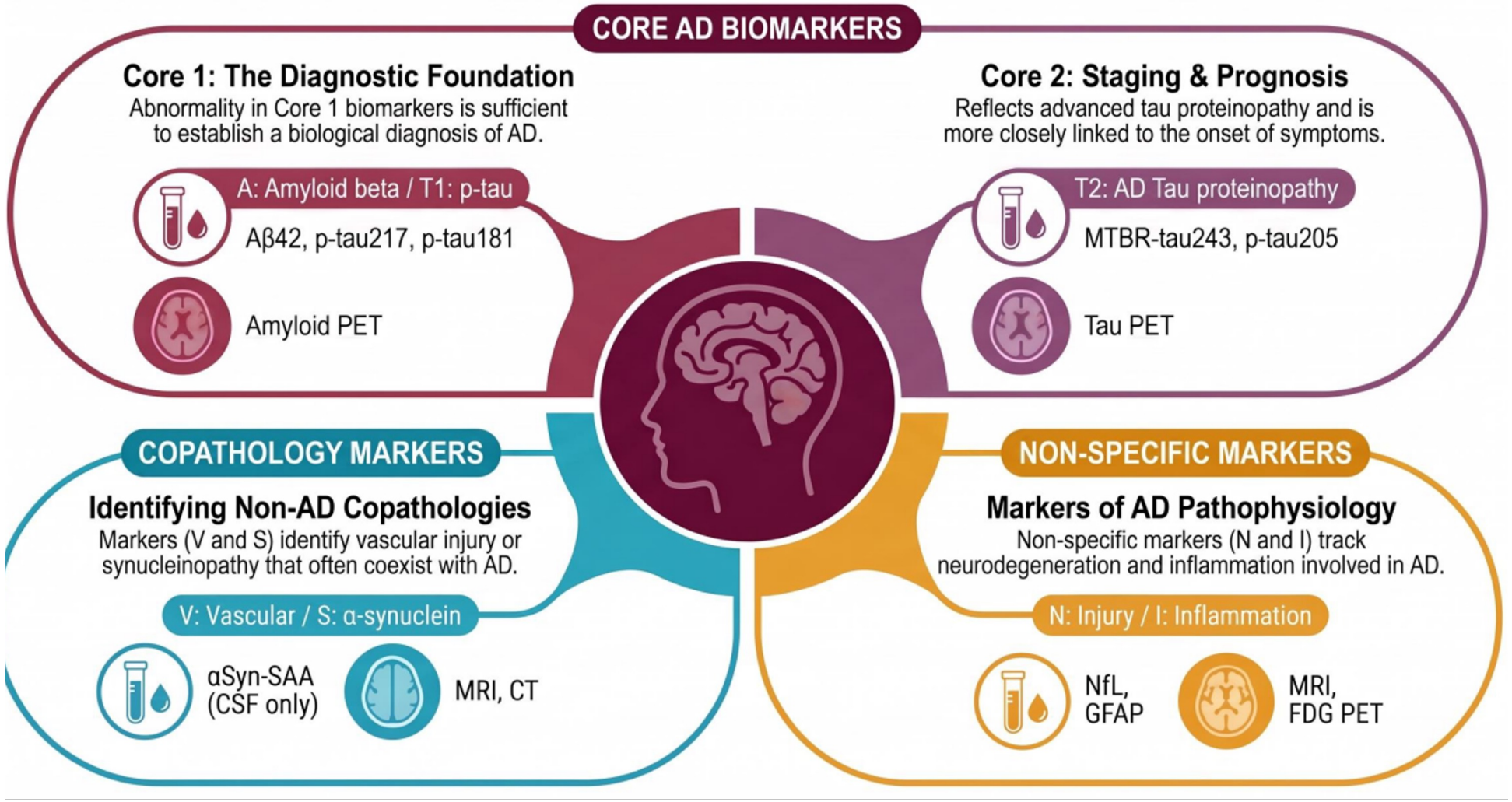
# AD staging framework based on the AD-related biomarker profile and AD clinical continuum

| | Cognitively Unimpaired | Mild Cognitive Impairment (MCI) | Dementia |
|---|---|---|---|
| **A (amyloid) T (tau) and N (neurode generation)** | Alzheimer's pathologic change Biomarker profile **A+ T- (N)-** | Prodromal Alzheimer's disease | |
| | Preclinical Alzheimer's Disease Biomarker profile **A+ T+ (N)- or A+ T+ (N)+** | | |

**Takeaway: Current AD criteria (NIA-AA, IWG-2) move the definition of AD toward underlying pathological processes, allowing for specific diagnosis as early as the presymptomatic phase.**

# Current AD Diagnostic Criteria (Jack CR et al. 2024)

The 2024 revised criteria define Alzheimer's Disease (AD) biologically. Diagnosis is anchored to "Core 1" biomarkers, while "Core 2" and non-core markers are used for staging, prognosis, and identifying co-existing conditions.



