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Review Article

Advances in Biomarkers for Early Detection and Precision Management of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common cause of dementia worldwide, yet its diagnosis has historically relied on clinical symptoms that often appear only after substantial neuronal damage has occurred. In recent years, substantial progress has been made in identifying reliable biomarkers that reflect the underlying pathological processes of AD, including amyloid deposition, tau pathology, and neurodegeneration. This review provides a comprehensive overview of established and emerging biomarkers, including cerebrospinal fluid and blood-based markers, neuroimaging techniques, and genetic indicators. Special attention is given to transformative, minimally invasive options, such as plasma phosphorylated tau at threonine 217 (p-tau 217) and exosome-derived molecules. We explore their clinical performance, integration into current diagnostic guidelines, and ongoing challenges related to assay standardization across analytical platforms, accessibility, and clinical implementation, as well as the promise of multimodal and digital approaches. By bridging validated tools with cutting-edge innovations, this article aims to support researchers and clinicians in achieving more precise, scalable, and equitable diagnosis and monitoring of AD, particularly as disease-modifying therapies become more widely available.

Keywords: Alzheimer's disease, Blood-based biomarkers, p-tau217, Amyloid-beta, AT(N) framework, Precision medicine

Background

Alzheimer's disease (AD) is characterized by progressive cognitive decline, synaptic dysfunction, and neuronal loss. The pathological hallmarks include extracellular deposition of amyloid-beta (Aβ) plaques and intracellular accumulation of hyperphosphorylated tau protein forming neurofibrillary tangles (Figure1). Despite advances in understanding disease mechanisms, clinical diagnosis still largely relies on cognitive assessment, which often occurs after significant neurodegeneration has already taken place. This has driven intense interest in biomarkers that can detect AD in its earliest stages [1].

Biomarkers have transformed the clinical and research landscape of AD by enabling the detection of pathological changes long before the onset of overt cognitive symptoms. Beyond supporting diagnosis, biomarkers facilitate risk stratification, disease staging, prognostic assessment, and monitoring of therapeutic response, thereby providing a foundation for precision medicine approaches in AD. The introduction of structured biomarker frameworks has been instrumental in this shift. The well-known Amyloid, Tau, Neurodegeneration (AT[N]) classification system provides a biological staging model based on data from magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), or positron emission tomography (PET) [2].

This review summarizes current and emerging biomarkers of AD, highlighting their biological significance, diagnostic performance, and clinical applicability in contemporary practice. The recent regulatory clearance of blood-based biomarker assays has further accelerated this transition, making it increasingly important to evaluate not only biomarker accuracy but also their appropriate clinical positioning, analytical standardization, and role within stepwise diagnostic pathways.

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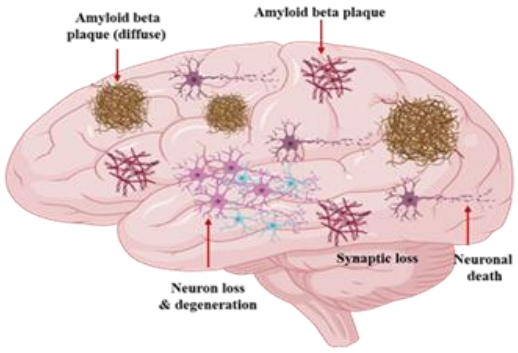


Figure 1. Pathological Hallmarks of Alzheimer's disease: Extracellular Amyloid-β Plaques and Intracellular Neurofibrillary Tangles of Hyperphosphorylated Tau Protein

Biological Framework of Alzheimer's Disease (AD) Biomarkers

The understanding of AD has evolved from a symptom-based disorder to a biologically defined disease characterized by specific pathological changes in the brain. Growing evidence indicates that amyloid deposition, tau pathology, and neurodegeneration begin many years before the onset of clinical symptoms, highlighting the importance of biomarkers for early detection and disease characterization [3] (Figure2).

