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Review article

Blood-based biomarkers for Alzheimer's disease: Advances in early detection and monitoring of age-related neurodegeneration

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ABSTRACT

Alzheimer's disease (AD) presents a critical global challenge, accounting for over 60 % of the 57 million current dementia cases worldwide, with prevalence projected to exceed 100 million by 2050. Traditional diagnostic approaches, such as cerebrospinal fluid (CSF) analysis and neuroimaging are constrained by invasiveness, high costs, and limited accessibility, particularly problematic in aging population where early detection is crucial for effective intervention. This review synthesizes recent advances in blood-based biomarkers for AD, specifically phosphorylated tau proteins (p-tau217, p-tau181), neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and the amyloid-β42/40 ratio. These minimally invasive biomarkers demonstrate exceptional diagnostic accuracy with p-tau217 achieving AUC values greater 0.93 and 91 % positive predictive value in detecting AD pathology, Critically, these biomarkers can identify pathological changes 15–20 years before symptom onset, with plasma p-tau217 levels increasing over 8.5 % annually during preclinical stages. We propose that dried blood spots (DBS), containing both arterial and venous blood components, offer superior representation of brain-derived substances at their first systematic distribution after cardiac output. Ultrasensitive technologies like Simoa and mass spectrometry now enable femtomolar-level detection, revolutionizing of AD diagnostics. However, challenges persist in assay standardization persist in assay standardization, and population-specific validation. Overcoming these barriers to integrate blood biomarkers with DBS technology represents a transformative shift toward accessible, scalable screening in aging communities, offering a paradigm shift in preventing age-related neurodegeneration through early detection and timely intervention.

1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide, accounting for over 60 % of the 57 million global dementia cases (Aramadaka et al., 2023). With rapid population aging, this number is projected to exceed 100 million by 2050 (Delaby et al., 2023), posing an escalating socio-economic and healthcare burden (Lanctôt et al., 2024). While recent advancements in disease-modifying therapies - such as anti-Aβ monoclonal antibodies (e.g., Lecanemab and Donanemab) - have demonstrated efficacy in slowing cognitive decline and reducing amyloid pathology in early-stage AD, their benefits are limited to this initial phase of the disease (Wang et al., 2025). Moreover, these treatments carry risks, including amyloid-related imaging abnormalities (ARIA) and vascular complications, necessitating careful patient selection and monitoring. Given that current medications remain ineffective in later stages, early and accurate diagnosis is paramount to maximize therapeutic outcomes. However, clinical diagnosis remains fraught with challenges - misdiagnosis and missed diagnosis rates reach 50 %, reflecting significant diagnostic delay (Wang et al., 2023). This stark reality necessitates the development of minimally invasive, scalable diagnostic technologies with high sensitivity, strong specificity, and clinical applicability to enable timely intervention and improve patient outcomes (Winchester et al., 2023).

Current diagnostic standards rely on CSF biomarker analysis and neuroimaging modalities, including magnetic resonance imaging (MRI) and positron emission tomography (PET). CSF analysis quantifies amyloid-β42 (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau)

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protein levels, effectively reflecting AD pathological changes and serving as the diagnostic gold standard for AD (Kim et al., 2022; Schöll et al., 2024). MRI supplements clinical diagnosis by quantifying structural brain alterations, particularly medial temporal lobe atrophy and hippocampal volume loss, which correlate with AD pathological staging. PET imaging enables non-invasive detection of cerebral amyloid deposition or glucose metabolism, demonstrating robust diagnostic capability in early-stage disease progression (Kim et al., 2022).

However, these established diagnostic modalities face persistent challenges and inherent limitations in clinical practice (Table 1). CSF analysis requires lumbar puncture, an invasive procedure associated with patient burden and limited suitability for large-scale screening, while MRI demonstrates reduced sensitivity during early disease stages when structural changes are minimal. PET imaging, despite its diagnostic strength, remains constrained by high cost, complex infrastructure requirements, and ionizing radiation exposure, collectively limiting its scalability and accessibility, especially in primary care and resource-limited settings (Delaby et al., 2023; Schöll et al., 2024). These limitations contribute to substantial diagnostic gaps worldwide, with WHO data indicating that up to 89 % of dementia cases in low- and middle-income countries remain undiagnosed (Kim et al., 2022; Schöll et al., 2024).

1.1. Emergence of blood-based biomarkers for Alzheimer's disease

The advent of blood-based biomarkers in recent years has revolutionized AD diagnostics, providing unprecedented opportunities for early detection through minimally invasive approaches. Compared with conventional diagnostic modalities, blood-based testing offers clear advantages in terms of patient acceptability, cost-effectiveness, and scalability, positioning it as a promising solution for large-scale population screening initiatives and frontline healthcare delivery in resource-constrained settings (Ausó et al., 2020; Mandal et al., 2023). Furthermore, blood-based biomarkers demonstrate the unique capacity to detect pathological deviations at prodromal disease stages (Braak I-II), thereby enabling early risk stratification (AUC=0.91), precise longitudinal disease monitoring (annual p-tau217 increase >8.5 %), and dynamic therapeutic response assessment at time points when structural imaging often remains inconclusive (Mattsson-Carlgren et al., 2020; Nasreddine et al., 2023).

Among these blood-based biomarkers, phosphorylated tau proteins (notably p-tau217 and p-tau181), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) have been rigorously validated as key blood-based biomarkers of AD. These biomarkers reflect complementary aspects of AD pathophysiology, encompassing tau pathology, neuroaxonal injury, and astrocytic activation, and collectively show strong concordance with established CSF and PET measures. In parallel, increasing evidence supports the diagnostic relevance of the plasma Aβ42/Aβ40 ratio as a peripheral surrogate of cerebral amyloid burden, leading to its incorporation into emerging diagnostic algorithms as a first-line screening metric (Chatterjee et al., 2023a; Chen et al., 2021).

Table 1
Comparison of Diagnostic Modalities for Early Alzheimer's Disease Detection.

Method	Pros	Cons
CSF Analysis	• Gold standard for AD pathology (Aβ42, t-tau, p-tau) • High sensitivity/ specificity (>90 %) • Detects early pathological changes (Braak I-II)	• Invasive (lumbar puncture) • Risk of complications (e.g., headaches, infection) • Poor scalability for population screening
MRI	• Non-invasive • Visualizes structural atrophy (hippocampal volume loss) • No radiation exposure	• Low sensitivity in early AD (structural changes appear late, Braak III-IV) • Expensive (~1000–1000–2000 per scan) • Limited to advanced stages
PET Imaging	• Detects amyloid deposition & glucose hypometabolism • High accuracy for early AD (Braak I-II) • Non-invasive	• Extremely costly (~$4500 per scan) • Requires radioactive tracers • Ionizing radiation exposure (7–8 mSv) • Limited accessibility
Blood Biomarkers (p-tau217, NfL, GFAP, Aβ42/40)	• Minimally invasive • Low cost (~$150 vs. PET) • High scalability for screening • Detects pathology earlier than MRI (Braak I-II) • Strong correlation with CSF/PET (AUC 0.91–0.93)	• Lack of standardized protocols • Inter-lab variability (reproducibility issues) • Limited longitudinal data for validation

1.2. Translational bottlenecks in blood biomarker implementation

Despite ground-breaking advancements in blood-based biomarker research, significant challenges impede widespread clinic adoption. A primary obstacle is the lack of standardized clinical application criteria for emerging blood biomarkers (p-tau217, p-tau181, GFAP, NfL). Methodological heterogeneity across studies has led to inconsistent reproducibility (k = 0.43–0.67 between centers), directly impeding clinical translation (Mattsson-Carlgren et al., 2020). Additionally, there is scarcity of head-to-head comparative studies among blood biomarkers and limited large-scale longitudinal data spanning the AD continuum (Chatterjee et al., 2023a; Rani et al., 2023). While novel platforms like single-molecule array (Simoa) technology have enhanced analytical sensitivity and specificity, significant gaps remain in technical standardization and real-world performance validation (Mandal et al., 2023).

1.3. Integrating Dried Blood Spot (DBS) sampling to bridge research and clinical practice

Clinical translation of blood-based biomarkers critically depends on practical sampling strategies enabling scalable, accessible, and standardised testing. DBS sampling offers a promising integration framework through minimally invasive collection, simplified logistics, and compatibility with decentralized primary-care settings. DBS reduces reliance on venipuncture, cold-chain transport, and specialized infrastructure, addressing key implementation barriers. Importantly, DBS facilitates repeated longitudinal measurements and remote or at-home collection, particularly relevant for early-stage detection and disease monitoring in aging populations.

This study systematically analyzes and validates blood biomarkers - plasma p-tau217, p-tau181, NfL, GFAP, and Aβ42/40 ratio - evaluating their performance in early AD detection and disease progression monitoring. Through comprehensive horizontal and vertical comparison, we will identify optimal diagnostic combinations and clinical application strategy. Additionally, this study explores standardization of detection techniques and multicentre data sharing, providing foundations for establishing unified clinical testing standards. These research efforts aim to bridge current knowledge gaps, advance blood biomarker translation from research to clinical practice, and provide evidence and guidance for early detection, disease monitoring, and clinical intervention of AD.