# The Reality of the Clinic: Why Biomarkers Matter

## Distribution of Conditions in Memory Clinic Patients

- 30% : Alzheimer's Disease
- 10% : Pure Vascular Cognitive Impairment
- 14% : Reversible Conditions
- 13% : No Cognitive Impairment
- 11% : Dementia with Lewy Bodies
- 22% : Other Conditions

*70% of memory clinic patients have conditions other than Alzheimer's. Biomarkers are essential to prevent misdiagnosis and inappropriate prescription of anti-amyloid therapies. Without biomarkers the diagnostic accuracy is about 60-70%.*

*Frisoni et al. 2025* ***The Lancet*** *Series on Alzheimer's Disease*

# The Evolution of Alzheimer's Diagnosis

## PURELY CLINICAL DIAGNOSIS

**60–70% ACCURACY**

Historically reliant on late-stage cognitive impairment and non-specific medial temporal atrophy.

## CLINICAL-BIOLOGICAL DIAGNOSIS

**90–95% ACCURACY**

Requires in-vivo biomarker confirmation of β-amyloid plaques and tau tangles. This molecular confirmation is now a mandatory prerequisite for newly approved anti-amyloid monoclonal antibodies (lecanemab, donanemab).

*Sources: Frisoni et al. 2025* ***The Lancet*** *Series on Alzheimer's Disease*

# The Biomarker Toolkit – pros and cons

| PET (Amyloid/Tau) | CSF | Blood (Plasma) | Structural MRI |
|---|---|---|---|
| Measures insoluble aggregates and topography. | Measures dynamic dysmetabolism (soluble Aβ42/40, p-tau181). | Measures p-tau217, p-tau181 and Aβ42/40 ratios. The emerging frontline tool. | Measures downstream neuronal/axonal loss (neurodegeneration). |
| Highly accurate for moderate/severe pathology. | Highly sensitive to early changes. | High positive/negative predictive value. | Late-stage and non-specific for molecular AD. |
| Extremely costly and limited availability. | Invasive lumbar puncture required | Massively scalable, simple blood draw. | |

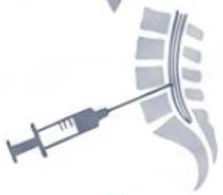
***CSF and PET biomarkers provide largely concordant evidence of AD pathology, but they are not fully interchangeable. Blood-based biomarkers (BBM) are increasingly used as scalable triage tests.***

# The Diagnostic Revolution

## THE HISTORICAL AND CURRENT PARADIGM

**Post-mortem reliance**

**Invasive & Expensive (CSF/PET)**



**Limited to specialized tertiary centers**

## THE NEW PARADIGM

- ✓ **Highly scalable plasma testing**
- ✓ **Primary-care accessible**
- ✓ **Molecular precision in living patients**

# 2025 Clinical Practice Guidelines

## Triage (Rule Out)

**≥ 90% Sensitivity**

**≥ 75% Specificity**

Safely rules out AD pathology in specialized care settings.