A major advance in this field was the introduction of the National Institute on Aging–Alzheimer's Association Research Framework, which established the AT(N) classification system. This framework categorizes biomarkers into three core groups: amyloid pathology (A), tau pathology (T), and neurodegeneration or neuronal injury (N). This sequential cascade is schematically illustrated in Figure 2. Amyloid biomarkers include reduced CSF Aβ42 levels and positive amyloid PET imaging, whereas tau biomarkers are represented by elevated phosphorylated tau (p-tau) concentrations and tau PET positivity. Markers of neurodegeneration include structural MRI, fluorodeoxyglucose-positron emission tomography (FDG-PET), and neurofilament light chain (NfL) measurements [3]. The AT(N) framework has provided a standardized approach for interpreting biomarkers and has improved consistency across research studies and clinical trials. More importantly, it has enabled the identification of individuals in the preclinical and prodromal stages of AD, when pathological changes are already present despite minimal or absent cognitive symptoms [4].

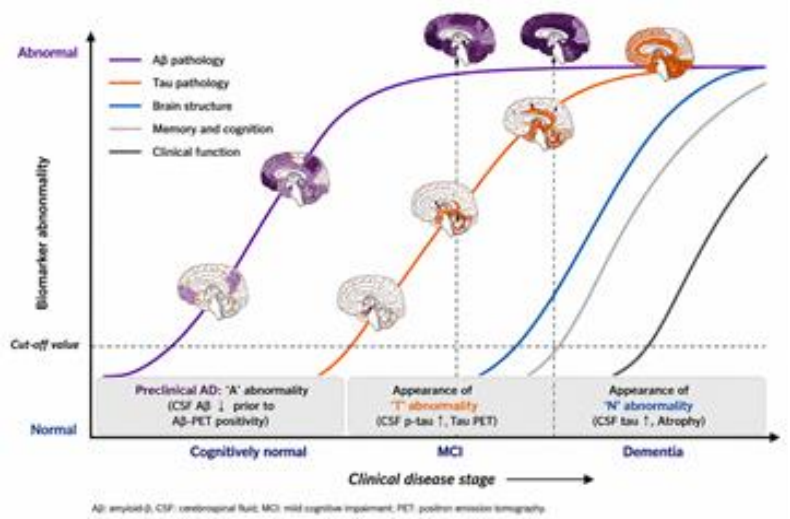


Figure 2. Dynamic Biomarker Cascade in Alzheimer's Disease from Preclinical Stages to Dementia
The sequential emergence of amyloid (A), tau (T), and neurodegeneration (N) biomarkers precedes measurable cognitive impairment and clinical dysfunction.

More recently, the 2024 Alzheimer's Association revised criteria further emphasized the role of

biomarkers in clinical diagnosis and disease staging. These updated recommendations recognize that AD can be diagnosed based on biological evidence of amyloid and tau pathology and support the increasing use of blood-based biomarkers as accessible tools for early detection and risk stratification [5]. Together, these advances have established biomarkers as the foundation of modern precision medicine approaches in AD.

The biological framework of AD also provides a foundation for biomarker-guided therapeutic interventions. The recent approval of disease-modifying therapies targeting amyloid pathology has increased the need for accurate biomarker-based patient selection, disease staging, and treatment monitoring. Consequently, biomarker assessment is becoming an integral component of both clinical research and routine patient care.

