

Biomarkers of Alzheimer's Disease: Review Article.

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Abstract

Alzheimer's disease (AD) is the leading cause of dementia worldwide, and early and accurate identification of its underlying pathology is increasingly important for diagnosis, prognosis, and therapeutic decision-making. Advances in biomarker research have shifted the diagnostic approach from a predominantly clinical and syndrome framework toward a biologically based definition of AD. This review summarizes the current evidence regarding established and emerging biomarkers of Alzheimer's disease, with particular emphasis on the amyloid, tau, and neurodegeneration framework. Amyloid biomarkers, including cerebrospinal fluid (CSF) A β 42 and the A β 42/A β 40 ratio, amyloid positron emission tomography (PET), and plasma A β measures, provide evidence of cerebral amyloid pathology. Tau biomarkers, including CSF and plasma phosphorylated tau (p-tau181, p-tau217, and p-tau231) and tau PET, provide information regarding AD-related tau pathology and may contribute to early detection and disease staging. Neurodegeneration can be assessed using CSF total tau, neurofilament light chain, structural magnetic resonance imaging (MRI), and fluorodeoxyglucose-PET. Blood-based biomarkers have emerged as promising, minimally invasive tools because of their potential accessibility, cost-effectiveness, and applicability to early disease detection. However, variability between assays, the lack of universally established cut-off values, and the need for clinical validation remain important challenges. Current evidence supports the complementary use of fluid and imaging biomarkers rather than reliance on a single marker. Future approaches integrating multimodal biomarkers with clinical information and artificial intelligence may improve diagnostic accuracy, disease staging, prognosis, and personalized management of Alzheimer's disease.

Keywords: Alzheimer's disease; biomarkers; amyloid-beta; tau; phosphorylated tau; neurodegeneration; cerebrospinal fluid; plasma biomarkers; amyloid positron emission tomography; tau positron emission tomography; magnetic resonance imaging; neurofilament light chain; early diagnosis; disease staging; artificial intelligence

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Introduction

I. Clinical applications of AD biomarkers

The diagnosis of AD has evolved in recent years, transitioning from a syndromal framework to a biological basis. In 2024, the National Institute on Aging and the Alzheimer's Association (NIA-AA) workgroup published updated research guidelines for the diagnosis and staging of AD, underscoring the critical role of characteristic biomarkers in establishing a definitive diagnosis. Biomarkers have been categorized based on their relevance to AD pathophysiology. Core biomarkers are those molecules that are associated with specific pathogenic mechanisms of AD (A β proteopathy, phosphorylated and secreted AD tau, or AD tau proteopathy) (Lista et al., 2024).

In addition, biomarkers of non-specific processes involved in AD

Alzheimer disease (AD) is the leading cause of dementia globally with a profound impact on individuals, families, and health care systems. Roughly 150 million cases of cognitive impairment worldwide are anticipated by 2050, with the majority being caused by AD. In the United States, this number is projected to be around 11 million, in part attributable to increasing life expectancy (Hansson et al., 2023).

In addition, because there are only a limited number of dementia specialists in practice as well as other barriers related to access of diagnostic and therapeutic resources, the US health care system is unprepared to meet the projected demand of treatment-eligible individuals with mild cognitive impairment (MCI) or mild dementia caused by AD (collectively called "early AD") (Gunes et al., 2022).

cerebrospinal fluid (CSF) concentrations of amyloid and tau proteins, and plasma concentrations of amyloid, tau, and other protein biomarkers. Topographic biomarkers are related to the regional consequences of AD pathology, such as regional hypometabolism on fluorodeoxyglucose (FDG)-PET, tau PET, and regional/local atrophy on structural magnetic resonance imaging (MRI) as shown in Figure 2 (Mielke et al., 2024).