2. Blood-based biomarkers in Alzheimer's disease

Blood-derived analytes have evolved from exploratory research tools into frontline candidates for early AD detection. Compared with CSF analysis (invasive lumbar puncture) and PET imaging (radiation and high cost) , plasma testing combines minimal invasiveness with scalability in primary-care settings. Drawing on studies published between

2019-2025, we synthesize current evidence for the five most widely validated plasma biomarkers - p-tau217, p-tau181, NfL, GFAP and the Aβ42/40 ratio, and map their analytical performance across state-of-the-art detection platforms. (Agarwal et al., 2023; Chatterjee et al., 2023a; Chen et al., 2023; Li and Mielke, 2019; Lim et al., 2020; Nakamura et al., 2018; Truffi et al., 2023). Table 2 provides a concise matrix of assay principles, limits of detection (LoD), dynamic ranges, throughput and key limitations to facilitate cross-platform comparisons.

2.1. Key blood biomarkers for AD diagnosis

With ultrasensitive detection technologies such as Simoa and novel proteomics approaches, blood-derived biomarkers have emerged as indispensable tools for early AD diagnosis and disease progression monitoring, overcoming limitations of traditional CSF and PET-based approaches (Álvarez-Sánchez et al., 2022; Schöll et al., 2024).

Diagnostic cut-off values are not uniformly established across all blood-based biomarkers. For certain biomarkers, such as plasma p-tau217 and the Aβ42/Aβ40 ratio, cut-offs have been proposed in specific studies or analytical platforms, typically calibrated against amyloid PET or CSF reference standards. However, for others including NfL and GFAP, no universally accepted diagnostic thresholds exist, reflecting biological non-specificity and substantial inter-assay and inter-population variability. Reported cut-off values should therefore be interpreted as context-dependent rather than universally applicable, and the absence of standardized thresholds remains a major barrier to clinical translation.

p-tau217: p-tau217, phosphorylated at Thr217, is the most robust blood-based biomarker for AD, reflecting cerebral tau pathology with high specificity. Palmqvist et al. (2024) demonstrated that p-tau217 combined with the Aβ42/Aβ40 ratio (as the Amyloid Probability Score 2 [APS2]) achieves exceptional diagnostic accuracy (AUC = 0.96–0.97) in distinguishing AD from non-AD neurodegenerative diseases in both primary and secondary care settings. The biomarker showed 91 % positive predictive value (PPV) and 92 % negative predictive value (NPV) for AD pathology, outperforming clinical assessments by dementia specialists (73 % accuracy) and primary care physicians (61 % accuracy). P-tau217 also strongly correlates with Braak staging ($r = 0.79$, $p < 0.001$) and outperforms (e.g., p-tau181) in early AD detection.

Critically challenges remain: (1) Cut-off variability across platforms (e.g., mass spectrometry vs. immunoassays), with intermediate results observed in 6–15 % cases when using two-cut-off approaches (Palmqvist et al., 2024); (2) Plasma p-tau217 levels are influenced by sample handling delays and freeze-thaw cycles, necessitating strict protocols; (3) Population differences requiring population-specific reference values (Wang et al., 2024).

While p-tau217 alone achieves AUC > 0.93, its integration with Aβ42/Aβ40 (APS2) further enhances accuracy, making it a viable alternative to CSF/PET in clinical practice. Assay standardization and validation in diverse populations are pivotal for widespread adoption.

p-tau181: p-tau181. phosphorylated at Thr181, reliably reflects tau pathology with a diagnostic accuracy of AUC = 0.91, effectively distinguishing AD dementia patients from cognitively unimpaired individuals and strongly correlating with cognitive decline and neurodegeneration. Despite these strengths, limitations include insufficient longitudinal studies to establish definitive diagnostic thresholds and standardized protocols; and its dynamic range plateaus earlier than p-tau217, limiting utility in preclinical stage (Simrén et al., 2021; Wang et al., 2023).

Nfl: Neurofilament light chain (NfL) is a marker of axonal injury demonstrating utility in detecting neurodegeneration in early symptomatic AD stages such as subjective cognitive decline (SCD) and mild cognitive impairment (MCI). Álvarez-Sánchez et al. (2022) reported that plasma NfL shows high sensitivity for distinguishing individuals with neurodegenerative diseases from healthy controls and performs well in identifying AD biomarker profiles using the Amyloid beta-Tau-Neurodegeneration (ATN) classification system (Álvarez-Sánchez et al., 2022). Plasma NfL achieved AUC values of 0.815 and 0.818 for differentiating ATN-positive from ATN-negative individuals in SCD and MCI populations, respectively, with specificity as high as 95.24 %, though sensitivity remained moderate.

Longitudinal plasma NfL trajectories closely track CSF NfL patterns across the AD continuum and correlate strongly with disease progression

Table 2
Comparative analysis of high-sensitivity biomarker detection platforms for Alzheimer's disease.

	Analytical Principle	Measured Targets	Limit of Detection (LOD)	Dynamic Range (log_{10})	Estimated Throughput (samples/day)	Key Limitations
IP-MS (MALDI-TOF) (Nakamura et al., 2018**)**	Immunoprecipitation + MALDI-TOF MS	Aβ1–42, Aβ1–40, APP669–711Ratios: Aβ40/42, APP669–711/42, Composite	~2.5 pM (ratio LOD est.)	~2–3 (estimated)	~30–60	Labor-intensive; pre-analytical variability; MALDI–TOF quantitation limits
CSF-Aβ assay (Nakamura et al., 2018**)**	Luminescence-based immunoassay (standard)	CSF Aβ1–42	Not specified in detail in this paper	High (immunoassay standard)	~100–200 (platform dependent)	Invasive collection; inter-lab variability; not widely scalable
PET Imaging (Nakamura et al., 2018**)**	Radiotracer-based imaging (PIB, FBP, FLUTE)	Brain Aβ burden (indirectly via SUVRs)	NA (imaging-based)	NA	Low (high cost & infrastructure required)	Expensive; not accessible everywhere; variability between tracers
Simoa® (Single Molecule Array) (Álvarez-Sánchez et al. (2022)**;** Singh et al. (2021)	Digital immunoassay (single molecule counting, ultrasensitive ELISA)	p-tau181, p-tau217, GFAP, NfL (Used in combination with Aβ42 from HISCL for ratios: p-tau217/Aβ42)	Sub-pg/mL range (e.g., p-tau217 LOD ~0.02 pg/mL; varies by kit)	~3–4 (platform dependent)	~100–200 (Quanterix HD-X platform typical)	Requires specialized equipment; relatively high cost per test; primarily research-use; performance varies by assay lot and operator proficiency
Ella (ProteinSimple) (Álvarez-Sánchez et al. (2022)	Microfluidic-based automated immunoassay (fluorescent detection)	p-tau217, GFAP, NfL, Aβ42 (dependent on cartridge type) Ratios: p-tau217/Aβ42 also evaluated	Typically, sub-pg/mL to low pg/mL (e.g., p-tau217 ~0.5 pg/mL; varies by cartridge)	~3 (varies slightly by analyte)	~72–144 (based on 3 cartridges/run, 90 min per run)	Limited multiplexing per run; lower throughput than Simoa; cartridge availability; primarily RUO (research use only)

Footnotes:IP–MS platform used a common internal standard (SIL-Aβ1–38) for normalization, enhancing robustness in peptide ratio calculation.
Composite biomarker = normalized score of Aβ40/42 and APP669–711/42 in a 1:1 weighted average.
PET SUVR cutoffs used for positivity were: PIB ≥ 1.40; FLUTE ≥ 0.55; FBP ≥ 1.05.
Throughput estimates are approximate, based on protocol and sample processing times reported in Methods.

in later clinical stages (Mazzeo et al., 2024). However, NfL is not AD-specific and increases in other neurodegenerative disorders.Its diagnostic utility improves when interpreted alongside AD-specific markers, particularly phosphorylated tau (p-tau181 or p-tau217) (Kawarabayashi et al., 2023; Novarella et al., 2025), supporting its integration within a multimodal biomarker framework.

GFAP: Glial fibrillary acidic protein (GFAP), a plasma biomarker of astrogliosis activation and neuroinflammation, increases progressively across the AD continuum - from cognitively unimpaired individuals to those with mild cognitive impairment (MCI) and AD dementia - reflecting escalating astrocytosis. Plasma GFAP detects early amyloid pathology with up to 85 % sensitivity, even 8–10 years before clinical onset (Chatterjee et al., 2023a). Chang et al. (2025) found plasma GFAP significantly elevated in MCI and AD groups compared to controls, with strong positive correlation to subcortical tau burden ($r = 0.50$, $p = 0.004$) and inverse correlation to global cognitive performance ($r = –0.393$, $p = 0.008$), underscoring a mechanistic link between astrocytic reactivity and tau pathology. Further longitudinal and comparative studies are needed to clarify its specificity relative to other neuroinflammatory markers and define its optimal clinical role (Schöll et al., 2024; Simrén et al., 2021).

Aβ42/Aβ40: The plasma Aβ42/Aβ40 ratio has emerged as a reliable peripheral marker for detecting cerebral amyloid pathology. Using the fully automated Lumipulse platform, plasma Aβ42/Aβ40 demonstrates high diagnostic accuracy for PET-confirmed amyloid positivity (AUC = 0.885, sensitivity = 86 %, specificity = 90 %) and exhibits predictive value for future cognitive decline across both cognitively unimpaired and impaired individuals (Trelle et al., 2025). The ratio shows cross-sectional associations with hippocampal-dependent memory deficits and tau accumulation, suggesting its utility as a marker of both amyloid burden and downstream neurodegeneration.

Emerging evidence indicates that reductions in CSF Aβ42/Aβ40 reflect not only insoluble fibrillar plaque burden but also accumulation of neurotoxic soluble Aβ42 protofibrils, which more directly drive neurodegenerative processes (Andersson et al., 2025). These protofibrils mediate relationship between cortical amyloid deposition and both decreased CSF Aβ42/Aβ40 ratios and increased CSF NfL and total tau, enhancing the biological plausibility of plasma Aβ42/Aβ40 ratio as an early and pathophysiologically meaningful biomarker.

