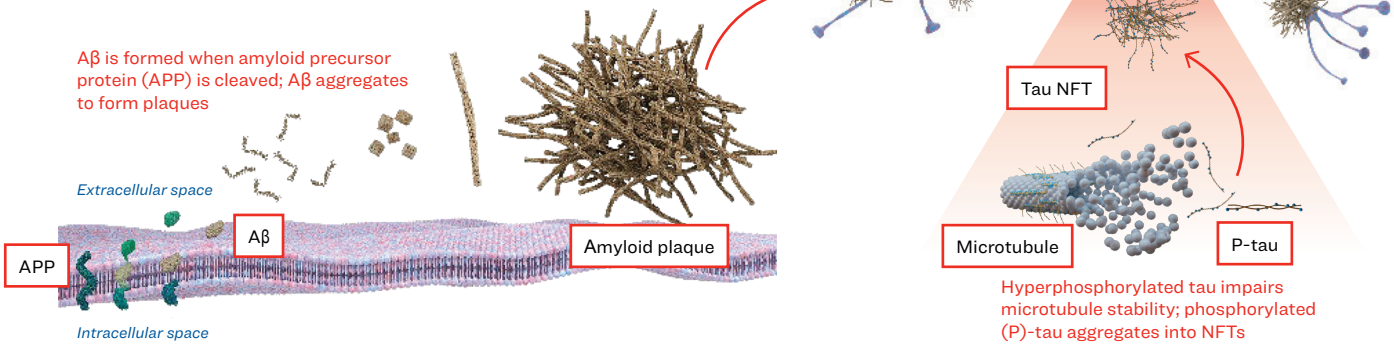
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BIOMARKERS IN ALZHEIMER'S DISEASE

Alzheimer's Disease (AD) Is Defined by Its Neuropathology[1-5]

- AD is a neurodegenerative disorder associated with cognitive, functional, and behavioral impairments
- The key neuropathologic features include
  - **Amyloid plaques:** extracellular protein aggregates between brain cells that disrupt neuronal communication
  - **Tau neurofibrillary tangles (NFTs)**: intracellular twisted filaments that block nutrient transport, leading to neuronal death
- Amyloid β (Aβ) accumulation begins approximately 20 years before cognitive symptoms appear; pathogenic Aβ is thought to contribute to tau changes, leading to NFTs
- Together, amyloid plaques and NFTs drive neurodegeneration



Biomarker Tests Help Identify AD Pathology[4,6-8]

- AD biomarkers are measurable biological indicators that reflect AD-associated pathology or the risk of developing symptoms; the table below maps AD pathology across the disease continuum and provides examples of biomarker tests

Pathology and Biomarker Tests Across the AD Continuum[6,9,10]*

Stage 1: Preclinical AD	Stage 2: Preclinical AD	Stage 3: AD With MCI	Stage 4: AD With Mild Dementia	Stage 5: AD With Moderate Dementia	Stage 6: AD With Severe Dementia		Biomarker Tests
Elevated amyloid						>	Amyloid PET
	Elevated tau NFTs (medial temporal lobe)					>	Tau PET†
		Elevated tau NFTs (neocortical)					
Aβ42/Aβ40, P-tau (181, 217, 231)						>	Key: ● CSF ■ Blood ◆ Both ◆ Aβ42/Aβ40, ● T-tau‡/Aβ42, ■ P-tau181, ◆ P-tau181/Aβ42, ■ P-tau217, ■ %P-tau217, ■ P-tau217/Aβ42, ■ P-tau231

The evidence summarized in this table is derived from research settings. This pattern is believed to represent the typical progression for individuals with AD, though considerable variability exists; note that the time spent in different stages of the disease varies by individual. Biomarker tests may not be clinically available, validated, or approved for use in all stages of AD or care settings.

- In clinical contexts, biomarker tests may be used to assist in the evaluation of individuals with cognitive impairment to support the identification and diagnosis of AD by
  - Confirming or ruling out AD pathology
  - Informing clinical decision-making
  - Staging the disease based on severity of pathology (certain tests only)
- Therapies for early symptomatic AD that can slow disease progression require evidence of amyloid positivity, making biomarker testing essential for timely diagnosis and treatment planning

Biomarker Tests for AD Include Neuroimaging and Fluid Assays[1,6,7,11-13]

Neuroimaging Biomarkers[1,6,7]		
Method	**What It Measures**	**How It Differs in AD Compared to Non-AD**
Amyloid PET	Amyloid plaques	↑
Tau PET	Tau NFTs	↑

While markers of neurodegeneration represent important steps in the AD process, they are not specific to AD and are therefore excluded from this table[6]

- **Neuroimaging biomarkers** reflect AD neuropathologic load
- **Fluid biomarkers (CSF and blood-based)** measure the concentration of AD-related peptides or proteins and reflect the net rate of production vs clearance at a given time
  - Examples include Aβ42/Aβ40 and P-tau (181, 217, 231)
  - Blood tests are emerging as less invasive, more scalable, and cost-friendly options*
    - Several P-tau assays, particularly P-tau217, have accuracy equivalent to CSF tests
    - Inclusion of blood tests into the clinical workflow may help improve diagnostic accuracy in primary and specialist care settings

Select Fluid Biomarkers[1,7,13-16]				
Biomarker	**What It Measures**	**How It Differs in AD Compared to Non-AD**	**Example Concordance With Amyloid PET (AUC)**	
			CSF	**Plasma**
Aβ42/Aβ40 ratio	Aggregation-prone Aβ42 isoform vs less aggregation-prone Aβ40 isoform; low ratio suggests plaque formation in the brain	↓	0.94[14]	0.84[15]
P-tau181	One of the most abundant P-tau species; seen more prominently in mature NFTs	↑	0.85[13]	0.77[13]
P-tau217	Highly specific biomarker; most closely associated with both amyloid and tau PET	↑	0.95[13]	0.97[13]
P-tau231	Predominant component of pre-tangles; may represent one of the earliest phosphorylation events that contributes to misfolding	↑	0.88[13]	0.79[13]

Concordance values come from research studies employing assays available for commercial and/or research use and may not be representative of all tests measuring this biomarker.

Research Is Evolving to Expand Diagnostic and Prognostic Tools in AD[6,17-19]

Examples of emerging fluid biomarkers:

- Neurofilament light chain (NfL)
  - Marker of axonal injury and neurodegeneration
  - Correlates with tau and FDG PET, brain atrophy, and cognitive decline
- Glial fibrillary acid protein (GFAP)
  - Marker of astrocytic reactivity and neuroinflammation
  - Correlates with amyloid PET, tau PET, FDG PET, and cognitive function

Note: These biomarkers are not specific to AD and may be elevated in other neurological conditions.

Prognostic potential:

- In cognitively unimpaired individuals, elevated plasma levels of P-tau217, P-tau181, NfL, and GFAP are associated with increased risk of progression to cognitive decline

As the prevalence of AD grows, available and emerging biomarker tools can help support primary care clinicians with specialist referral, timely diagnosis, and treatment planning.[1,6,7]

*Consider test accuracy. Commercially available blood-based biomarker tests demonstrate variable accuracy. Guidelines recommend using blood tests with a sensitivity of ≥90% and specificity of 85% for the purpose of triaging patients in the primary care setting.[20] †While the most common pattern, PET-detectable medial temporal tauopathy does not always precede neocortical tauopathy in the early stages of AD.[6]

AUC=area under the curve. CSF=cerebrospinal fluid. FDG=fluorodeoxyglucose. MCI=mild cognitive impairment. MRI=magnetic resonance imaging. PET=positron emission tomography. T-tau=total tau.

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