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Review Article

EMERGING BLOOD-BASED BIOMARKERS IN ALZHEIMER'S DISEASE: FOCUS ON TAU, NFL, AND GFAP

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ABSTRACT

Alzheimer's disease (AD) is characterised by progressive neurological disorder marked by the gradual decline of memory and cognitive abilities, affecting daily functioning and quality of life, imposing a leading socioeconomic disruption and healthcare burden. For the effective interventions, treatment and management, early diagnosis is important though conventional techniques like imaging and cerebrospinal fluid tests are invasive and costly. The inclusion of blood-based biomarkers provides a transformative approach for the early detection and disease monitoring. The purpose of this review is to critically evaluate the emerging evidence on Tau181, Tau217, NfL, and GFAP, aiming to delineate their role in reshaping future strategies for detection, monitoring, and intervention. Tau 217, among the tau isoforms biomarkers, demonstrated as a superior candidate with regards to diagnostic accuracy and stronger co-relation with Amyloid Positron Emission Tomography and disease progression, while compared to Tau 181. As the frontrunner biomarker, Tau 217 has emerged for AD with NfL and GFAP that provide precious complementary insights. Axonal degeneration is reflected by NfL while astrocytic activation is indicated by GFAP. Both serve as complementary markers. Combined multi-marker panels integrating these biomarkers enhanced sensitivity and specificity for AD detection. Therefore, these blood-based biomarkers provide a potential and revolutionary AD diagnosis and management by enabling non-invasive, early, and precise disease characterization.

KEYWORDS: Alzheimer's Disease (AD), Tau Biomarkers, NfL, GFAP.

Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia and is associated with an increasing worldwide health and socioeconomic burden[1]. AD affects more than 55 million people worldwide and this number is expected to nearly double by 2050 due to aging populations[2]. Mortality rates due to AD continue to increase. In 2024, AD was the fifth leading cause of death among older adults[1]. Apart from mortality, the disease has serious socioeconomic impacts. In 2025, the value of unpaid caregiving was more than 19.6 billion hours valued at $446 billion AD places tremendous psychological and physical strain on caregivers, often leading to burnout and negative health outcomes[1]. Current diagnostic approaches involve a combination of clinical evaluation, neuropsychological testing, neuroimaging, and analysis of cerebrospinal fluid (CSF) biomarkers. Structural MRI and functional imaging modalities such as FDG-PET provide insight into brain atrophy and metabolic dysfunction while amyloid and tau PET imaging enable visualization of pathological aggregates with high specificity [3]. However, these approaches have significant limitations lumbar puncture is invasive and often poorly tolerated, neuroimaging techniques are expensive and require specialized infrastructure, and are impractical for large scale population screening or frequently longitudinal monitoring [4]. Thus, although current approaches

are accurate in diagnosis, they are limited in terms of accessibility and scalability. Hence, there is an urgent need for minimally invasive and cost-effective biomarkers that could be used in different healthcare settings.

In this context, Blood-based biomarkers represent a transformative approach for AD diagnosis and monitoring. The most promising blood-based biomarkers are phosphorylated tau species (p-tau), Neurofilament Light Chain (NfL) and Glial Fibrillary Acidic Protein (GFAP), each reflecting different pathological aspects of AD[5]. These biomarkers demonstrate potential applications in early diagnosis, disease staging, prognosis, therapeutic monitoring, and clinical trial participant selection[6]. The purpose of this review is to critically evaluates the emerging evidence on Tau181, Tau217, NfL, and GFAP, aiming to delineate their role in reshaping future strategies for detection, monitoring, and intervention.

Tau Biomarkers

Tau protein is a microtubule-associated protein that stabilizes neuronal microtubules. Abnormal tau phosphorylation leads to tau aggregation and neurofibrillary tangles. This is a hallmark of AD and tauopathies. Phosphorylated tau isoforms, including p-tau181 and p-tau217, correlate strongly with amyloid pathology as well as cognitive decline and disease progression and have attracted interest as biomarkers for diagnosis and monitoring. Blood tau assays may provide a non-intrusive alternative to cerebrospinal fluid (CSF)-based tests that are more widely available and widely used in neurodegenerative disease research (Figure 1)[7-10].