The assay's relatively low cost - approximately 1/30th that of PET imaging - and widespread availability make it attractive for frontline screening. However, pre-analytical variability (e.g., sample collection, processing, and assay platform) necessitates harmonized protocols and inter-laboratory standardization for robust clinical and research implementation (Chatterjee et al., 2023a; Chen et al., 2021). Table 3 summarizes key characteristics of five leading plasma biomarker candidates - p-tau217, p-tau181, Aβ42/Aβ40 ratio, GFAP, and neurofilament light (NfL) - including diagnostic accuracy, pathophysiological specificity, stage sensitivity, and practical considerations for clinical application.

2.2. Advantages and limitations of blood biomarkers

As outlined in Section 1.0, the emergence of blood-based biomarkers offers a transformative potential for AD diagnostics, theoretically combining the minimal invasiveness of venepuncture with the scalability required for population-level screening (Chen et al., 2024; Padala and Newhouse, 2023; Wang et al., 2023). However, the translation of these biomarkers from controlled research cohorts to heterogeneous clinical environments is currently obstructed by substantial technical, biological, and economic barriers. This section critically examines these translational bottlenecks, analyzing the physics of ultrasensitive detection, the physiological confounders inherent to peripheral matrices, and the regulatory gaps limiting widespread adoption.

2.2.1. The sensitivity frontier: platform dependency and economic viability

The fundamental challenge in blood-based AD diagnostics is the massive dilution of CNS-derived proteins upon entry into the systemic circulation. Core biomarkers such as p-tau217, p-tau181, and the Aβ42/Aβ40 ratio typically occur at sub-picogram or low-picogram per millilitre levels (e.g., plasma p-tau217 in AD: 0.40 ± 0.25 pg/mL; non-AD: 0.17 ± 0.14 pg/mL), exceeding the sensitivity range of conventional ELISA-based platforms. Consequently, detection requires ultrasensitive technologies such as Single Molecule Array (Simoa) and immunoprecipitation-liquid chromatography–tandem mass spectrometry (IP-LC-MS/MS), both of which have demonstrated diagnostic AUCs > 0.94 for key plasma biomarkers (Van Waalwijk Van Doorn et al., 2017).

However, these technologies are characterized by critical limitations. Simoa is proprietary to Quanterix, while IP-MS requires extensive sample preparation (immunoprecipitation, digestion, isotopic labeling,

Table 3
Comparative Overview of Plasma Biomarkers for Alzheimer's Disease.

Biomarker	Pathological Target	Diagnostic Accuracy (AUC)	Stage Sensitivity	Clinical and Pathological Associations	Key Limitations	Ref.
p-tau217	Tau phosphorylation at threonine-217	AUC 0.92–0.96 vs. PET amyloid and tau	Preclinical to symptomatic AD stages	Strongest plasma correlate of both amyloid and tau PET; predicts clinical progression	Currently limited assay availability; affected by co-pathologies in some cases	Barthélemy et al. (2020); Palmqvist et al. (2020); Janelidze et al. (2024)
p-tau181	Tau phosphorylation at threonine-181	AUC 0.88–0.93 vs. PET amyloid and CSF tau	Mild cognitive impairment to AD dementia	Tracks with tau PET, cognitive decline; differentiates AD from controls	Slightly less sensitive than p-tau217 in preclinical AD; moderate overlap with non-AD tauopathies	Janelidze et al. (2020); Simrén et al. (2021)
Aβ42/Aβ40 ratio	Soluble amyloid-β species	AUC 0.88–0.90 vs. amyloid PET (Lumipulse)	Among earliest biomarkers to become abnormal	Correlates with PET and CSF amyloid; predicts future cognitive decline; reflects protofibrillar Aβ42 burden	Pre-analytical variability; standardization and platform harmonization required	Trelle et al. (2025); Andersson et al. (2025); Chatterjee et al. (2023a)
GFAP	Reactive astrocytosis and inflammation	AUC ~0.85 for amyloid PET positivity	Early accumulation, rises before clinical onset	Elevated in preclinical AD; correlates with amyloid and tau load; sensitive to astrocytic response	Low specificity: also elevated in multiple sclerosis, traumatic brain injury, and other conditions	Chatterjee et al. (2023a); Chatterjee et al. (2023b); Chang et al. (2025); Abu-Rumeileh et al. (2020)
NfL	Axonal damage and neurodegeneration	AUC ~0.78–0.85 across AD spectrum	Mid to late preclinical stages through dementia	Correlates with brain atrophy, cognitive decline; increases in many neurodegenerative disorders	Not disease-specific; elevated in FTD, ALS, MS, and other conditions	Álvarez-Sánchez et al. (2022); Mattsson et al. (2019); Mattsson-Carlgren et al. (2023)

Footnote: Aβ = amyloid-beta; CSF = cerebrospinal fluid; GFAP = glial fibrillary acidic protein; NfL = neurofilament light; PET = positron emission tomography; AD = Alzheimer's disease; FTD = frontotemporal dementia; MS = multiple sclerosis; ALS = amyotrophic lateral sclerosis. Diagnostic accuracy reflects reported performance primarily against amyloid or tau PET imaging or CSF biomarkers, where applicable.

LC-MS readout), typically processing one sample in 6–8 h at a per-test cost of $200–400 or even higher in commercial settings. Although Simoa allows higher throughput, the high reagent and maintenance costs render it impractical for routine deployment. Moreover, absolute biomarker concentrations measured across platforms can differ by up to 2–3 fold (e.g., 0.2 vs. 0.6 pg/mL for p-tau217) (Palmqvist et al., 2021), complicating cut-off harmonization and reducing inter-study comparability. Crucially, no WHO- or IFCC-certified international reference standards currently exist for plasma p-tau217, impeding cross-platform calibration and multi-center meta-analyses.

Therefore, while blood biomarkers may approach CSF-level diagnostic performance, their clinical utility is constrained by sensitivity requirements, platform dependency, high operational costs, and a lack of universal standardization, posing substantial barriers to large-scale implementation, particularly in low-resource and primary care settings.

2.2.2. *Biological confounders: the hematological and renal filters*

Unlike CSF, which is in direct contact with the brain parachyma, plasma is a systemic fluid subject to the metabolic clearance and physiological noise of the entire body. Two primary biological confounders significantly impact the interpretation of blood biomarkers. One prominent one is the hematocrit (HCT) effect if whole blood or whole blood in DBS is being used as the sampling matrix. Variations in red blood cell volume significantly affect blood viscosity, spot morphology, and analyte distribution. For instance, blood with high HCT (≥50 %) may inhibit the spreading of blood of filter paper if DBS is used as sampling matrix, yielding artificially elevated analyte concentrations, while blood with low HCT (≤35 %) may experience signal dilution, resulting from winder wider spreading (Kaareddy et al., 2023).

The second biological confounder is the renal function. Peripheral clearance rates significantly alter the steady-state concentration of biomarkers, independent of brain pathology. This is most critical for serum NfL, a marker of axonal injury. Recent large-scale population studies, notably by Lu et al. (2024), have definitively shown that serum NfL levels are inversely correlated with the estimated glomerular filtration rate (eGFR). Specifically, Lu et al. reported a 6.34 pg/mL increase in serum NfL for every log-unit decrease in eGFR, along with a strong positive association with the urinary albumin-creatinine ratio (UACR) (Lu et al., 2024). In aging populations where chronic kidney disease (CKD) is comorbid with dementia, elevated NfL may reflect renal insufficiency rather than neurodegeneration. Without algorithmic correction for eGFR, blood-based NfL measurements risk yielding high rates of false-positive diagnoses.