Cerebrospinal Fluid Biomarkers

CSF biomarkers are widely used for the biological detection and characterization of AD. Analysis of CSF obtained via lumbar puncture reflects the key pathological processes of AD, including amyloid deposition and tau-related neurodegeneration. The classical CSF biomarker profile consists of decreased amyloid-β42 (Aβ42) or a reduced Aβ42/Aβ40 ratio, along with increased levels of total tau (t-tau) and p-tau. Among tau biomarkers, p-tau at threonine 217 (p-tau217) has recently gained particular attention due to its strong association with amyloid and tau PET imaging. Although CSF biomarkers remain the biological reference standard, their clinical utility is constrained by the invasive nature of lumbar puncture, limited patient acceptance, and restricted availability outside specialized centers. In contrast, blood-based biomarkers offer markedly greater accessibility and suitability for repeated sampling, albeit with generally lower absolute concentrations of CNS-derived proteins and greater susceptibility to peripheral confounding factors. Although CSF biomarkers remain an important biological reference standard, their clinical use is limited by the invasive nature of lumbar puncture, patient acceptance, and restricted availability outside specialized centers. In contemporary diagnostic pathways, high-performance blood-based biomarkers are increasingly being used for initial assessment or triage, particularly when the clinical probability of AD needs to be established efficiently. CSF biomarkers or amyloid PET may then be reserved for cases with indeterminate or discordant blood biomarker results, diagnostically complex presentations, or research settings requiring reference-standard confirmation. Thus, blood-based biomarkers are increasingly complementing and, in selected clinical contexts, reducing the need for invasive CSF testing rather than completely replacing it.

Table 1. Summary of Key Biomarkers in AD

Biomarker	Sample	AT(N)	Diagnostic Performance	Clinical Utility
Aβ42/Aβ40	CSF	A	AUC ≈ 0.90–0.95	Early diagnosis
p-tau217	CSF/Blood	T	AUC ≈ 0.95–0.98	Diagnosis and staging
p-tau181	CSF/Blood	T	AUC ≈ 0.90–0.94	Disease monitoring
NfL	CSF/Blood	N	AUC ≈ 0.75–0.85	Neurodegeneration
GFAP	Blood	N/I	AUC ≈ 0.80–0.90	Early astrocyte activation
Amyloid PET	Imaging	A	>0.95	Confirmation
Tau PET	Imaging	T	>0.90	Staging

* Diagnostic performance values are approximate ranges derived from representative studies and may vary according to assay platform, study population, reference standard, and clinical setting; they should not be interpreted as universal performance estimates.

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positron emission tomography; Aβ, amyloid-beta; AT(N) amyloid, tau, neurodegeneration; p-tau, phosphorylated tau**;** NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; AUC, area under the curve.

Blood-Based Biomarkers

Blood biomarkers are a non-invasive alternative for large-scale screening and longitudinal monitoring [6]. These biomarkers have emerged as a major advance in AD research. Among them, plasma p-tau at threonine 217 (p-tau217) has shown particularly high diagnostic accuracy for Alzheimer's pathology. Large cohort studies report AUC values of approximately 0.95–0.98 for detecting amyloid-β PET positivity and about 0.95–0.97 for tau PET positivity, indicating performance comparable to or even exceeding established CSF biomarkers [7]. In May 2025, the FDA cleared two blood-based Alzheimer's tests. In May 2025, the FDA cleared two blood-based AD tests for specific clinical indications. The Fujirebio Lumipulse G p-tau217/β-amyloid 1-42 ratio test was cleared to aid in the assessment of AD pathology in symptomatic

adults aged 55 years and older, while the Roche Elecsys p-tau181 test was cleared for use in primary care to help rule out amyloid pathology and potentially reduce unnecessary referrals for CSF analysis or amyloid PET. These regulatory clearances represent important progress toward integrating blood-based biomarkers into clinical diagnostic pathways, but they should not be interpreted as authorization for unrestricted population-wide screening [8].