To date, no fluid biomarkers have been conclusively linked to an individual clinical phenotype of AD; however, according to their regional distribution differences, there are corresponding molecular, metabolic, and degenerative imaging biomarkers for the different phenotypes of AD. The existing literature is predominantly focused on biomarkers of AD pathology, where the main clinical value of their uses is to discriminate between phenotypes that are associated with AD vs. non-AD pathologies, and to measure the advances in underlying biology such as plasma and CSF levels of phosphorylated tau (pTau). Currently, there is no single biomarker or biomarker algorithm that can differentiate between AD phenotypes with conclusive diagnostic accuracy, underscoring the importance of clinical evaluation (Schöll et al., 2024).

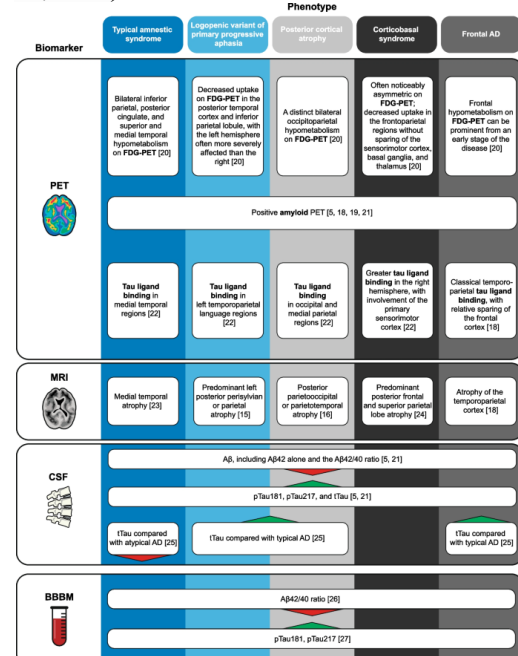


Figure 2: Summary of anticipated biomarker results for the different clinical phenotypes of AD (Schöll et al., 2024).

III. Amyloid biomarkers (A)

Amyloid-β (Aβ) accumulation is one of the characteristic pathological changes of Alzheimer's disease. Aβ peptides are produced from amyloid precursor protein and can

pathophysiology (neuropil dysfunction or neuroinflammation) can provide valuable support for auxiliary diagnosis and staging. Finally, biomarkers of non-AD co-pathology (vascular brain injury or α-synuclein) can help identify coexisting pathologies that frequently occur alongside AD in older adults (Hampel et al., 2023).

According to the guidelines, abnormalities in Core 1 biomarkers (i.e., amyloid PET, CSF Aβ 42/40, CSF p-tau 181/Aβ 42, CSF t-tau/Aβ 42, and accurate plasma biomarkers) can confirm the diagnosis of AD as in Figure 1. Unlike previous guidelines, which focused on the clinical presentation, CSF biomarkers, and neuroimaging, the 2024 update introduced BBMs into the diagnostic framework. Accurate plasma biomarkers need to meet the requirement of a minimum accuracy of 90% in detecting abnormal amyloid PET within the intended population (Hansson et al., 2022).

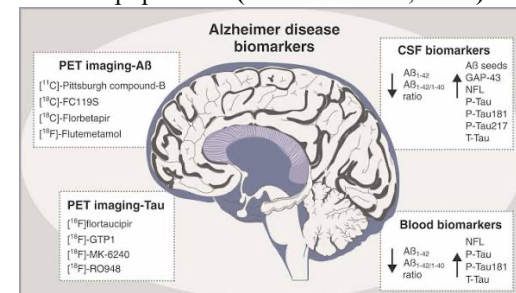


Figure 1: Biomarkers in Alzheimer disease (Klyucherev et al., 2022).

However, standardized cut-offs for these biomarkers and their association with clinical prognosis have not yet been formally established for BBMs. For patients with abnormal BBMs, further confirmation of the diagnosis through CSF tests or PET imaging is required, which is equivalent to the accuracy of the approved CSF test. Core 2 biomarkers (tau-PET and certain soluble tau fragments associated with tau proteinopathy) can be used for staging, prognosis, and as indicators of biological treatment effects, but they cannot be used as a stand-alone diagnostic test for AD in most cases. When Core 1 biomarker results are normal, any abnormalities in Core 2 biomarker results should be interpreted with caution (Grande et al., 2025).