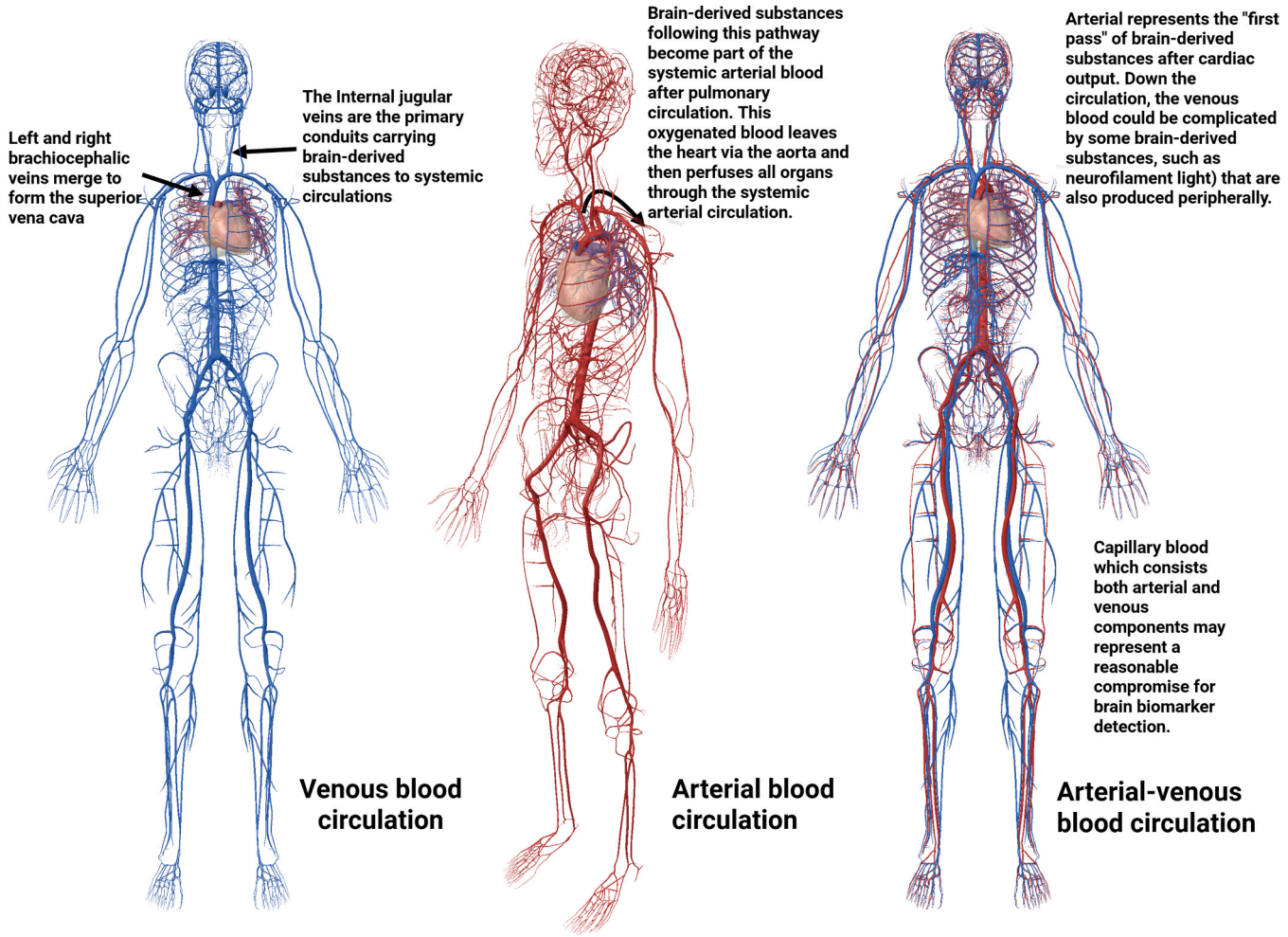

Fig. 1. This diagram illustrates the systemic circulation pathways of brain-derived substances, highlighting the roles of arterial, venous, and capillary blood compartments. The left and right brachiocephalic veins merge to form the superior vena cava, while the internal jugular veins serve as primary conduits for transporting brain-derived substances to systemic circulation. After pulmonary circulation, these substances enter systemic arterial blood via the aorta, marking their "first pass" after cardiac output. Venous blood may contain confounding peripherally produced biomarkers (e.g., neurofilament light), whereas capillary blood - a mix of arterial and venous components - may offer a balanced alternative for brain biomarker detection. The blood circulation diagram was created using *3DBody Anatomy*™.

2.2.3. Potentials and challenges of using DBS as matrices for CNS biomarkers

Detecting brain-derived biomarkers (such as p-tau217 or Aβ42) in peripheral blood is fundamentally a challenge of signal-to-noise ratio. These proteins originate in the CNS and drain into systemic circulation primarily via the internal jugular veins, eventually distributing via cardiac output. Based on the physiological principles depicted in Fig. 1, capillary blood—a mixture of arterial and venous blood—may theoretically offer superior representation of brain-derived biomarkers by capturing the arterial component before extensive peripheral mixing (Kong et al., 2025). Unlike venous blood, which represents the return circulation after passage through tissue beds, capillary sampling captures the signal upstream of potential peripheral metabolic sinks. Consequently, the veno-arterial difference observed in venous samples - caused by proteolytic degradation, tissue absorption, or renal clearance—is minimized in capillary DBS. Kong et al. (2025) empirically demonstrated this concept, showing that unique metabolic markers for drug-resistant epilepsy were identifiable in capillary DBS but undetectable in matched venous blood samples, confirming capillary sampling's potential to preserve labile CNS signals.

However, several factors complicate interpretation. While proteins such as amyloid-beta traverse the blood-brain barrier bidirectionally through specific transport mechanisms—particularly via receptor-mediated efflux systems like LRP1 and bulk flow clearance pathways—transport efficiency varies considerably among different protein biomarkers (Shibata et al., 2000; Tarasoff-Conway et al., 2015). The relationship between brain pathology and systemic protein concentrations is further complicated by peripheral production sources and differential clearance rates, making interpretation of blood-based protein biomarkers more complex than that of smaller metabolites with more predictable barrier permeability (Khalil et al., 2018). Additionally, biological differences between capillary and venous blood add matrix variability, with capillary blood having higher salt and lower protein concentrations. Pharmacokinetic studies show capillary DBS samples have 20–30 % lower concentrations of certain analytes compared to venous DBS, leading to potential underestimation of systemic levels (Zailani and Ho, 2023).

Environmental conditions such as temperature and humidity also impact DBS integrity. “Coffee ring” and “volcano” effects during drying lead to analyte redistribution toward the periphery, resulting in underestimation when central punches are analyzed. Experimental studies report 20–30 % concentration differences between central and peripheral spots under suboptimal drying conditions (Kaareddy et al., 2023).

Collectively, these confounders necessitate rigorous preanalytical control and validation to ensure biomarker reliability, particularly in multisite or decentralized settings where the complex interplay between brain-to-blood transport, peripheral metabolism, and technical factors must be carefully considered.

2.2.4. Regulatory and quality-control gaps

Despite the promising utility of DBS for therapeutic drug and disease response monitoring, clinical implementation remains hindered by the absence of harmonized regulatory guidelines and standardized validation frameworks. The lack of universal reference ranges for DBS measurements and the need for cross-validation with plasma/serum concentrations impede clinical acceptance (Zailani and Ho, 2023). Most DBS-based assays are validated as laboratory-developed tests (LDTs), with heterogeneous analytical performance across institutions and platforms (Kaareddy et al., 2023; Zailani and Ho, 2023).

Regulatory guidelines specific to DBS-based assays remain underdeveloped. While frameworks such as FDA (2018) and ICH M10 provide principles for bioanalytical validation, they offer limited provisions for matrix-specific challenges - hematocrit effects, spot homogeneity, protein adsorption to filter cards, and sample volume variability - all of which significantly affect assay precision and recovery (Iacuzzi et al., 2021; Kaareddy et al., 2023).

Huber et al. (2024) showed that DBS venous samples (DPSvenous) correlated significantly with plasma for all AD biomarkers except Aβ42. In the validation cohort, DPSvenous measurements of GFAP, NfL, p-tau181, and p-tau217 successfully differentiated CSF Aβ-positive from Aβ-negative individuals and correlated with cognitive decline. These findings demonstrate that DBS venous sampling can measure AD-related blood biomarkers reliably, extending their utility to remote settings through simplified sampling, storage, and logistics.

While CLSI EP09-A3 and EMA guidelines mandate inter-platform comparability and bias estimation for alternative matrices, many current DBS protocols fall short of these regulatory thresholds, especially in home-sampling and point-of-care contexts. DBS-specific certification frameworks - akin to ISO 15189 or IFCC schemes - are urgently needed to support clinical translation, particularly for Alzheimer's-related biomarkers intended for early screening or remote monitoring.

2.3. Synthesis and future outlook

The evidence summarized underscores plasma p-tau217 as the single most robust biomarker for Alzheimer's disease diagnosis, achieving exceptional specificity and sensitivity (AUC = 0.93). However, recent advances further highlight that integrating multiple biomarkers (e.g., p-tau217, GFAP, and Aβ42/Aβ40 ratio) significantly enhances diagnostic accuracy, elevating the overall performance to an impressive AUC of 0.97, thus reinforcing their clinical utility (Palmqvist et al., 2024). Nonetheless, critical gaps persist, primarily arising from assay harmonization challenges, pronounced variability in optimal diagnostic cut-off points, and insufficient population-specific validation across diverse cohorts. Section 3 will thus propose strategic longitudinal study designs specifically tailored to address these methodological limitations, facilitating the clinical translation and standardized application of blood biomarkers across global settings.

3. Blood Biomarkers in Alzheimer’s Disease Progression and Disease Monitoring

3.1. The evolvement of blood biomarkers over time in AD progression (p-tau217, p-tau181; NFL; GFAP)

Table 4 summarizes the stage-specific utility and longitudinal trajectories of key plasma biomarkers. p-tau217 and Aβ42/Aβ40 are particularly effective for detecting early amyloid pathology in preclinical stages (Braak I-II), showing predictive value for conversion to AD years before symptom onset. Conversely, markers of neuroinjury (NfL) and neuroinflammation (GFAP) tend to track closely with symptom severity and neurodegeneration in later disease stages (Braak III-IV), providing a dynamic profile of disease progression.

The major biological and clinical confounders influencing blood-based biomarker interpretation are summarised in Table 5.

3.2. Longitudinal studies

3.2.1. Familial AD studies and population cohorts

Longitudinal studies are essential for understanding the predictive value and clinical applications of blood-based biomarkers in AD progression. Emerging evidence from population cohorts and familial AD studies demonstrates that blood biomarker levels (p-tau217, p-tau181 and NfL) increase dynamically as disease advances, with changes predating clinical symptoms by years or decades (Park et al., 2019). Research in familial AD cohorts reveals that plasma p-tau217 and p-tau181 rise significantly during preclinical stages, predicting disease onset and cognitive decline more than a decade before symptom manifestation (Shahid et al., 2022).

In population-based studies, NfL, a non-specific marker of neurodegenerative damage, exhibits distinct temporal trajectories (Hamilton et al., 2023; Kivisäkk et al., 2022). Elevated blood NfL levels correlate

Table 4
Summary of Plasma Biomarkers for Alzheimer's Disease: Stage-Specific Accuracy, Longitudinal Utility, and Concordance with CSF and PET Benchmarks.