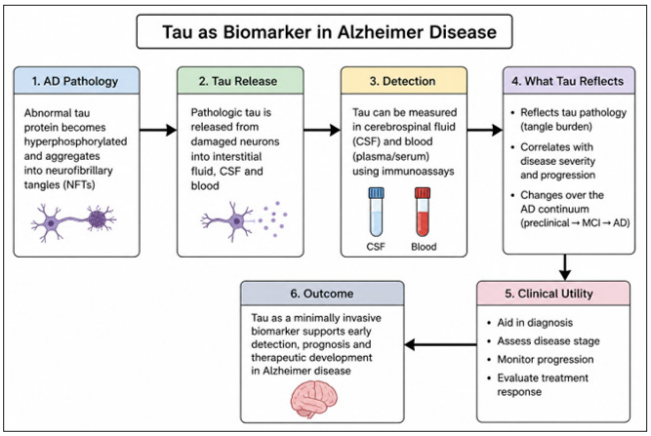

Figure 1.Tau as Biomarker in AD

Tau 181

Tau protein abnormalities are central to the pathology of Alzheimer's disease (AD). p-tau181 was the first plasma biomarker which could be reliably measured within the phosphorylated tau isoforms and thus represented a breakthrough in blood-based diagnostics. Its value as a diagnostic and prognostic tool has been extensively studied and it correlates with amyloid pathology and cognitive decline, but with limitations in specificity[11-13].

Historically, phosphorylated tau at threonine 181 (p-tau181) was the first plasma tau biomarker validated for AD. Initially developed in cerebrospinal fluid (CSF), its translation to blood assays was a paradigm shift, offering a minimally invasive alternative to lumbar puncture. Early landmark studies showed that plasma p-tau181 could accurately distinguish AD from healthy controls and non-AD dementias[11,12]. This breakthrough allows for large-scale population studies and clinical trial recruitment without the need for invasive CSF sampling. Also, p-tau181 was used as a reference point for newer tau isoforms (e.g., p-tau217). Its pioneering role for biomarker development still provides the basis for further advances and has influenced the development of blood-based diagnostics in neurodegenerative research[13,14].

Plasma p-tau181 is strongly associated with amyloid PET positivity and is a robust biomarker of underlying AD pathology. Elevated levels are consistently associated with amyloid burden and tau deposition, reflecting disease progression[15,16]. Its prognostic value is supported by longitudinal studies showing that patients with higher plasma p-tau181 are more likely to progress from mild cognitive impairment (MCI) to AD dementia[17,18]. Cano et al. (2024) demonstrated predictive accuracy in real-world cohorts, while Verberk et al. (2023) highlighted its utility in tracking cognitive decline. This correlation makes p-tau181 a useful biomarker for disease staging and monitoring of therapeutic interventions.

Despite its strengths, p-tau181 has limitations in specificity. Elevated levels appear not just in AD but also in other tauopathies, such as frontotemporal lobar degeneration (FTLD). This reduces its ability to differentiate between conditions [19,20]. Comparative studies show that p-tau217 has better specificity, particularly in distinguishing AD from non-AD dementias[21]. Analytical variability in different tests further complicates consistency, with differences between labs affecting diagnostic thresholds[22]. Meta-analyses confirm that while p-tau181 remains strong, newer biomarkers outperform it in precision[23]. Thus, while p-tau181 continues to be a standard, its limitations point to the need for multi-marker panels that combine tau isoforms with complementary biomarkers like NfL and GFAP to improve diagnostic accuracy[24].

Tau 217

Phosphorylation of the tau protein is central of AD pathology; as for blood-based biomarkers, p-tau217 is a leading candidate biomarker compared to the long-validated p-tau181. It is more closely correlated with amyloid PET and clinical progression, and has superior specificity against other tauopathies[25-27]. Phosphorylated tau at threonine 217 (p-tau217) is now considered a superior biomarker for AD compared to the p-tau181 that was often studied earlier. Although the first plasma tau biomarker to be validated was p-tau181, p-tau217 can more accurately differentiate AD