II. Biomarker profiles for typical and atypical phenotypes of AD

The majority of AD biomarkers can be classified into pathophysiologic biomarkers and topographic biomarkers; both can help clinicians to recognize, differentiate, and diagnose AD phenotypes. Pathophysiologic biomarkers related to AD lesions include amyloid positron emission tomography (PET),

prodromal stages of disease progression, and some have demonstrated the potential to predict cognitive decline (Arslan et al., 2024).

CSF A β 42 concentration and A β 42/40 ratio decrease and correlate inversely with the extent of A β plaque deposition, and concentrations of tTau and pTau correlate with the intensity of neurodegeneration and neurofibrillary tangles, respectively. The presence of a decreased CSF A β 42/40 ratio typically indicates AD pathology, even in those with atypical clinical features or irregular CSF findings for other analytes (Blennow et al., 2023).

With respect to a “FTD-phenotype,” the pTau181/A β 42 ratio is useful for the identification of both the behavioral and semantic variants of frontal AD and in differentiating these patients from those with frontotemporal dementia. CSF pTau 231 (pTau231) is another pTau epitope that has demonstrated the potential to aid in diagnosis of early AD and detect incipient AD pathology, not confined to the clinical phenotype (Garcia-Escobar et al., 2024).

VI. AD Neuropathologic Changes

The AT(N) classification system for AD has proven useful in the research setting to identify individuals with specific biomarker profiles who may be more likely to have AD. This classification system was largely built on results of the Alzheimer's Disease Neuroimaging Initiative using infrastructure supported by the National Institute on Aging and Alzheimer's Disease Research Centers. In the research setting, individuals are defined as having AD neuropathologic change and placed on the AD spectrum of preclinical disease based on the presence of amyloid positivity (A+) even if cognitively unimpaired (CU) (Teunissen et al., 2022).

CSF biomarkers and amyloid PET have proven valuable in the recruitment of participants for clinical trials and are used as a surrogate reference standard given their concordance with pathology. Tau positivity (T+) and neurodegeneration (N+) are considered later stages of the disease and considered necessary for cognitive decline (Alber et al., 2022).

The Geneva roadmap for biomarker development, which is modeled after cancer biomarker development, describes a 5-phase framework. The amyloid and tau biomarkers discussed in this article are all approaching the end of phase 3 development, where these biomarkers are studied in retrospective and longitudinal cohorts. A few have some prospective validation studies (phase 4) underway. Phase 5 is focused on clinical

aggregate to form amyloid plaques in the brain. Biomarkers in the A category provide evidence of this amyloid pathology. One important biomarker is cerebrospinal fluid (CSF) A β 42. In Alzheimer's disease, the concentration of A β 42 in CSF generally decreases because A β 42 becomes deposited in amyloid plaques within the brain. The A β 42/A β 40 ratio is often more informative than A β 42 alone because it accounts for differences in the overall production of amyloid peptides. A reduced CSF A β 42/A β 40 ratio is therefore evidence supporting cerebral amyloid pathology (Pais et al., 2023).

IV. Magnetic Resonance Imaging markers

MRI changes are topographic biomarkers of AD, and structural MRI in patients with AD shows atrophy of grey matter and volume loss, indicating neurodegeneration. Serial structural MRI imaging is often used to measure disease progression as this approach has lower variance than single structural MRI. Some data indicate that serial structural MRI may have the potential to evaluate therapeutic efficacy in clinical practice, as serial structural MRI measurements could permit clinical trials to be performed with smaller sample sizes than would be possible using traditional clinical assessments (Palmqvist et al., 2023).