Other studies show plasma p-tau217 assays [9] (ALZpath, Janssen, MSD/Lilly) achieve overall percent agreement of 80%-90% with florbetapir PET. They can reduce the need for confirmatory PET/CSF by 58-80% when using two-cutpoint strategies. Other promising markers include plasma Aβ42/40, glial fibrillary acidic protein (GFAP: astrocyte reactivity), and NfL (axonal injury). Multi-marker panels combined with age, apolipoprotein E (APOE) genotype, and AI algorithms further boost accuracy. APOE genotype may provide complementary information on underlying risk, but it should be interpreted as a susceptibility factor rather than a diagnostic marker of established AD pathology. Pre-analytical factors (tube type, freeze-thaw cycles) and comorbidities (renal impairment) require careful standardization [10]. Compared with CSF assays, high-performing plasma biomarkers, particularly p-tau217-based assays, can achieve very high diagnostic accuracy for detecting AD pathology in well-characterized cohorts. However, their performance may vary across analytical platforms and clinical populations because of pre-analytical factors, peripheral sources of biomarkers, comorbidities such as renal dysfunction, and differences in cohort characteristics. Therefore, high diagnostic accuracy in research cohorts should not be interpreted as evidence that blood biomarkers universally outperform or fully replace CSF biomarkers in all clinical settings. Although blood biomarkers are rapidly transforming clinical practice, neuroimaging biomarkers remain indispensable for confirming pathology and disease staging.

Neuroimaging Biomarkers

Neuroimaging biomarkers provide a unique opportunity to visualize AD pathology *in vivo*. Amyloid PET enables direct detection of cerebral amyloid deposition, whereas tau PET offers insights into the spatial distribution and progression of tau pathology that closely mirrors clinical disease severity. Structural MRI remains essential for assessing hippocampal atrophy and cortical neurodegeneration, while FDG-PET reflects regional cerebral hypometabolism associated with neuronal dysfunction. Together, these modalities contribute to diagnosis, disease staging, differential diagnosis, and therapeutic monitoring [11].

MRI identifies characteristic patterns of hippocampal and medial temporal lobe atrophy, whereas FDG-PET detects regional cerebral hypometabolism, particularly within temporoparietal cortical regions. Although these modalities lack specificity for AD pathology, they provide valuable information for differential diagnosis, disease staging, and longitudinal monitoring. Collectively, molecular imaging biomarkers offer unparalleled insights into the biological processes underlying AD and continue to play a central role in clinical trials.

Emerging and Next-Generation Biomarkers

Importantly, these emerging biomarkers do not have equivalent levels of clinical validation. Some, such as plasma GFAP and NfL, have accumulated substantial evidence across multiple cohorts and may complement established biomarkers in selected clinical or research settings. In contrast, exosome-derived biomarkers, retinal biomarkers, synaptic biomarkers, and many digital measures remain primarily investigational and require larger prospective, multicenter, and clinically relevant validation studies before routine diagnostic implementation. Emerging biomarkers represent one of the most rapidly advancing areas of AD research. Among these emerging approaches, exosome-derived biomarkers have attracted considerable attention because extracellular vesicles of neuronal origin may be detectable in peripheral circulation and can carry disease-relevant cargo, including amyloid-β, tau proteins, microRNAs, and inflammatory mediators. However, the mechanisms governing their trafficking between the central nervous system and peripheral circulation, including interactions with the blood-brain barrier, remain incompletely understood, including amyloid-β, tau proteins, microRNAs, and inflammatory mediators (Figure3). Recent advances in retinal imaging and digital health technologies further expand the spectrum of potential biomarkers by providing scalable, minimally invasive tools for disease detection and monitoring (Figure4).

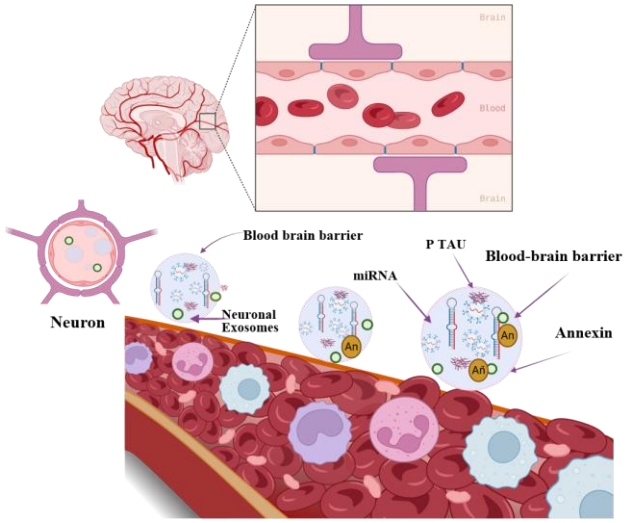


Figure 3. Emerging Role of Exosome-Derived Biomarkers in Alzheimer's Disease: Detection of Pathogenic Proteins (Aβ, tau) and Regulatory miRNAs from Neuronal Exosomes