## Confirmation (Rule In)

**≥ 90% Sensitivity**

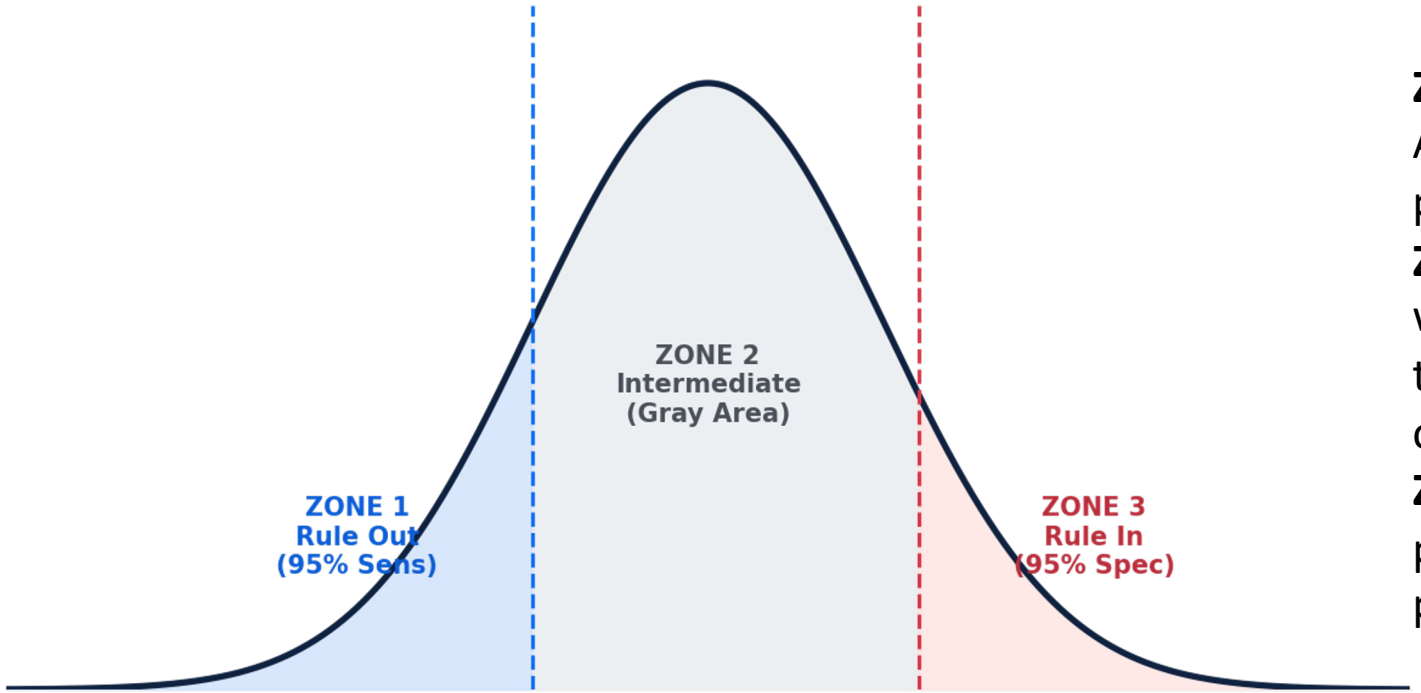
**≥ 90% Specificity**

Serves as a direct substitute for amyloid PET imaging or CSF biomarker testing.

**Clinical Context Imperative: BBM tests must be paired with comprehensive clinical evaluation by a memory disorder professional; they are not standalone diagnostics.**

*Sources: Palmqvist S et al.: Alzheimer's Association Clinical Practice Guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings. Alzheimers Dement. 2025*

# Memory Clinic Implementation: The Dual-Cutoff Strategy



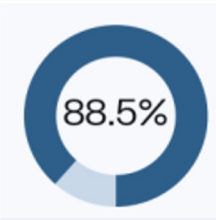
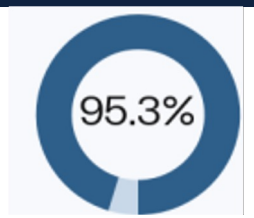
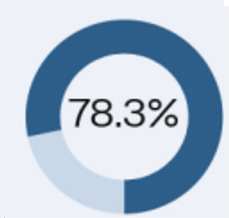
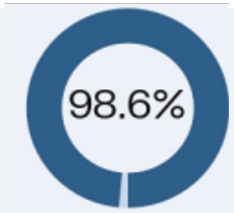
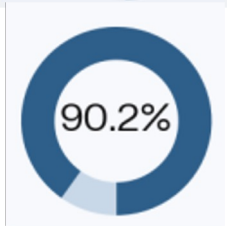
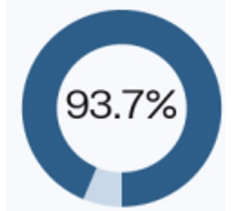

**ZONE 1: Rule Out:** Set at 95% sensitivity. A negative result safely redirects the patient away from the AD pathway.
**ZONE 2: Intermediate:** The "gray area" where blood results are ambiguous. Only these patients require confirmatory CSF or amyloid PET testing.
**ZONE 3: Rule In:** Set at 95% specificity. A positive result confidently diagnoses AD pathology.