There are additional MRI measures such as: diffusion tensor imaging MRI, to assess damage to white matter; resting state functional MRI, to assess changes in functional brain connectivity that are thought to precede structural brain changes; and T2-weighted or susceptibility-weighted MRI, to assess vascular activity and identify cerebral amyloid angiopathy. However, these techniques are not currently used in the majority of clinical trials or in routine clinical practice but may become increasingly important to manage amyloid-related imaging abnormalities (ARIA) with the use of anti-amyloids (Bouwman et al., 2022).

V. CSF biomarkers

CSF biomarkers can be used to detect both A β and tau peptides and, in most patients, alterations in these biomarkers can be detected earlier than changes in neuroimaging biomarkers. CSF tau indicates neuronal death, and, therefore, it can be elevated in atypical phenotypes as well as in non-AD dementias; an increase in pTau is more specific to AD pathology in both typical and atypical presentations. CSF biomarkers include A β (1–42) (A β 42), A β (1–40) (A β 40), pTau 181 (pTau181), pTau 217 (pTau217), and total tau (tTau). These markers have been shown to accurately identify AD-associated biologic changes, even at pre-symptomatic and

The total analytical error associated with any diagnostic assay must be much lower than the magnitude of change among the levels of individuals with the disease of interest, controls, and individuals with other diseases. AB measurements in the blood do not meet these criteria. The Global Biomarker Standardization Consortium, an initiative by the Alzheimer's Association to standardize and validate biomarker assays, reported poor correlation among 11 different plasma AB42/40 assays conducted at 11 different sites. A head-to-head comparison of 8 plasma AB42/40 assays showed that mass spectrometry-based methods were more accurate than most of the immunoassays in detecting brain AB pathology (Mielke et al., 2024).

➤ Phosphorylated Tau

Hyperphosphorylated tau is a hallmark of AD neuropathologic change, and NFT formation as evident in PET imaging tracks well with [¹⁸F]fluorodeoxyglucose (FDG)-PET and cognitive changes. P-tau biomarkers are effective BBBs, both in isolation and in combination panels, for predicting positive amyloid status. More than 80 p-tau targets are under investigation, with p-tau217 and p-tau181 being the most promising. P-tau231 may have use as a state marker, but this is yet to be verified. p-tau217 levels, as measured by the Lilly Research Laboratories (Indianapolis, IN) electrochemiluminescence method outperformed plasma AB42/AB40 and plasma NFL in predicting CSF AB pathology, with AUC of 0.73 in clinically unimpaired individuals and 0.86 in people with AD. Preliminary evidence suggests that p-tau217 levels increase in preclinical stages of AD, and correlate with brain AB burden (Klyucherev et al., 2022).

IX. Future perspectives for biomarkers

Neuroimaging and CSF biomarkers are currently well-established methods for accurate diagnosis of AD. Simple BBMs offer significant promise for advancing AD research, drug development, and clinical practice, particularly because of their cost-effectiveness and potential for broad clinical accessibility and population screening during the early stages of AD. However, the complexity of AD pathology poses challenges for single biomarkers to fully capture the intracerebral pathology, predict disease progression, and meet other clinical demands (Bouwman et al., 2022).

The combined use of fluid and imaging biomarkers can provide comprehensive biological insights at multiple levels, thereby offering new opportunities for

implementation and guidelines for use. Our clinical care model must incorporate these tools to accelerate diagnosis and expand access (Wojdala et al., 2023).

VII. Early AD Diagnosis

Over the past decade, 2 expert working groups—the International Working Group for New Research Criteria for the Diagnosis of AD and the National Institute on Aging–Alzheimer's Association (NIA-AA) International Working Group—have been working to align research efforts and facilitate communications by developing new criteria and a new vocabulary for the stages of AD. The NIA-AA has the goal of separating the clinical syndrome (clinically identified impairment) from biology (etiology and neuropathology) (Kaštelan et al., 2023).