Genetic Biomarkers

Genetic biomarkers play a crucial role in identifying individuals at increased risk of developing AD, often decades before the onset of clinical symptoms. Among all known genetic risk factors, the APOE ε4 allele remains the strongest susceptibility gene for sporadic late-onset AD. Carriers of one APOE ε4 allele exhibit a substantially increased risk of developing AD, while homozygous carriers may experience an earlier age of onset and accelerated amyloid accumulation. In contrast, the APOE ε2 allele appears to confer partial protection against disease development [12]. Beyond APOE, genome-wide association studies have identified numerous additional loci associated with AD susceptibility, including *TREM2, ABCA7, BIN1, CLU, CR1, PICALM, and SORL1*. These genes are involved in diverse biological pathways, including lipid metabolism, endosomal trafficking, synaptic function, and innate immune responses. Among them, *TREM2* has emerged as a particularly important regulator of microglial activation and neuroinflammatory processes [13, 14]. Polygenic risk scores (PRS) may improve risk stratification when combined with fluid biomarkers such as plasma p-tau217 and amyloid measures, particularly in research settings. However, PRS are not currently established for routine clinical use because their performance and calibration may vary across populations, and many existing models have been developed using datasets with limited representation of diverse genetic ancestries. Further validation across ancestries and clinically relevant populations is therefore required before widespread clinical implementation [15]. Genetic markers indicate susceptibility rather than active pathology and therefore are insufficient alone for diagnosis.

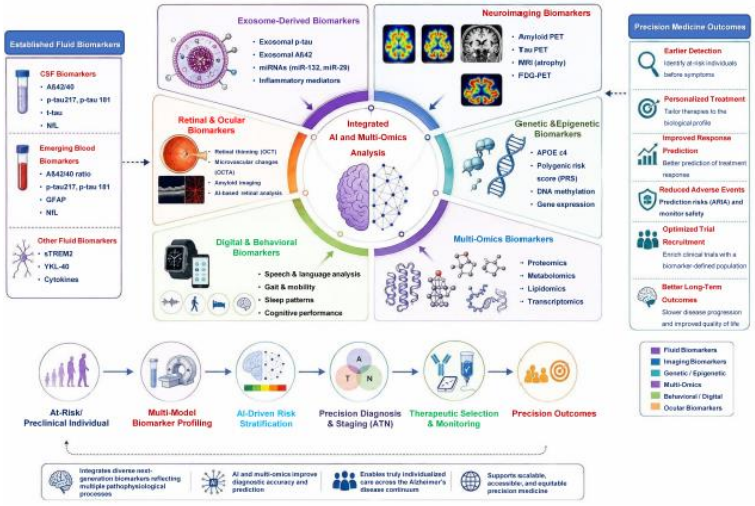


Figure 4. Next-Generation Biomarkers and Precision Medicine in Alzheimer's Disease
Integration of blood-based, exosome-derived, neuroimaging, genetic, retinal, digital, and multi-omics biomarkers through artificial intelligence enables practical applications including personalized risk stratification, biological disease staging, selection of disease-modifying therapies, and longitudinal treatment monitoring.