**The Big Impact: By utilizing this dual-cutoff architecture, specialized clinics can safely avoid up to 65% of invasive lumbar punctures without sacrificing diagnostic accuracy.**

*Sources: Palmqvist S et al. Alzheimers Dement. 2025,* Schindler *et al. Nat Rev Neurol.* 2024, *Brodini G et al. Alzheimers Dement. 2026*

# Diagnostic Accuracy of pTau217 Blood Test

Performance vs. amyloid PET across clinical cohorts with different disease prevalence

| Cohort | Amyloid Prevalence (PET-positive) | PPV (Positive Predictive Value) | NPV (Negative Predictive Value) |
|---|---|---|---|
| **Overall Validation Cohort (N = 958)** | 39.5% amyPET+ |   |   |
| **Primary Care (N = 238)** | 21.4% amyPET+ |   |   |
| **Secondary / Tertiary Care (N = 720)** | 45.4% amyPET+ |   |   |

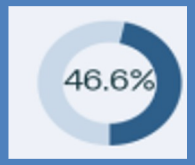
*Source: Plasma pTau217 assay clinical validation data; amyloid PET used as reference standard.*

# Elecsys pTau181 Blood Test: Actual & Modelled PPV/NPV

**Performance vs. amyloid PET (RD006263 study) and modelled predictive values across prevalences**

## Actual Observed Performance

*Study RD006263, N = 650, prevalence 22.5%*

| | | | |
|---|---|---|---|
| Cut-off = 0.934 pg/ml (original) | Sensitivity 83.6%, Specificity 72.2% |   Positive Predictive Value |   Negative Predictive Value |

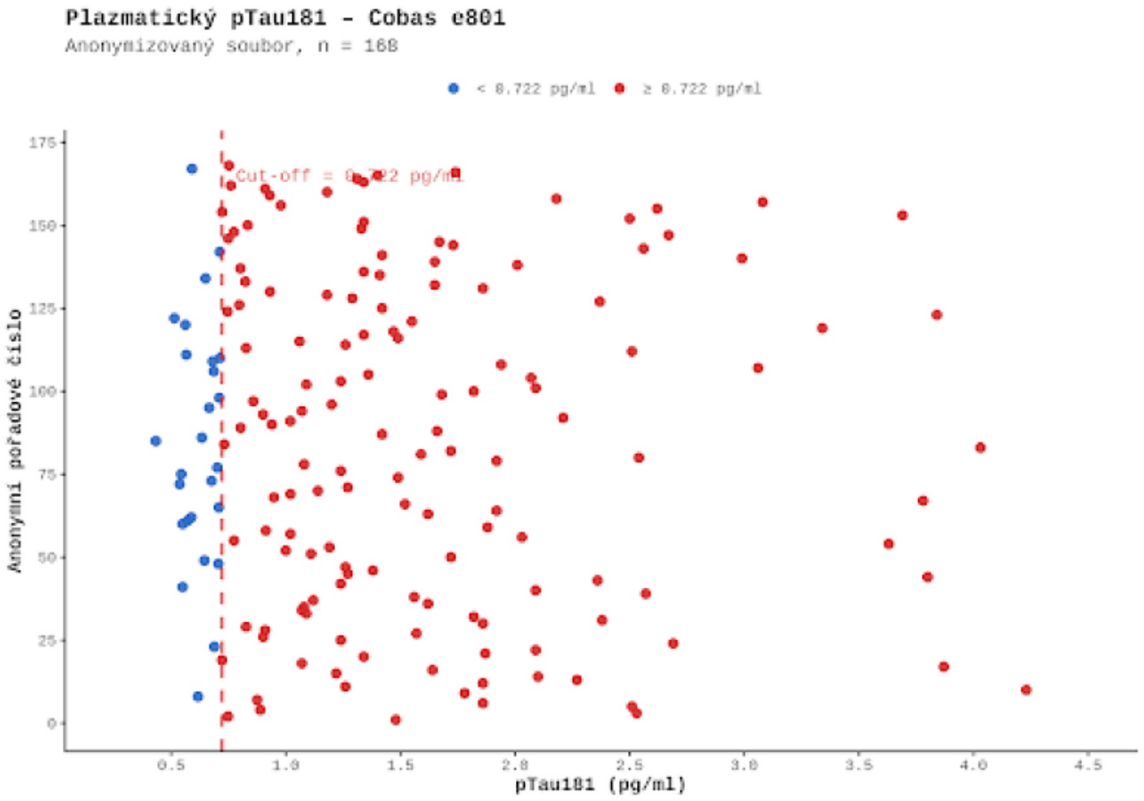
**Updated cut-off (July 2026)** New cut-off set at 0.722 pg/ml; New NPV = 94.8% for ruling out amyloid pathology.

