Evolution of the Biomarker Classification System for Describing Biological Changes in Alzheimer's Disease

AD-M2240

ALZHEIMER'S DISEASE (AD) IS A PROGRESSIVE NEURODEGENERATIVE DISEASE[1,2]

AD begins with the deposition of **amyloid (A)** plaques, which then leads to build-up of **tau (T)** tangles in the brain and gradual damage to the brain cells or **neurodegeneration (N)**.

TEMPORAL EVOLUTION OF AT(N), BASED ON THE 2018 RESEARCH FRAMEWORK[1,2]

Abnormal changes in biomarkers are detected years before the onset of clinical symptoms. These changes may occur at different times and follow distinct time trajectories across the AD continuum.

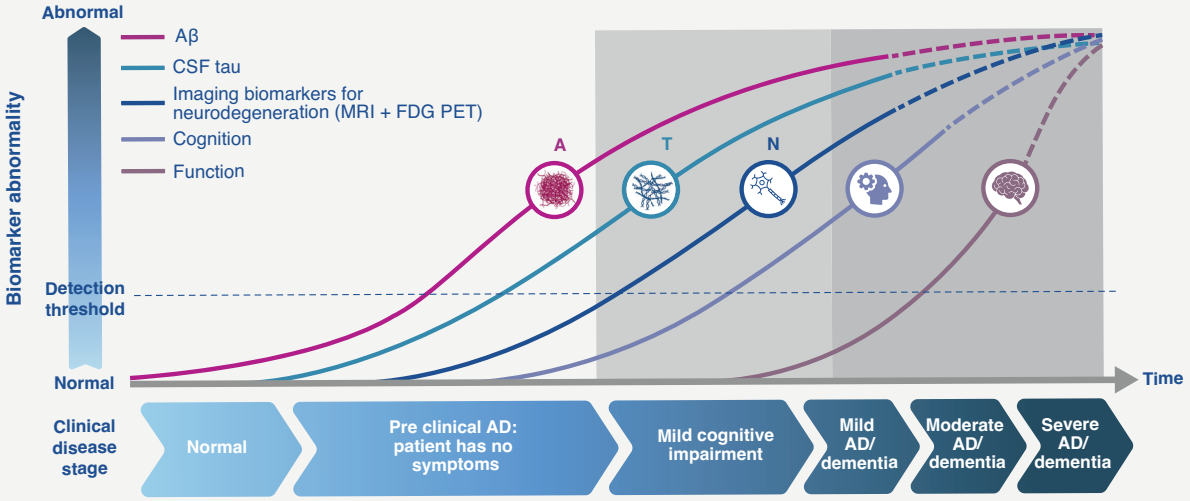

Figure adapted from Hampel H, et al. Nat Rev Neurol. 2021;17(9):580–589 and Hampel H, et al. Neurodegener Dis Manag. 2022;12(5):231–239

THE AT(N) CRITERIA[3,4]

The AT(N) classification system was published by the NIA-AA as a research framework for the diagnosis and evaluation of AD based on temporal changes in AD biomarkers. The AT(N) criteria was designed to overcome the conceptual limitations of conventional diagnostic classifications based on clinical symptoms.

The framework is based on the following principles:[3]

AD is associated with unique pathological changes, making diagnosis possible using the associated biomarkers	AD pathological changes occur as a continuum and can be detected long before clinical symptoms appear	Symptoms are a result of the underlying disease process and are not necessary to diagnose AD

THE FORMER 2018 AT(N) CLASSIFICATION SYSTEM[3]

AD pathophysiology	Biomarker	Neuroimaging		CSF
AMYLOID PLAQUES	A	Amyloid PET	OR	Aβ42 or Aβ42/40
TAU TANGLES	T	Tau PET	OR	p-tau
NEURODEGENERATION	N	Metabolic PET MRI	OR	t-tau

Figure adapted from Jack CR Jr, et al. Alzheimer's Dement. 2018;14(4):535–562

A aggregated Aβ or associated pathologic state

T aggregated tau or associated pathologic state

N neurodegeneration or neuronal injury

The 2018 recommendations were intended as a research framework, not as diagnostic criteria or guidelines; they served as general principles to inform diagnosis and staging of AD.[3]

EVOLUTION OF THE AT(N) CRITERIA[4]

The 2024 biomarker classification system is an update of the 2018 research framework that incorporates the following major developments in AD biomarkers:

- Availability of BBM assays with accurate diagnostic performance.
- Research demonstrating that imaging, CSF, and BBMs within a pathobiological biomarker category are interchangable for some intended uses.

THE UPDATED 2024 ALZHEIMER'S ASSOCIATION CLASSIFICATION SYSTEM[4]

Core AD biomarkers

Core 1: Early-changing biomarkers		Imaging	CSF	BBM
Aβ proteinopathy	A	Amyloid PET		
Phosphorylated and secreted AD tau	T_1			p-tau217
Hybrid ratios			*Aβ42/40* *p-tau181/Aβ42* *t-tau/Aβ42*	*%p-tau217*
Core 2: Later-changing biomarkers				
AD tau proteinopathy	T_2	Tau PET	MTBR-tau243, p-tau205, np-tau	MTBR-tau243, p-tau205

Non-core AD biomarkers

Biomarkers of non-specific processes involved in AD pathophysiology

		Imaging	CSF	BBM
Injury, dysfunction, or degeneration of neuropil	N	FDG PET, MRI	NfL	NfL
Astrocytic activation	I		GFAP	GFAP