Neuroinflammatory Biomarkers

Neuroinflammation is increasingly recognized as a central contributor to AD pathogenesis rather than a secondary consequence of neurodegeneration. Activation of microglia and astrocytes occurs early in the disease process and may influence amyloid deposition, tau propagation, synaptic dysfunction, and neuronal loss [16]. Among these, plasma GFAP has accumulated the strongest clinical evidence to date and is already being incorporated into research and selected clinical algorithms as an early marker of astrocytic activation; other markers (soluble Triggering Receptor Expressed on Myeloid cells 2 [sTREM2], chitinase-3-like protein 1 [YKL-40], monocyte chemoattractant protein-1 [MCP-1], etc.) remain primarily investigational. Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) is one of the most extensively studied markers of microglial activation and has been associated with disease progression and cognitive decline. Elevated levels of GFAP, particularly in plasma, have emerged as sensitive indicators of astrocytic activation and may become abnormal even before detectable cognitive impairment [17]. Additional inflammatory markers under investigation include YKL-40 (CHI3L1), MCP-1, osteopontin, interleukin-6, and tumor necrosis factor-alpha. While these markers individually exhibit variable diagnostic performance, their integration into multimarker panels may improve characterization of disease heterogeneity and progression [18]. Given the growing evidence linking immune dysregulation to AD pathology, neuroinflammatory biomarkers may provide valuable insights into disease mechanisms and serve as potential tools for monitoring future immunomodulatory therapies [19].

Synaptic Biomarkers

Synaptic dysfunction is considered one of the earliest pathological events in AD and correlates more strongly with cognitive decline than amyloid plaque burden alone. Neurogranin and synaptosomal-associated protein 25 (SNAP-25) in CSF have been validated in multiple cohorts and correlate with cognitive decline, yet they are not yet part of routine clinical practice. Synaptic vesicle glycoprotein 2A (SV2A) PET imaging is still in the early clinical-research stage. Other promising synaptic biomarkers include SNAP-25, growth-associated protein 43, and synaptotagmin, all of which reflect different aspects of synaptic damage and neurotransmission [20]. Recent advances in molecular imaging have also enabled the assessment of synaptic density using SV2A PET imaging. Early studies suggest that reductions in SV2A binding correlate with disease severity and may provide a direct measure of synaptic loss in vivo [21]. As therapeutic strategies increasingly target early pathological changes, synaptic biomarkers may become important tools for identifying patients at risk of cognitive decline and evaluating treatment efficacy.

Retinal Biomarkers

The retina has emerged as a promising window into neurodegenerative processes occurring within the central nervous system. Because the retina shares embryological and anatomical characteristics with the brain, retinal imaging may provide a non-invasive and cost-effective approach for detecting early AD-related changes. Optical coherence tomography (OCT) studies have reported thinning of the retinal nerve fiber layer, ganglion cell layer, and macular structures in individuals with mild cognitive impairment and early AD. Furthermore, OCT angiography has revealed alterations in retinal microvascular density and perfusion that may reflect early cerebrovascular dysfunction [22]. Retinal amyloid imaging and AI-assisted image analysis are also under study. Despite their scalability, variability among studies, limited disease specificity, and lack of large multicenter validation currently preclude routine clinical use.

Digital Biomarkers and Artificial Intelligence

Digital biomarkers represent one of the fastest-growing areas in AD research. Advances in wearable sensors, smartphones, speech analysis platforms, and artificial intelligence have enabled continuous and objective monitoring of cognitive and behavioral changes outside traditional clinical settings [23]. Among the most promising digital biomarkers are alterations in speech and language patterns, which may precede overt cognitive impairment. Wearable technologies have also facilitated the evaluation of gait dynamics, physical activity, sleep patterns, and circadian rhythm disturbances. These measures may provide valuable information regarding disease progression and functional decline. The integration of artificial intelligence with multimodal datasets, including blood biomarkers, neuroimaging findings, genetic information, and digital health data, has the potential to improve diagnostic accuracy and enable individualized risk prediction. Although several challenges remain regarding validation, standardization, and data privacy, digital biomarkers are expected to play an increasingly important role in future precision medicine frameworks for AD [24, 25]. Although many emerging biomarkers remain investigational, several have demonstrated

potential to complement established AT(N) biomarkers and may eventually be incorporated into clinical diagnostic pathways. Their integration into routine practice will depend on further validation, standardization, and demonstration of clinical utility. Nevertheless, validation, standardization, privacy, and regulatory requirements remain substantial barriers. Digital biomarkers should therefore currently be regarded as complementary investigational tools rather than standalone diagnostic tests.