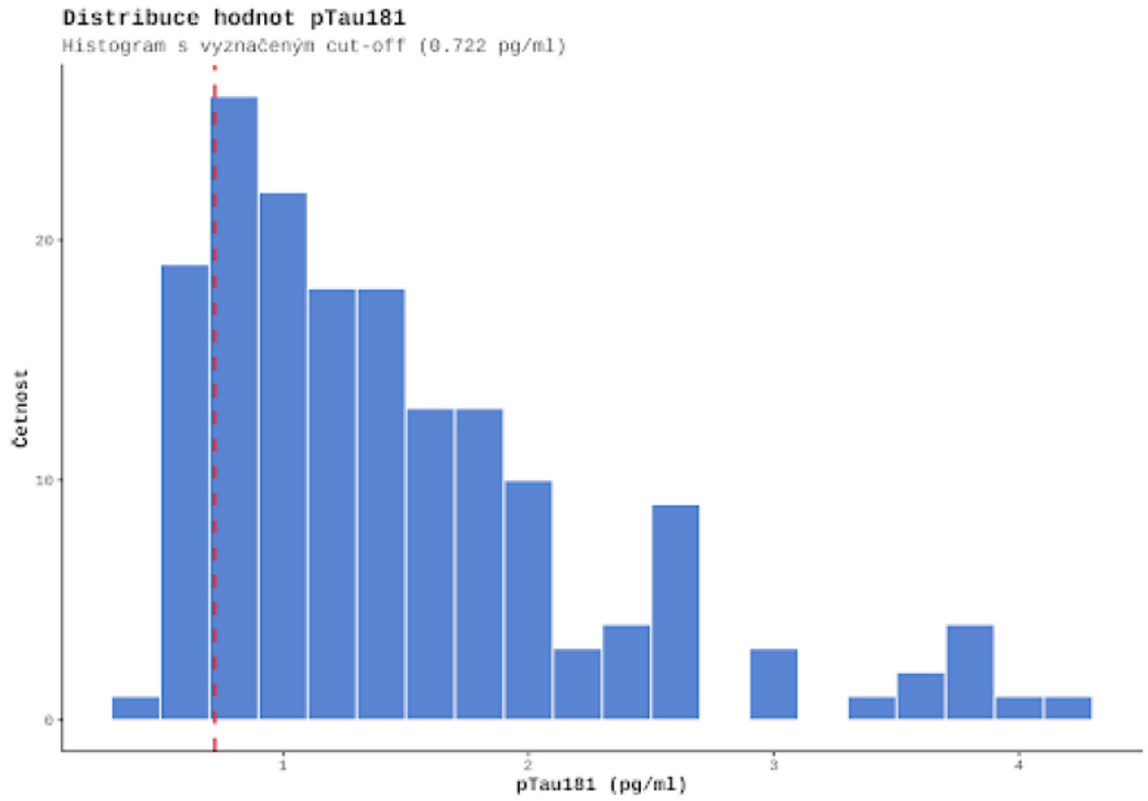
## Modelled PPV/NPV by Amyloid Prevalence

| Prevalence | PPV | NPV |
|---|---|---|
| **10%** | 25.0% | 97.5% |
| **20%** | 42.9% | 94.6% |
| **30%** | 56.3% | 91.1% |
| **40%** | 66.7% | 86.8% |
| **50%** | 75.0% | 81.5% |