Biomarkers of non-AD co-pathology

		Imaging	CSF	BBM
Vascular brain injury	V	Infarction on MRI or CT, WMH		
α-synuclein	S		α-Syn-SAA	

Figure adapted from Jack Cr Jr, et al. Alzheimers Dement. 2024;20(8):5143–5169

Core biomarkers[4,5]

- **Early-changing Core 1 biomarkers** (amyloid PET, approved CSF biomarkers, and accurate plasma biomarkers [especially p-tau217]) reflect the presence of AD neuropathologic change more generally (i.e., both neuritic plaques and tangles).
  - » **Hybrid ratios:** diagnostic assays employ analyte ratios instead of individual analyte values to normalize any inter-individual differences.
- **Later-changing Core 2 biomarkers** (T2 biofluid and tau PET) may be sufficient to confirm AD pathology, and when combined with Core 1 biomarkers, can be used to stage biological disease severity and provide prognostic information.

Non-core biomarkers[4]

- Includes neurodegeneration (N) and three new biomarker categories: inflammatory/immune mechanisms (I), vascular brain injury (V), and α-synucleinopathy (S).
- V and S biomarkers are relevant because AD most often occurs with co-pathologies in older adults.

According to the Alzheimer's Association, an abnormal Core 1 biomarker result is sufficient to biologically define AD and inform clinical decision making throughout the disease continuum.[4] However, the IWG recommends that AD should be defined as a clinical-biological entity. Therefore, the presence of objective cognitive deficits and AD biomarkers is needed for AD diagnosis.[6]

INTEGRATING BIOLOGICAL AND CLINICAL STAGING[4]

- Biological staging (A–D based on the extent of amyloid and tau deposition) may be achieved using PET or a combination of core fluid biomarkers and PET because:
  - » PET and fluid measures are not equivalent; hence, stages A–D with PET should not be treated as equivalent to stages A–D for fluid biomarkers.
  - » CSF Aβ42/40, p-tau181/Aβ42, t-tau/Aβ42, and accurate Core 1 plasma assays can establish that an individual is in biological stage A or higher but cannot discriminate between PET stages A–D at present.

Biological staging		Clinical staging
Combination of amyloid and tau PET A to D depending on extent of A and T **OR** **Core 1 fluid biomarkers and tau PET** A to D depending on extent of A and T	+	0 to 6 depending on clinical symptoms

The integrated staging below should be regarded as a tool for diagnosis, staging/prognosis, and treatment assignment but not as indicators of the stage of the natural history of the disease post treatment.[4]

	Preclinical AD		Subjective cognitive impairment	MCI due to AD	Mild AD dementia	Moderate AD dementia	Severe AD dementia
	Stage 0	Clinical stage 1	Clinical stage 2	Clinical stage 3	Clinical stage 4–6		
Initial biological stage (A)	X	1A	2A	3A	4–6A		
Early biological stage (B)	X	1B	2B	3B	4–6B		
Intermediate biological stage (C)	X	1C	2C	3C	4–6C		
Advanced biological stage (D)	X	1D	2D	3D	4–6D		

Table adapted from Jack Cr Jr, et al. Alzheimers Dement. 2024;20(8):5143–5169

This integrated classification system remains a research framework, and more work is required to implement it in clinical practice.[4] Importantly, the IWG cautions that individuals who are biomarker-positive but cognitively normal should be considered at risk for AD and not be labeled as having AD.[6]

SUMMARY[3,4,6]

- Unique pathological changes in AD appear long before clinical symptoms and help support the diagnosis of AD using biomarkers.
- The biomarker classification system is a research framework for the diagnosis and evaluation of AD based on temporal changes in AD biomarkers.
  - » **Early-changing Core 1 biomarkers:** an abnormal result is sufficient to establish an AD diagnosis.
  - » **Later-changing Core 2 biomarkers** may be sufficient to confirm AD pathology, and when combined with Core 1 biomarkers, can be used to stage biological disease severity and provide prognostic information.
- A staging scheme is described that integrates biological stages with clinical stages.

ABBREVIATIONS

α-Syn-SAA, alpha-synuclein seed amplification assay; A, amyloid; Aβ, amyloid beta; AD, Alzheimer's disease; BBM, blood-based biomarker; CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; GFAP, glial fibrillary acidic protein; I, inflammatory/immune mechanisms; IWG, International Working Group MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MTBR-tau243, microtubule-binding region of tau containing the residue 243; N, neurodegeneration; NfL, neurofilament light chain; NIA-AA, National Institute on Aging and Alzheimer's Association; np, non-phosphorylated; PET, positron emission tomography; p-tau, phosphorylated tau; S, alpha-synucleinopathy; T, tau; t-tau, total tau; V, vascular brain injury; WMH, white matter hyperintensities.

REFERENCES

1. Hampel H, et al. Nat Rev Neurol. 2021;17(9):580–589; 2. Hampel H, et al. Neurodegener Dis Manag. 2022;12(5):231–239; 3. Jack CR Jr, et al. Alzheimer's Dement. 2018;14(4):535–562; 4. Jack CR Jr, et al. Alzheimers Dement. 2024;20(8):5143–5169; 5. Hu Y, et al. Med. 2024;5(10):1206–1226; 6. Dubois B, et al. JAMA Neurol 2024;81(12):1304–1311