Biomarker	Stage of AD Progression	Clinical Utility and Findings	Comparison to CSF/PET	Longitudinal Predictive Value	Ref.
p-tau217	Braak III–IV	Early detection, high predictive accuracy (**AUC: 0.93–0.96**)	Strong correlation (CSF r = 0.79, PET r = 0.75)	Predictive of cognitive decline and AD onset (4 years)	Barthélemy et al. (2020); Palmqvist et al. (2024)
p-tau181	Mainly MCI and dementia stages; becomes abnormal at higher amyloid burdens	Predicts Aβ PET positivity in MCI/dementia (**AUC=0.877**); less sensitive in preclinical stage (**AUC=0.769** in CU); improves with APOE/GFAP (**AUC=0.895**)	Significant concordance with CSF/PET, but inferior to p-tau217 especially in early stages	Supported by previous longitudinal cohorts for MCI-AD transition; this study is cross-sectional	Janelidze et al. (2020)
NfL	Across AD continuum; notably rises during MCI-AD conversion, reflects neuroaxonal damage (non-specific)	Predicts conversion from MCI to AD (**AUC=0.77**, 4 years); correlates with cognitive decline, brain atrophy	Highly correlated with CSF NfL (r > 0.8), and with brain atrophy, but not specific to Aβ/tau	Rises independently predict cognitive decline & MCI-AD conversion (AUC=0.77, 4 years); as accurate as MRI	Mattsson-Carlgren et al. (2023)
GFAP	Earliest phase, neuroinflammatory marker	Predicts Aβ positivity/AD risk, **AUC 0.75–0.94**, early sensitive, less specific	Plasma GFAP superior to CSF GFAP, PET r = 0.6–0.8	Elevated up to 8–10 years before symptoms, predicts cognitive decline/amyloidosis longitudinally	Chatterjee et al. (2023a)
Aβ42/Aβ40	Early or preclinical stage; can distinguish aMCI and AD from controls	AUC = 0.89, Sensitivity = 89 %, Specificity = 93 % (SUVR ≥1.11)	Up to 93 % agreement with CSF	Predicts cognitive decline and amyloid accumulation ≥ 8 years prior to symptom onset	Trelle et al. (2025); Chatterjee et al. (2023a); Nakamura et al. (2018)

Table 5
Major Biological and Clinical Confounders Influencing Blood-Based Biomarker Interpretation.

Confounder Category	Specific Factor	Affected Biomarker(s)	Mechanism & Impact on Interpretation	Reference
Systemic Physiology	Renal Function (eGFR)	**NfL** (Serum/Plasma)	Reduced renal filtration significantly increases systemic NfL levels independent of brain pathology. Lower eGFR correlates with higher NfL (approx. 6.34 pg/mL increase per log-unit decrease in eGFR), creating a high risk of false positives in patients with chronic kidney disease (CKD).	Lu et al. (2024)
Comorbidities	Systemic Inflammation & Non-AD Conditions	GFAP, NfL	GFAP levels can be elevated by inflammatory comorbidities, while NfL is non-specific and increases in other neurodegenerative disorders (e.g., Multiple Sclerosis, TBI), reducing specificity for Alzheimer's pathology without multi-marker integration.	Leipp et al. (2024); Kawarabayashi et al. (2023); Novarella et al. (2025)
Sample Matrix (DBS)	Hematocrit (HCT) Effect	All DBS Analytes	Variations in red blood cell volume alter blood viscosity and spot spreading. High HCT (≥50 %) inhibits spreading (overestimation), while low HCT (≤35 %) increases spreading (signal dilution).	Kaareddy et al. (2023)
Systemic Circulation Pathway	Capillary vs. Venous Composition	Brain-derived markers	Capillary sampling captures brain biomarkers during arterial "first pass", potentially minimizing peripheral metabolic confounders and noise often present in venous blood.	Kong et al. (2025)
Pre-Analytical Variables	Sample Handling & Processing Delays	p-tau217, General	Delays in centrifugation (>2 h) or improper storage can alter biomarker levels by > 15 %. p-tau217 is particularly sensitive to handling delays and freeze-thaw cycles.	Weber et al. (2024)
Pre-Analytical Variables	Anticoagulant Type	General	The choice of blood collection tube impacts quantification; for example, EDTA versus citrate tubes can result in 10–20 % concentration differences.	Weber et al. (2024)
Environmental Factors	DBS Drying Conditions	DBS Analytes	Humidity and temperature affect drying, causing "coffee ring" or "volcano" effects where analytes redistribute to the periphery. This can cause 20–30 % concentration differences between central and peripheral punches.	Kaareddy et al. (2023)
Demographics	Population Diversity	p-tau217	Population-specific differences exist, necessitating specific reference values to avoid bias and ensure probability reliability across different cohorts.	Wang et al. (2024)

strongly with accelerated cognitive decline and dementia risk, mirroring disease severity and clinical staging. Longitudinal cohort data (n = 1502) demonstrate that annual NfL increases of 18.9 % in AD progressors align closely with hippocampal atrophy rates (r = 0.82, p < 0.001), outperforming traditional cognitive assessments in predicting 3-year conversion from MCI to AD dementia (AUC = 0.88 vs. 0.72) (Mattsson-Carlgren et al., 2023).

Mechanistically, the sequential emergence of biomarkers reflects AD pathology progression: p-tau217 elevations precede GFAP increases by 5–7 years, marking the transition from amyloidosis to tauopathy and neuroinflammation. Clinically, this temporal specificity enables risk stratification for preclinical AD populations; in the DIAN study, plasma p-tau217 predicted symptom onset within a 2-year margin of error (Llibre-Guerra et al., 2025).

3.2.2. *Predicting MCI conversion to AD using blood biomarkers*

Blood-based biomarkers have demonstrated exceptional performance in predicting the conversion from MCI to AD dementia. Meta-analyses indicate that plasma p-tau181, p-tau217 and the Aβ42/Aβ40 ratio exhibit high sensitivity and specificity for predicting progression from amnestic MCI to AD dementia, with p-tau217 and p-tau181 emerging as the most robust predictors (Chen et al., 2021; Park et al., 2019). Longitudinal studies of MCI patients revealed that higher baseline plasma p-tau181 and p-tau217 levels were strongly associated with increased risk of dementia conversion over 3 years (hazard ratio [HR] = 5.3, 95 % CI 3.8–7.1), underscoring their utility in tracking disease trajectories (Kivisäkk et al., 2022; Palmqvist et al., 2019).

Multimarker panels integrating GFAP, NfL, phosphorylated tau, and Aβ42/40 further enhance predictive accuracy (Chen et al., 2021; Jia

et al., 2021; Xu et al., 2022). Combining p-tau217, GFAP, and Aβ42/40 improved the area under the curve (AUC) from 0.89 (single marker) to 0.96 for predicting MCI-to-AD progression within 5 years ($p < 0.001$), highlighting the advantage of multimodal blood biomarker profiling in early diagnosis and personalized prognosis (Janelidze et al., 2024).

In conclusion, longitudinal investigations in familial AD and population-based cohorts have established blood-based biomarkers as pivotal tools for early disease prediction, progression monitoring, and risk assessment of MCI conversion to AD dementia.

3.3. Comparison with CSF biomarkers

3.3.1. How blood-based markers mirror CSF and imaging findings

The ability of blood-based biomarkers to accurately reflect CSF and neuroimaging findings has become a central focus in AD diagnostics. Substantial evidence confirms strong concordance between key plasma AD biomarkers and their CSF/neuroimaging counterparts. p-tau217 and p-tau181 exhibit significant correlations with CSF levels ($r = 0.78–0.85$, $p < 0.001$), with p-tau217 demonstrating exceptional diagnostic performance, achieving 92 % sensitivity in distinguishing AD from other neurodegenerative disorders but also shows robust correlations with cerebral amyloid-β (Aβ) deposition on PET imaging (SUVR ≥1.11; $r = 0.75$, $p < 0.001$) (Barthélemy et al., 2020; Teunissen et al., 2025).

Barthelemy et al., (2020) further validate the clinical utility of plasma p-tau217, reporting an area under the curve (AUC) of 0.92 for discriminating amyloid-positive individuals - a performance comparable to CSF-based assays (AUC = 0.94, ΔAUC = 0.02, $p = 0.12$) (Hofmann et al., 2024). Mechanistically, the tight association between plasma p-tau217 and amyloid PET reflects its role in early tau phosphorylation events downstream of Aβ pathology (Braak stages I-II). Plasma p-tau217 elevations occur 15–20 years before expected symptom onset in autosomal dominant AD, paralleling CSF p-tau217 trajectories ($r = 0.88$) and hippocampal atrophy rates ($\beta = -0.42$/year, $p < 0.001$) (Daniels et al., 2024).

Plasma NfL and GFAP levels align with neurodegenerative changes observed in CSF and neuroimaging. Plasma NfL concentrations correlate strongly with CSF NfL ($r = 0.82–0.89$, $p < 0.001$) and track axonal injury progression, with longitudinal increases of 18.9 % annually in AD patients versus 4.2 % in stable controls ($p < 0.001$) (Mattsson et al., 2019). Elevated plasma NfL (>27 pg/mL) predicts accelerated hippocampal atrophy ($\beta = -0.34$/year, $p = 0.002$) and 3-year conversion from MCI to AD dementia (HR = 5.3, 95 % CI 3.8–7.1).