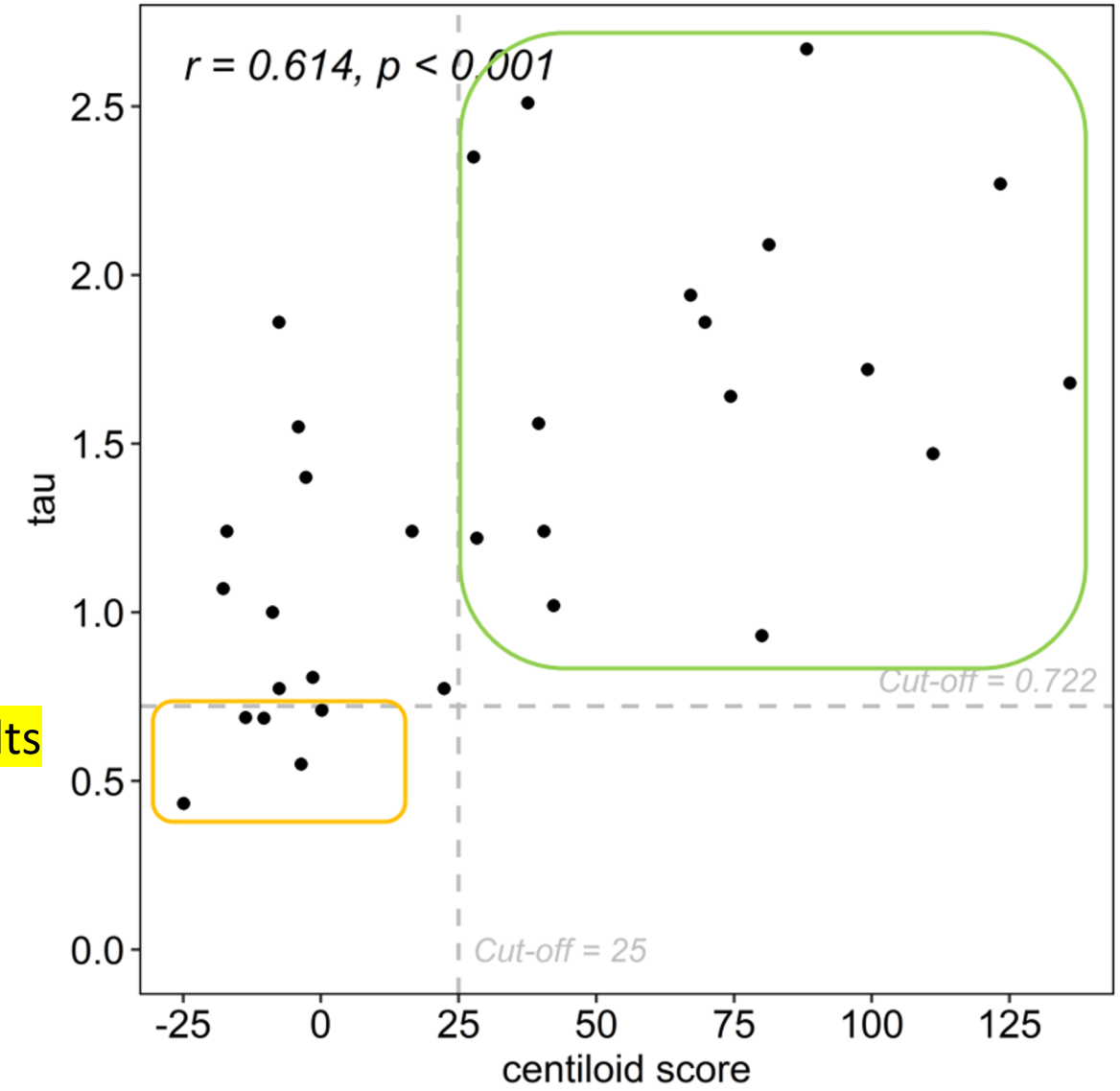
*Source: Plasma pTau181 assay validation study data; amyloid PET used as reference standard.*