This goal has some scientific validity. However, the difficulty with this task is that we do not fully understand the underlying pathology of the clinical syndrome. A purely biomarker-based diagnosis demands robust evidence of biomarker positivity leading to an extremely high likelihood of subsequent clinical progression. However, data on the longitudinal follow-up of CU individuals who are amyloid biomarker-positive indicate that having evidence of amyloid in the brain does not necessarily mean that a person will develop dementia or even cognitive impairment in their lifetime, the presence of amyloid is only associated with an increased risk of developing dementia due to AD (Kaštelan et al., 2023).

VIII. Molecular Biomarkers and Genetics

➤ Blood-Based AB42/AB40

AB is the primary neuropathologic hallmark of AD. CSF and amyloid PET biomarkers may be abnormal 20 years before symptom onset. CSF AB42 and AB40 levels are also the best-known biomarkers of AD. According to the amyloid cascade hypothesis, proteolytic cleavage of the amyloid precursor protein (APP) produces multiple soluble peptides, including AB40 and AB42, which form soluble oligomers, and then protofibrils, fibrils, and fibrillar plaques. The production of AB stimulates the development of NFTs and neuroinflammation, which leads to a further increase in amyloid. The accumulation of AB42 into plaques is signaled by the decrease in soluble AB42 in the CSF as well as a change in the AB42/AB40 ratio: the first sign of a pathologic process (Bouwman et al., 2022).

There are difficulties with sampling AB concentrations in the blood. AB is also made peripherally, and concentrations may not always reflect central amyloid accumulation.

		risk, not diagnostic
Emerging	G FAP and other blood/CSF proteins	G lial activation and other disease processes

References

- Alber, J., Bouwman, F., den Haan, J., Rissman, R. A., De Groef, L., Koronyo-Hamaoui, M., ... & Alzheimer's Association ISTAART "The Eye as a Biomarker for AD" Professional Interest Area. (2024). Retina pathology as a target for biomarkers for Alzheimer's disease: Current status, ophthalmopathological background, challenges, and future directions. *Alzheimer's & Dementia*, 20(1), 728-740.
- Arslan, B., Zetterberg, H., & Ashton, N. J. (2024). Blood-based biomarkers in Alzheimer's disease—moving towards a new era of diagnostics. *Clinical Chemistry and Laboratory Medicine (CCLM)*, 62(6), 1063-1069.
- Blennow, K., Galasko, D., Perneczky, R., Quevenco, F. C., van der Flier, W. M., Akinwonmi, A., ... & Zetterberg, H. (2023). The potential clinical value of plasma biomarkers in Alzheimer's disease. *Alzheimer's & Dementia*, 19(12), 5805-5816.
- Bouwman, F. H., Frisoni, G. B., Johnson, S. C., Chen, X., Engelborghs, S., Ikeuchi, T., ... & Teunissen, C. (2022). Clinical application of CSF biomarkers for Alzheimer's disease: From rationale to ratios. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 14(1), e12314.
- Garcia-Escobar, G., Manero, R. M., Fernández-Lebrero, A., Ois, A., Navalpotro-Gómez, I., Puente-Periz, V., ... & Jiménez-Balado, J. (2024). Blood biomarkers of Alzheimer's disease and cognition: a literature review. *Biomolecules*, 14(1), 93.
- Grande, G., Valletta, M., Rizzuto, D., Xia, X., Qiu, C., Orsini, N., ... & Vetrano, D. L. (2025). Blood-based biomarkers of Alzheimer's disease and incident dementia in the community. *Nature Medicine*, 31(6), 2027-2035.

personalized medicine and effective disease management. In the future, multidimensional data, including multimodal PET/MRI, fluid biomarkers, and clinical information, may be integrated using artificial intelligence methods to achieve optimal combinations, thereby enabling accurate diagnosis and personalized treatment of AD (Mielke et al., 2024).