GFAP is strongly associated with amyloid PET positivity (AUC = 0.88), FDG-PET hypometabolism ($r = -0.71$), and global brain atrophy ($r = 0.68$), reflecting its role in neuroinflammation across multiple AD pathology stages (Abu-Rumeileh et al., 2020). Plasma GFAP elevations precede clinical symptoms by 10–15 years, mirroring amyloid deposition (Centiloid >20) and microglial activation on [11 C]PBR28 PET ($r = 0.76$) (Chatterjee et al., 2023b). Overall, GFAP elevations reflect Aβ-driven astrocytic responses, while NfL escalates during later neurodegenerative phases (Braak stages III–IV) (Chiotis et al., 2023).

3.3.2. Blood biomarkers can replace CSF and PET measures

While debates persist regarding whether blood-based biomarkers can fully replace CSF analysis and PET imaging, recent studies demonstrate that multimodal blood biomarker panels - combining phosphorylated tau species (p-tau217, p-tau181) and the Aβ42/40 ratio - achieve diagnostic accuracy comparable to gold-standard methods (Park et al., 2019). The Alzheimer's Disease Neuroimaging Initiative (ADNI) revealed that plasma Aβ42/Aβ40 identifies cerebral amyloid pathology with 79 % sensitivity and 66 % specificity. When integrated with p-tau181 and MRI-based hippocampal volumetry, specificity escalates to 96 % (AUC = 0.97), underscoring the synergistic value of combining blood biomarkers with neuroimaging (Manjavong et al., 2024).

Current limitations including methodological inconsistencies, lack of standardized detection protocols, and insufficient clinical validation, preclude blood-based biomarkers from fully replacing CSF analysis or PET imaging. However, their potential in presymptomatic screening and primary care settings is transformative. Blood biomarkers may partially supplant invasive, costly CSF sampling and PET scans, particularly in resource-limited regions, advancing AD diagnostics toward cost-effective and accessible paradigms (Palmqvist et al., 2025; Teunissen et al., 2025). Plasma p-tau217 demonstrates 94 % concordance with tau PET (SUVR ≥1.25) in early AD stages, while the Aβ42/Aβ40 achieves 89 % sensitivity for amyloid PET positivity at 1/30th the cost (Pais et al., 2023). When combined with MRI volumetry (e.g., hippocampal atrophy rates), blood biomarker panels (p-tau217 + Aβ42/Aβ40 + GFAP) attain diagnostic accuracy comparable to CSF/PET (AUC = 0.96 vs. 0.98, ΔAUC = 0.02, $p = 0.12$) (Ashton et al., 2024).

In summary, blood-based biomarkers recapitulate AD pathological features identified by CSF analysis and neuroimaging but also demonstrate potential to partially or fully supplant traditional diagnostic modalities.

4. Cutting-edge blood biomarker detection technologies

4.1. Ultrasensitive immunoassays: Simoa, Ella and other ELISA-based assays

Recent advancements in ultrasensitive immunoassay technologies have revolutionized the study and clinical translation of blood-based biomarkers for AD (Li and Mielke, 2019; Tzartos et al., 2022). Single-molecule array (Simoa) technology has emerged as a cornerstone platform due to its unparalleled sensitivity, enabling femtomolar (fM)-level analyte detection in plasma or serum. using digital ELISA principles for reliable quantification of low-abundance biomarkers like p-tau217 and NfL (Table 2) (Álvarez-Sánchez et al., 2022; Singh et al., 2021; Tanaka et al., 2021).

Simoa-detected plasma p-tau217 differentiated AD from non-AD dementias with 94 % sensitivity and 91 % specificity (AUC = 0.96), matching CSF p-tau217 performance (ΔAUC = 0.01, $p = 0.34$) (Palmqvist et al., 2020). Simoa quantified preclinical p-tau217 elevations 15–20 years before expected symptom onset, correlating strongly with amyloid PET Centiloid scores ($r = 0.85$, $p < 0.001$) and hippocampal atrophy rates ($\beta = -0.38$/year, $p < 0.001$) (Pandey et al., 2025).

Similarly, microfluidic-based platforms such as the Ella system offer automated, reproducible detection with reduced inter-operator variability, although throughput is generally lower compared to Simoa. (Álvarez-Sánchez et al., 2022; Ding et al., 2021).

However, current ultrasensitive immunoassay technologies face several practical challenges, including insufficient standardization, poor inter-laboratory comparability, and significant impacts from pre-analytical variables (e.g., blood collection tube types, sample storage conditions) (Ding et al., 2021; Singh et al., 2021). These limitations highlight the urgent need for multicenter, multi-platform collaborative studies to establish standardized protocols and promote data sharing, critical for clinical adoption.

In conclusion, ultrasensitive immunoassay technologies - exemplified by Simoa and Ella platforms - provide critical technical support for early diagnosis, disease monitoring, and precision medicine applications of blood-based AD biomarkers, showing promise for eventually replacing traditional invasive diagnostic approaches.

4.2. MS-based approaches: PRM, SRM, LC-MS, and PTMs

Mass spectrometry (MS) has emerged as a vital complementary tool to antibody-based assays for detecting blood-based biomarkers. Compared to conventional immunoassays, MS offers superior sensitivity and specificity, enabling quantification of ultra-low-abundance analytes and discrimination of structurally similar protein isoforms - critical advantages for AD biomarker research and clinical validation. Targeted MS platforms, particularly selected reaction monitoring (SRM/MRM)

and parallel reaction monitoring (PRM), utilize triple quadrupole or high-resolution mass spectrometers to selectively isolate and fragment specific peptides, enabling highly specific multiplexed detection without antibody dependency. Isotope-labeled internal standards permit absolute quantification of target analytes (Korecka and Shaw, 2021).

Aβ42/Aβ40 Ratio: The plasma Aβ42/Aβ40 ratio serves as a critical indicator for early detection of cerebral amyloid deposition. MS-based approaches using immunoprecipitation coupled with liquid chromatography-tandem mass spectrometry (IP-LC-MS/MS) enable high-precision quantification of plasma Aβ species. Nakamura et al. developed an IP-MS assay targeting APP669–711, Aβ42, and Aβ40, demonstrating that the plasma Aβ42/Aβ40 ratio accurately predicts cerebral amyloid plaque burden. In independent Japanese and Australian cohorts, this biomarker panel achieved AUCs of 96.7 % and 94.1 %, respectively, for discriminating amyloid-PET-positive individuals from controls, with approximately 90 % overall diagnostic accuracy (Nakamura et al., 2018).

Such assays have been commercialized for clinical use (e.g., PrecivityAD® test), offering a high-throughput and standardized platform for early AD screening utilizing advanced mass spectrometry platforms, including the proprietary Stable Isotope Spike Absolute Quantification (SISAQ™) for precise peptide quantification and the Stable Isotope Labeling Kinetic (SILK™) platform, which measure protein metabolism dynamics by incorporating stable isotope-labeled amino acids (e.g., 13C6 leucine) into newly synthesized proteins (Wildburger et al., 2018). The SILK™ methodology provides dynamic biomarker endpoints that enable rapid drug effect detection within days rather than months. Integration of $A\beta_{42}/A\beta_{40}$ with complementary biomarkers (e.g., phosphorylated tau) may further enhance diagnostic precision, positioning mass spectrometry as a cornerstone technology in AD diagnostics (Pais et al., 2023).

Phosphorylated Tau (p-tau): Tau protein, particularly its phosphorylated isoforms (e.g., p-tau181, p-tau217), represents a central focus in AD blood biomarker research. Despite the challenge of detecting ultralow plasma concentrations, recent MS advancements have achieved remarkable breakthroughs. Barthélemy et al. developed an ultrasensitive MS-based workflow to quantify plasma p-tau181 and p-tau217 by immunoprecipitating tau from 20 mL of plasma, concentrating it into a 25 μL, followed by nanoflow liquid chromatography coupled with high-resolution parallel reaction monitoring (PRM)-MS for reliable p-tau quantification (Korecka and Shaw, 2021). Plasma p-tau217 exhibited superior specificity over p-tau181 in detecting early AD pathology, with AUC of 0.92 for distinguishing amyloid-PET-positive from amyloid-PET-negative individuals. This underscores MS's ability to detect trace-level p-tau in blood and differentiate tau phosphorylation sites, providing molecular specificity critical for identifying AD-specific pathological changes (Barthélemy et al., 2020).

MS has elucidated the complex post-translational modification (PTM) landscape of tau in AD. PRM-MS analyses identified 29 distinct phosphorylation sites on full-length tau in AD brain tissue and 12 sites on truncated tau fragments in CSF, far exceeding those observed in controls. Hyperphosphorylation at specific residues (e.g., T217) correlates strongly with AD progression and directly informed plasma p-tau217 biomarker development, highlighting MS as indispensable for unraveling tau pathophysiology and advancing biomarker innovation (Korecka and Shaw, 2021).

NfL: Neurofilament light chain (NfL), a non-specific biomarker of neuroaxonal injury, is elevated in AD and other CNS disorders. While plasma NfL is predominantly measured via ultrasensitive immunoassays (e.g., Simoa), MS-based approaches are emerging to characterize NfL proteoforms with structural precision. Coulton et al. reported a multiplatform workflow combining immunoprecipitation with three monoclonal antibodies and nanoflow liquid chromatography-high-resolution mass spectrometry (nLC-HRMS) to quantify site-specific NfL fragments in plasma (Coulton et al., 2024). This method enables multi-site quantification of NfL proteoforms, resolving post-translational modifications (PTMs) and truncation variants that may reflect distinct neurodegenerative mechanisms. In a study of 102 older adults, this method detected significantly elevated levels of specific NfL peptide fragments in plasma of cognitively unimpaired individuals with preclinical AD pathology, compared to controls ($p < 0.05$).