# BRNO Memory Clinic Implementation study of p-tau181



# Correlation between p-tau181 levels and amyloid-PET centiloid score

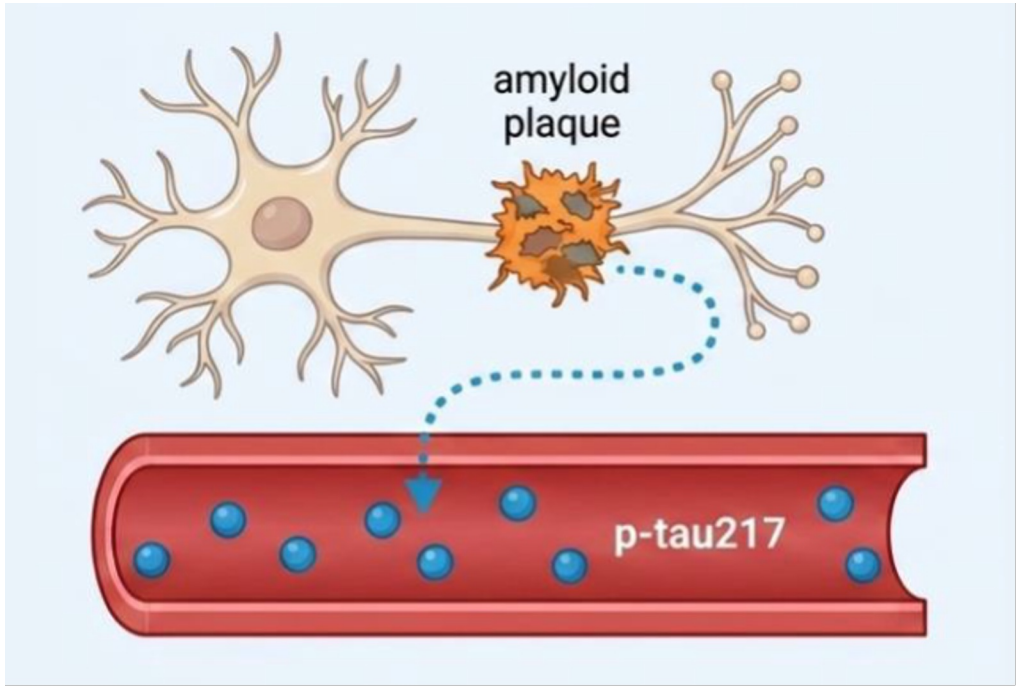



True positive results
(60% of p-tau181 positive)

True negative results
NPV 100%

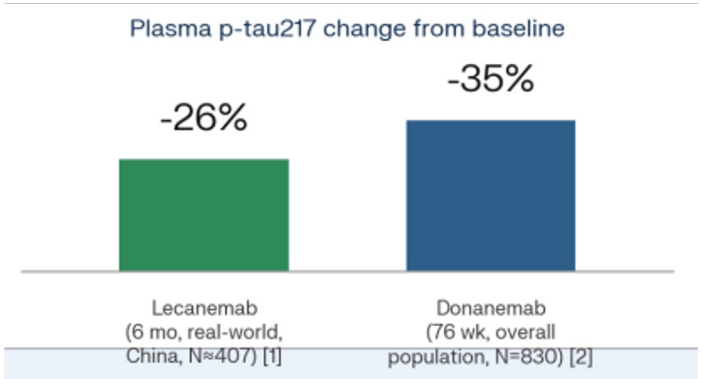
# The Gamechanger: Plasma p-tau217

## Early Detection




The most robust primary marker. Detects amyloid accumulation in the earliest stages, outperforming p-tau181 and p-tau231.

## Therapeutic Monitoring




**Lecanemab (-26%):** 6 months, real-world cohort, China (N=407). Plasma p-tau217 fell significantly by month 3 and reached ≈26% below baseline at 6 months, paralleling amyloid-PET reduction and reflecting plaque clearance.

**Donanemab (-35%):** 76 weeks, overall population, TRAILBLAZER-ALZ 2 (N=830). Plasma p-tau217 fell 35% at 76 weeks at group level, but individual-level accuracy for detecting amyloid clearance (<24.1 Centiloids) was suboptimal (AUC 0.61 at 52 weeks).

**Takeaway:** p-tau217 reductions reflect group-level biologic response for both drugs, but are not currently validated to confirm amyloid clearance for an individual patient.

*Sources: Li et al., Brain 2025/2026 [1]; Collins EC et al., Alzheimers Dement 2026 [2]*

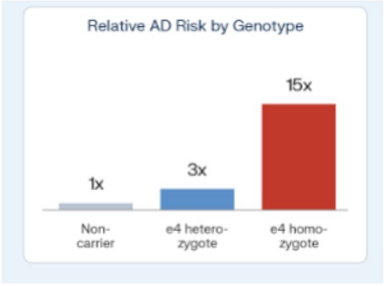
# The Next Frontier in Staging and Treatment Effect

## Monitoring MTBR-tau, BD-tau and GFAP

| Biomarker | Target Pathology | Clinical Utility | Key Source |
|---|---|---|---|
| **p-tau217** | Early Amyloid/Tau | Primary triage & therapy tracking. | Collins et al. 2026 [1] |
| **MTBR-tau243** | Neurofibrillary Tangles | Disease staging & symptom confirmation. Correlates tightly with tau-PET and symptomatic cognitive decline; helps identify patients most likely to benefit from new disease modifying therapies | Horie et al., Nat Med 2025 [2] |
| **BD-tau (Brain-Derived)** | AD-type Neurodegeneration | Highly specific to the brain, avoids peripheral 'big tau' confounds (unlike general NfL). | Gonzalez-Ortiz et al., Nat Commun 2024 [3] |
| **GFAP** | Astrocytic Activation | Tracks neuroinflammation during effective anti-amyloid therapy. | Teunissen et al., Alzheimers Dement 2024 [4] |