Clinical Utility, Guidelines, and Diagnostic Performance

The appropriate sequence should depend on the intended use of the test. Screening, diagnosis, staging, prognosis, and treatment monitoring require different performance characteristics and thresholds. A highly sensitive blood test may be useful to rule out pathology, whereas a confirmatory test requires high specificity. The clinical value of any biomarker should therefore be judged not only by AUC but also by predictive values, calibration, impact on clinical decisions, patient outcomes, and cost-effectiveness. The 2024 criteria integrate biomarkers into a clinical-biological staging framework and support the use of blood tests in selected symptomatic individuals [5]. A practical approach is to use a high-performance plasma biomarker such as p-tau217 as an initial assessment in appropriate patients. A clearly negative result can substantially reduce the likelihood of AD pathology, whereas intermediate or positive results may require confirmation with CSF biomarkers or amyloid PET, depending on clinical context, availability, and patient preference. Tau PET or MRI can assist with staging and differential diagnosis. Longitudinal plasma p-tau217, NfL, and imaging may also support treatment monitoring, although the optimal markers and thresholds for routine therapeutic decisions require further validation.

Limitations and Future Perspectives

The main challenge is that high diagnostic accuracy against a reference standard does not automatically demonstrate clinical utility. Many biomarker studies are performed in selected memory-clinic cohorts with relatively clear disease phenotypes, which may overestimate performance in heterogeneous primary-care populations. Future studies should include prospective real-world cohorts, diverse ages and ancestries, relevant comorbidities, and predefined clinical endpoints. This issue is particularly important because many biomarker validation cohorts have historically been enriched for participants of European ancestry and may not adequately represent Asian, African, Hispanic/Latino, and other underrepresented populations. Differences in genetic ancestry, comorbidity profiles, socioeconomic conditions, healthcare access, and baseline biomarker distributions may influence assay performance and clinical thresholds. Future studies should therefore evaluate calibration, diagnostic accuracy, and clinical utility across diverse populations and healthcare settings to ensure that biomarker-guided precision medicine does not widen existing health disparities. Important barriers include assay harmonization, differences among analytical platforms, limited validation in diverse populations, cost and accessibility, and ethical issues surrounding preclinical diagnosis. Multimodal integration of blood, imaging, genetic, and digital data through AI and multi-omics may improve precision, but such models require external validation and clinically meaningful outcomes before routine adoption [26]. In particular, the high cost of advanced assays and limited infrastructure in resource-limited settings continue to restrict equitable access, underscoring the need for more affordable and widely deployable solutions.

Conclusion

Biomarkers have shifted AD assessment from predominantly symptom-based diagnosis toward biological characterization. CSF and neuroimaging remain important reference standards, while blood biomarkers, especially plasma p-tau217, offer highly accessible approaches for detecting amyloid and tau pathology and supporting staging and monitoring. Genetic, inflammatory, synaptic, retinal, exosome-derived, and digital biomarkers may provide complementary information, but many remain investigational. Translation into routine care will depend on analytical standardization, validation across diverse populations, appropriate clinical thresholds, and evidence that biomarker-guided decisions improve patient outcomes.

Authors' Contributions

Writing - original draft: M.M;
Conceptualization and supervision: H.A. and G.B;
Conceptualization and supervision, writing - review and editing: S.T.

Conflict of Interest

The authors declared no conflicts of interest.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical guidelines and with approval from the Research Ethics Committee of Islamic Azad University- North Tehran Branch

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Use of Artificial Intelligence
Artificial intelligence (AI) tools were used to assist with language paraphrasing and the conceptual design of selected schematic figures. All outputs were critically reviewed, edited, and approved by the authors, who take full responsibility for the final content of the manuscript.

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