MS analyses revealed that NfL exists in CSF as multiple proteolytic fragments, suggesting similarly complex blood composition. Unlike conventional immunoassays, detecting a single epitope of NfL, MS enables simultaneous profiling of multiple protein regions, identifying distinct PTMs and cleavage variants. This capability enhances diagnostic specificity and precision, potentially differentiating AD-related NfL alterations from elevations caused by other neurological conditions (e.g., traumatic brain injury, multiple sclerosis) (Coulton et al., 2024).

PTMs of AD-Associated Proteins: Post-translational modifications of AD-associated proteins play pivotal roles in disease pathogenesis and represent both a focal point and challenge in blood biomarker research. Aberrant tau hyperphosphorylation, an AD hallmark, exemplifies this complexity. Phosphorylation at specific residues - includingT181, T217, and S202 - disrupts neuronal function and generates measurable biofluid biomarkers. MS offers unparalleled advantages in resolving site-specific phosphorylation events by directly detecting and quantifying distinct phosphopeptides, circumventing cross-reactivity and assay variability inherent to antibody-based approaches (Donovan et al., 2013; Oeckl and Otto, 2019).

Detecting low-abundance PTMs presents significant technical challenges. Plasma p-tau exists at picogram-per-milliliter concentrations, necessitating extensive sample enrichment and ultrahigh-sensitivity MS for reliable quantification. Similarly, N-terminal truncation and pyroglutamylation of Aβ peptides - modifications abundant in AD brain deposits, occur at trace levels in peripheral blood, requiring MS platforms with exceptional sensitivity and selectivity. Furthermore, proteolytic fragments and PTMs of structural proteins like NfL may confound disease specificity, underscoring the need for precise molecular characterization. Integrating MS into blood biomarker research is critical for PTM profiling. Beyond identifying novel PTM-derived biomarkers, MS enables multiplexed quantification of coexisting modification states (e.g., phosphorylation at T217/S214 alongside ubiquitination), providing a holistic view of AD molecular pathology (Barthélemy et al., 2020; Weber et al., 2024).

In summary, MS-based approaches including PRM, SRM, and LC-MS have demonstrated significant breakthroughs in detecting AD blood biomarkers. Practical applications have validated their capability in quantifying core biomarkers (Aβ42, p-tau, and NfL) and characterizing PTMs. These methodologies enhance detection accuracy and consistency while providing novel perspectives and tools for early AD diagnosis and mechanistic investigations.

4.3. Proteomics and multi-omics approaches

4.3.1. High-throughput proteomics: SomaScan

Traditional biomarker detection relies on single or limited target quantitative analyses of known proteins, whilst aptamer-based high-throughput proteomic platforms like SomaScan, achieve simultaneous quantitative detection ranging from hundreds to over 11,000 proteins (Pietzner et al., 2021). The SomaScan platform employs Slow Off-rate Modified Aptamer (SOMAmer) technology, utilising highly specific DNA aptamers to recognise and bind target proteins, enabling detection of 1000–7000 proteins in a single assay with sensitivity reaching picomolar (pM) sensitivity and a dynamic range spanning approximately 10^6 – 10^7 fold concentration intervals, suitable for simultaneous quantification of both high- and low-abundance plasma proteins.

However, the platform presents certain limitations: approximately 14 % of aptamers exhibit non-specific binding (7 % recognizing non-target proteins and 7 % recognizing isoforms), 32 % of aptamers are affected by single nucleotide polymorphisms (SNPs) resulting in altered affinity, and 27.6 % demonstrate significant cross-reactivity in

heterologous plasma, indicating the necessity for validation using complementary platforms in clinical applications (Joshi and Mayr, 2018). SomaScan technology exhibits high concordance with traditional immunoassays in CSF biomarker detection, identifying 667 proteins significantly correlated with CSF amyloid levels; in plasma, a combination of 44 proteins, age, and APOE ε4 status predicts brain amyloid burden, achieving AUC = 0.78 in the discovery cohort (n = 516) and AUC = 0.68 in the validation cohort (n = 365) (Shi et al., 2019). Multi-platform comparative studies reveal excellent reproducibility for SomaScan 7 K and 11 K platforms, with median coefficients of variation (CV) for plasma protein measurements of 5.8 % (7 K) to 6.8 % (11 K), compared to Olink Explore 3 K's substantially higher CV of 35.7 %. Additionally, SomaScan's protein coverage far exceeds comparative platforms, detecting 11,000 + proteins versus Olink's approximately 5400, providing significant advantages in discovering novel biomarkers (Puerta et al., 2024).

4.3.2. Metabolomics and lipidomics

Plasma metabolomics and lipidomics have validated significant abnormalities in multiple pathways including energy metabolism, neurotransmitter synthesis, and amino acid metabolism in AD patients, alongside the central role of lipid metabolism dysregulation in AD pathogenesis. Key metabolites from the tricarboxylic acid cycle (e.g., diacylglycerol DG 16:0/18:2, HR = 1.7, P = 0.007), branched-chain amino acids (e.g., palmitoleamide, HR = 2.0, P = 0.001), and choline compounds (e.g., oleamide, HR = 1.8, P = 0.002) were significantly elevated in progressive mild cognitive impairment (pMCI), serving as potential markers for predicting progression rates (Oka et al., 2024).

Untargeted LC-MS/MS large-scale lipidomic analysis of AD patients aged 75–97 years in the Sydney MAS study revealed significantly elevated overall levels of sphingomyelins (SM), cholesteryl esters (ChE), and triglycerides (TG) (identified using Glmnet models, all AUC > 0.80); diacylglycerols (DG) were significantly increased in AD patients (P < 0.05), whilst phosphatidylcholines (PC) and ceramides (Cer), despite changes at individual species levels, demonstrated slightly inferior overall classification performance (<80 %) (Liu et al., 2021).

Sphingolipid metabolic pathway abnormalities specifically manifested as approximately 30 % reduction in acid sphingomyelinase activity in CSF (P < 0.01), positively correlating with cognitive scores (MMSE) (r ≈ 0.52, P < 0.001); total sphingomyelin levels in CSF decreased by approximately 20 % whilst ceramide levels increased by approximately 25 %, with these changes significantly correlating with CSF $A\beta_{42}$ levels (r ≈ 0.45) and p-tau concentrations (r ≈ 0.48) respectively (all P < 0.01). These quantitative relationships suggest that sphingolipid metabolism disruption may serve as a potential early warning indicator of AD progression (Lin et al., 2019).

In a metabolomics study, acetyl-L-carnitine significantly decreased between healthy controls and AD patients: from 5.6 ± 1.3 μmol/L to 3.5 ± 0.6 μmol/L (approximately 38 % reduction, P < 0.001), suggesting mitochondrial β-oxidation dysfunction and energy metabolism abnormalities. Specific diacylglycerol (DG) species demonstrated significant accumulation in AD patient plasma; for example, DG 16:0/18:2 levels were approximately 20 % higher than healthy controls, correlating with neuronal membrane stability damage and signal transduction pathway disruption (Cox model HR ≈ 1.7–2.0; P < 0.01) (Han et al., 2011).

4.3.3. Integration and clinical translation

These studies highlight the critical value of multi-omics integration - systematic integration of proteomic, metabolomic, and lipidomic data to construct comprehensive molecular maps, identify potential pathological mechanisms and AD molecular subtypes, providing evidence for early diagnosis and personalised treatment. Machine learning-integrated multi-modal models significantly outperform single biomarkers in diagnostic accuracy and predictive capability.

However, clinical translation remains constrained by absent detection standards, insufficient sample sizes, and data integration complexity. Batch effects between different datasets contribute 30–50 % of total data variation; most studies include only dozens to hundreds of samples, far below requirements for stable multi-omics modelling, while substantial dimensional disparities exist between datasets (e.g., 10^4–10^6 level features). There is an urgent need for unified quality control procedures, expanded validation cohorts, and development of more efficient bioinformatics analytical methods (Li et al., 2021; Weiner et al., 2023).

4.4. Dried blood spot testing: enable at-home or point-of-care AD screening

DBS and DPS sampling methods involve applying 10–65 μL of whole blood onto specialized filter paper cards and air-drying at room temperature, creating a stable biological specimen. Using this micro-volume sampling approach, biomarker measurements for GFAP, NfL, Aβ40, Aβ42, p-tau181, and p-tau217 were evaluated in discovery (n = 154) and validation (n = 115) cohorts. Results showed high correlation with conventional EDTA plasma measurements (R > 0.7 for all markers except Aβ42) and robust discrimination between amyloid-positive and amyloid-negative individuals (AUC = 0.87), demonstrating both the method's suitability for remote sampling and reliable quantitative performance (Huber et al., 2024).

Since DBS and DPS sampling methods do not require venipuncture, individuals or caregivers can easily collect samples after minimal training. In the United States, Quest Diagnostics has commercially introduced the AD-Detect™ service, priced at approximately $399 with an additional physician service fee of about $13. At the 2025 American Academy of Neurology (AAN) meeting, Quest presented data demonstrating that their plasma-based Aβ42/40 and p-tau217 test achieved over 90 % sensitivity and specificity in detecting MCI. Testing of 4326 real-world samples revealed a distribution of 42 % amyloid-positive, 51 % amyloid-negative, and 7 % indeterminate results, confirming the feasibility and accuracy of this remote sampling approach for routine clinical applications (Bader et al., 2020; Huber et al., 2024).

DBS samples do not require cold-chain logistics for storage and can remain stable at room temperature. Huber et al. demonstrated that NfL, Aβ40, and Aβ42 remain stable at room temperature or 4°C for at least six months, and p-tau181 is stable at 4°C for a similar duration. GFAP showed an initial concentration decline (approximately 10–15 %) during the first week at room temperature but remained quantifiable over extended storage periods. Consequently, samples can be reliably transported using standard logistic services, significantly reducing both transportation complexity and associated costs (Huber et al., 2024).