*Sources: [1] Collins EC, et al. Plasma P-tau217 for detecting amyloid clearance after donanemab in Alzheimer's disease. Alzheimers Dement. 2026. ; [2] Horie K, et al. Plasma MTBR-tau243 biomarker identifies tau tangle pathology in Alzheimer's disease. Nat Med. 2025;31:2044-2053. ; [3] Gonzalez-Ortiz F, et al. Plasma brain-derived tau is an amyloid-associated neurodegeneration biomarker in Alzheimer's disease. Nat Commun. 2024;15:2984. ;[4] Teunissen C, Willis BA, Bhagunde P, et al. Pharmacokinetic/pharmacodynamic analyses of plasma biomarkers with lecanemab. Alzheimers Dement. 2024;20(Suppl 6):e09196.*

# Why APOE Testing Matters

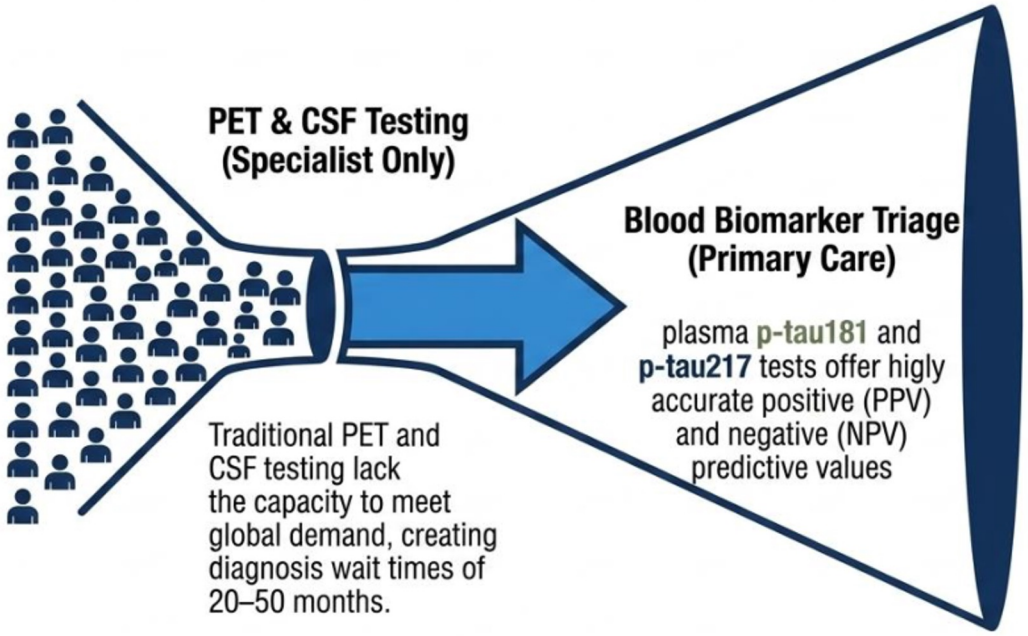

**Risk Impact.**ε4 heterozygotes have approximately 2–4-fold higher risk of AD, ε4 homozygotes up to ~15-fold higher risk of AD

**Biomarker Impact.** APOE4 carriers show significantly higher baseline levels of plasma p-tau217, BD-tau, and GFAP compared to non-carriers, driving faster cognitive decline.

**Treatment Safety (ARIA).** Genotyping is a mandatory safety gate. APOE ε4 hetero and homozygotes has significantly higher risk of Amyloid-Related Imaging Abnormalities (ARIA E/H) during anti-amyloid therapy

# Conclusion – Key Takeaway

## The Blood Biomarker Catalyst




**IMPACT**

**Integrating blood tests early in the diagnostic journey reduces the need for expensive, specialized CSF and PET scans by 80% to 90%, democratizing access to accurate diagnosis globally.**

- Early identification of individuals at risk of AD
- Highly scalable and suitable forpopulation-level implementation
- Substantially less expensive than amyloid PET
- Minimally invasive (in contrast to CSF)
- Reliable and capable of providing efficient triage
- Improve access to early AD diagnostics, including for underserved populations
- Potential future roles in definitive diagnosis, biological staging, and monitoring treatment response as a BBM panel

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Thank you for your attention!