The major biomarkers of Alzheimer's disease can therefore be summarized as follows: (Kaštelan et al., 2023)

Category	Major biomarkers	What they indicate
Amyloid	CSF Aβ42, CSF Aβ42/Aβ40, plasma Aβ42/Aβ40, amyloid PET	amyloid plaque pathology
Tau	CSF p-tau, plasma p-tau181, p-tau217, p-tau231, tau PET	Alzheimer's -related tau pathology
Neurodegeneration	CSF t-tau, plasma/C SF NfL, MRI atrophy, FDG-PET	neuronal injury or degeneration
Genetic	APOE ε4	Increased genetic risk

- Palmqvist, S., Stomrud, E., Cullen, N., Janelidze, S., Manuilova, E., Jethwa, A., ... & Hansson, O. (2023). An accurate fully automated panel of plasma biomarkers for Alzheimer's disease. *Alzheimer's & Dementia*, 19(4), 1204-1215.
- Schöll, M., Verberk, I. M., Del Campo, M., Delaby, C., Therriault, J., Chong, J. R., ... & Alcolea, D. (2024). Challenges in the practical implementation of blood biomarkers for Alzheimer's disease. *The Lancet Healthy Longevity*, 5(10).
- Teunissen, C. E., Verberk, I. M., Thijssen, E. H., Vermunt, L., Hansson, O., Zetterberg, H., ... & Del Campo, M. (2022). Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *The Lancet Neurology*, 21(1), 66-77.
- Wojdala, A. L., Bellomo, G., Gaetani, L., Toja, A., Chipi, E., Shan, D., ... & Parnetti, L. (2023). Trajectories of CSF and plasma biomarkers across Alzheimer's disease continuum: disease staging by NF-L, p-tau181, and GFAP. *Neurobiology of Disease*, 189, 106356.
- Gunes, S., Aizawa, Y., Sugashi, T., Sugimoto, M., & Rodrigues, P. P. (2022). Biomarkers for Alzheimer's disease in the current state: a narrative review. *International journal of molecular sciences*, 23(9), 4962.
- Hampel, H., Hu, Y., Cummings, J., Mattke, S., Iwatsubo, T., Nakamura, A., ... & Schindler, S. E. (2023). Blood-based biomarkers for Alzheimer's disease: current state and future use in a transformed global healthcare landscape. *Neuron*, 111(18), 2781-2799.
- Hansson, O., Blennow, K., Zetterberg, H., & Dage, J. (2023). Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nature aging*, 3(5), 506-519.
- Hansson, O., Edelmayer, R. M., Boxer, A. L., Carrillo, M. C., Mielke, M. M., Rabinovici, G. D., ... & Teunissen, C. E. (2022). The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimer's & Dementia*, 18(12), 2669-2686.
- Kaštelan, S., Braš, M., Pjevač, N., Bakija, I., Tomić, Z., Pjevač Keleminić, N., & Gverović Antunica, A. (2023). Tear biomarkers and Alzheimer's disease. *International journal of molecular sciences*, 24(17), 13429.
- Klyucherev, T. O., Olszewski, P., Shalimova, A. A., Chubarev, V. N., Tarasov, V. V., Attwood, M. M., ... & Schiöth, H. B. (2022). Advances in the development of new biomarkers for Alzheimer's disease. *Translational neurodegeneration*, 11(1), 25.
- Lista, S., Imbimbo, B. P., Grasso, M., Fidilio, A., Emanuele, E., Minoretti, P., ... & Caraci, F. (2024). Tracking neuroinflammatory biomarkers in Alzheimer's disease: a strategy for individualized therapeutic approaches?. *Journal of neuroinflammation*, 21(1), 187.
- Mielke, M. M., Anderson, M., Ashford, J. W., Jeromin, A., Lin, P. J., Rosen, A., ... & Udeh-Momoh, C. T. (2024). Recommendations for clinical implementation of blood-based biomarkers for Alzheimer's disease. *Alzheimer's & Dementia*, 20(11), 8216-8224.
- Pais, M. V., Forlenza, O. V., & Diniz, B. S. (2023). Plasma biomarkers of Alzheimer's disease: a review of available assays, recent developments, and implications for clinical practice. *Journal of Alzheimer's disease reports*, 7(1), 355-380.