Point-of-care (POC) testing remains a significant research objective. Li et al. developed a paper-based microfluidic chip integrating plasma separation, sample preprocessing, and biomarker detection, enabling the full analytical process from a 10–20 μL finger-prick blood sample to result readout within 30 min. The device achieves picomolar to nanomolar (pM–nM) analytical sensitivity, making it particularly suitable for primary care and community health settings (Li and Steckl, 2019). Additionally, multiplexed biomarker detection technologies have been developed for POC applications. Devices employing surface-enhanced Raman scattering (SERS) and fluorescence-based detection can simultaneously measure key plasma biomarkers (p-tau217, GFAP, NfL), yielding AUC of approximately 0.78 with sensitivity and specificity of approximately 80–85 % for distinguishing AD from cognitively normal individuals (Huber et al., 2024).

However, challenges remain. More than 50 % of DBS samples showed unreliable quantification of Aβ42, with low correlation coefficients (R^2 ranging from 0.14 to 0.02) for the Aβ42/40 ratio, necessitating further methodological optimization regarding extraction efficiency and analytical sensitivity. Moreover, expanding home-based testing requires robust quality control systems and regulatory frameworks to ensure sampling quality by non-professional users and effective integration of testing outcomes into subsequent medical care (Schöll

et al., 2024).

Importantly, current evidence for DBS-based AD biomarker testing is heterogeneous. While multiple studies support analytical feasibility and concordance with matched venous plasma measurements under controlled conditions, clinical-level validation - particularly large, prospective, multicentre evaluations against reference standards such as amyloid PET or CSF biomarkers remains limited. Therefore, DBS should currently be viewed as a promising translational sampling strategy rather than an established, stand-alone clinical diagnostic pathway.

5. Clinical translation and standardization efforts

Driven by advances in detection technologies, the field of blood-based biomarkers for Alzheimer's disease has made significant progress. This section highlights how cutting-edge methods - including ultrasensitive immunoassays, mass spectrometry, multi-omics, and remote sampling - have transformed blood biomarkers from theoretical promise to clinical research reality.

5.1. Ongoing clinical trials validating blood biomarkers

A growing number of large-scale clinical trials and multicenter studies have generated invaluable data for blood biomarker research in AD. The AHEAD 3–45 trial, enrolling individuals with no or early symptoms, reported that plasma p-tau217 combined with the Aβ42/40 ratio achieved AUC of 0.92 (95 % CI: 0.90–0.94), with 88 % sensitivity and 87 % specificity for predicting Aβ PET positivity demonstrating high accuracy in identifying high-risk individuals (Janelidze et al., 2024). Similarly, multicenter cohort studies such as BioFINDER-2 have strengthened sample robustness and improved biomarker testing reproducibility. In an analysis including both European and American participants, Barthélemy et al. found that plasma p-tau217 reached an AUC of 0.94 (95 % CI: 0.92–0.96), with 92 % sensitivity and 89 % specificity for predicting Aβ PET positivity, performing as well as or better than CSF p-tau217. These results were validated in external cohorts from WashU and Sant Pau, underscoring the stability of blood biomarkers across diverse populations (Barthélemy et al., 2024).

Efforts to standardize biomarker detection procedures, such as harmonized sampling protocols in ADNI, are noted but will be discussed in detail in Section 5.3. Overall, these performance data provide a solid foundation for clinical application of blood-based AD biomarkers. However, moving from validation to routine clinical practice requires careful navigation of complex regulatory processes, which are the focus of the next section.

5.2. Regulatory considerations: FDA/EMA approval challenges for blood-based AD diagnostics

As summarised in Table 6, regulatory pathways diverge significantly between regions. While the US FDA has utilized the Breakthrough Device Designation to accelerate approval for blood-based assays (e.g., Lumipulse), the European IVDR framework emphasizes stringent clinical utility data and post-market surveillance prior to CE marking (Hansson et al., 2023).

The regulatory framework aims to ensure that blood-based diagnostic products achieve high accuracy and consistency across multiple centers and populations, underpinned by evidence spanning clinical trials, technical standards, and real-world data. Ongoing standardization and surveillance are central to successful clinical translation of these novel assays. Details of the technical harmonization required to achieve these regulatory benchmarks will be discussed in the following section.

5.3. Assay standardization and reproducibility

While blood biomarkers show outstanding diagnostic performance in clinical research, different detection platforms (e.g. ultrasensitive immunoassay platform Simoa & mass spectrometry LC-MS) influence the consistency and reproducibility of results (Mattsson et al., 2011). In a multi-platform comparative study on plasma Aβ42/40, the LC-MS assay demonstrated higher accuracy (AUC = 0.85–0.87) than certain immunoassays (AUC = 0.64–0.78) (Weber et al., 2024). Moreover, discrepancies in plasma p-tau assays are significant: absolute concentration measurements of p-tau217 differ by 15–20 % across immunoassay platforms. Multicenter quality control studies reported between-laboratory coefficients of variation (CV) for p-tau, Aβ42/40, and NfL ranging from 12 to 15 %, exceeding the clinical ideal threshold of ≤ 10 % (Hansson et al., 2023; Teunissen et al., 2022).

Furthermore, internationally recognized cut-off values for blood biomarkers remain elusive, with reported thresholds varying by over 30 % across different studies and platforms. This inconsistency is driven by pre-analytical variables: anticoagulant choice (e.g., EDTA versus citrate tubes) can lead to 10–20 % concentration differences, and delays in sample processing (e.g., centrifugation delayed by more than 2 h) may alter biomarker levels by over 15 % (Weber et al., 2024).

Therefore, constructing a unified international reference standard and implementing stringent quality control systems are critical to reduce variations introduced by cross-platform, cross-laboratory, and pre-analytical procedures. Only through harmonized assay protocols and shared calibration standards can blood biomarkers reach the consistency required for reliable clinical translation.

Table 6
The core differences in the approval pathways for blood-based AD diagnostic products between the FDA and EMA/IVDR.

Item	FDA(US)	EMA/IVDR (EU)
Approval path	510(k) or De Novo	CE marking
Clinical validation scale	Manufacturers submit analytical and clinical studies, typically prospective and multi-site, comparing the test to a reference standard (amyloid PET or CSF)	well-designed clinical studies like FDA expectations
performance requirement	No fixed sensitivity, specificity thresholds, but must show high accuracy relative to the standard	clinical performance consistent with "state of the art". No numeric cut-off is prescribed by law.
Post-market surveillance	Mandatory adverse event reporting (21 CFR 803) requires continuous monitoring and reporting of deaths, severe injuries, and major malfunctions. The FDA may require post-market monitoring for high-risk devices (Section 522). There is no regular PSUR requirement (PMAs require 5-year reporting). For breakthrough products, real-world data is typically required for post-market submissions.	Articles 78–81 of the IVDR establish a formal post-market surveillance (PMS) system. Class C/D products are required to submit a PSUR (Post-Market Performance and Safety Summary Report) annually, including risk analysis and trend data. Major safety incidents must be reported to the competent authorities.

5.4. Machine learning-enabled interpretation of blood biomarkers

Machine learning (ML) models can enhance clinical utility of blood-based biomarkers by translating multi-analyte measurements into calibrated risk estimates and actionable decision support. First, ML facilitates multi-marker integration by combining phosphorylated tau species (e.g., p-tau217 and p-tau181), the Aβ42/Aβ40 ratio, NfL, GFAP, and clinical variables (e.g., age, sex, APOE status, and comorbidities), improving diagnostic discrimination relative to single-biomarker interpretation.(Milà-Alomà et al., 2022) Second, ML enables confounder-aware modelling by capturing non-linear associations and interaction effects (e.g., renal function influencing NfL; inflammatory comorbidities

affecting GFAP) (Lu et al., 2024), reducing false positives and improving transportability across cohorts(Leipp et al., 2024). Third, longitudinal ML frameworks (e.g., mixed-effects learning and time-series models) can leverage repeated sampling to estimate conversion risk from cognitively unimpaired status or MCI to dementia, and track biomarker trajectories in response to disease-modifying therapies (Ren et al., 2025).

Importantly, ML-based biomarker applications require robust external validation, calibration (i.e., probability reliability), and transparent reporting to mitigate overfitting and dataset shift, particularly when deployed in primary care settings. From a translational perspective, integrating scalable sampling strategies - including DBS collection - with rigorously validated ML models may support decentralized screening workflows, triage for confirmatory PET/CSF testing, and individualized monitoring across the AD continuum.

6. Conclusion and future directions

Blood-based biomarkers have emerged as transformative tools for early detection and monitoring of AD, offering minimally invasive, cost-effective, and scalable alternatives to traditional CSF and neuroimaging methods. Among them, plasma p-tau217 has shown unparalleled diagnostic accuracy and longitudinal predictive value, especially when integrated with other markers like GFAP, NfL, and the Aβ42/40 ratio.

Despite their promise, several barriers hinder clinical adoption, including pre-analytical variability, inter-platform inconsistencies, and lack of global standardization and regulatory frameworks. Future research must prioritize multicenter longitudinal studies, assay harmonization, and development of universally accepted diagnostic thresholds. Furthermore, integrating blood biomarkers with digital health tools and machine learning platforms - particularly in point-of-care and at-home testing formats - holds tremendous potential for democratizing AD diagnostics and enabling personalized, preventive interventions at scale. Efforts must also focus on inclusive validation across diverse populations to ensure equitable global application.

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