from non-AD dementia than p-tau181. Palmqvist et al. (2020) reported that p-tau217 outperformed p-tau181 in sensitivity and specificity, particularly in early disease stages[25]. The researchers confirmed its robustness across diverse cohorts, highlighting its reproducibility in blood assays[26]. Meta-analyses likewise support its superior ability in predicting both amyloid positivity and cognitive decline[27,28]. It has been reported that the weight of evidence clearly supports p-tau217 as the next-generation biomarker that could replace p-tau181 as a standard for clinical and research use in the near future[29]. Plasma p-tau217 has a stronger association with amyloid positron emission tomography (PET) positivity than p-tau181, suggesting that it is a better biomarker of AD pathology. Previous researches demonstrated that p-tau217 levels predicted amyloid positivity even in preclinical stages[30]. Longitudinal studies have reported association between higher baseline p-tau217 levels with the greater cognitive decline and risk of conversion from MCI to AD dementia[31]. Earlier reports validated its predictive accuracy in real-world cohorts and its utility in monitoring disease progression [32]. The high association between p-tau217 measurements and tau pathology makes it a candidate biomarker for AD diagnosis, AD treatment response and AD disease staging[33].

One key benefit of p-tau217 is that it is specific to AD as opposed to other tauopathies. p-tau217 has better discriminatory ability than p-tau181, which can also be elevated in frontotemporal lobar degeneration (FTLD) and other non-AD dementias[34]. p-tau217 significantly decreased the rates of misclassification in differential diagnosis[35]. Meta-analysis by Antonioni et al. (2025) confirmed the superiority of p-tau217 over p-tau181 for the distinction of AD from non-AD dementias[36]. This specificity makes it more useful for clinical trial recruitment, precision medicine and staging disease progression. Further validation studies in real-world contexts confirm its contribution to improving diagnostic accuracy in diverse populations[37]. Thus, p-tau217 will likely be an important biomarker in clinical practice that will reshape diagnostic frameworks in AD and related disorders[38].

Neurofilament Light Chain (NfL)

Neurofilament light chain (NfL) is a 64-kDa type IV intermediate filament protein that forms part of the neuronal cytoskeleton and is predominantly expressed in large caliber myelinated axons[39]. Proteolytic cleavage of NfL and release into CSF are due to axonal injury and neurodegeneration disrupting the neurofilament network[40].

In AD, plasma and serum NfL levels are consistently elevated compared to cognitively unimpaired controls with meta-analyses reporting ~1.7–1.8-fold increases[40]. Elevated NfL is strongly associated with more rapid cognitive decline on MMSE and CDR-SOB scales, greater hippocampal and cortical atrophy, increased neurodegenerative burden on MRI and higher clinical severity across disease stages[39]. Longitudinal studies indicates that baseline NfL predicts conversion from preclinical to prodromal AD with ~80% accuracy, and presymptomatic converters have ~20% higher serum NfL before overt symptoms[41]. In prodromal and dementia stage AD higher baseline NfL tracks faster worsening on cognitive tests (r=0.6–0.8) with CSF elevations preceding plasma increases but maintaining parallel trajectories[42]. Discrimination of dementia from controls often achieves AUC >0.95 and recent validation studies support plasma NfL as a scalable surrogate endpoint in therapeutic trials[43].

However, NfL's lack of disease specificity is now definitively contrasted by 2025 data demonstrating p-Tau217 superiority a prospective study of 341 unselected participants showed plasma p-tau217 achieved 96% accuracy distinguishing AD from bv FTD and 93% accuracy from psychiatric disorders while NfL showed no significant difference between AD and bv FTD (P=0.788)[44]. This critical finding validates p-Tau217 as the disease specific biomarker for AD differential diagnosis. The major limitation of NfL lies in its lack of disease specificity as it reflects generic neuroaxonal injury rather than AD specific pathology[40].

Despite its limited specificity NfL has substantial clinical utility[40]. Validated cut-off values now provide 2024 prognostic precision a cross-sectional and longitudinal study identified 19.45 pg/mL for SCD and 20.45 pg/mL for MCI with these thresholds achieving AUC 0.82 for detecting AD biomarker profiles and good accuracy (80%) in identifying progressive SCD[45]. Its dynamic responsiveness makes it valuable for monitoring therapeutic efficacy and stratifying patients in clinical trials particularly as a pharmacodynamic biomarker in ALS and AD[39]. NfL complements phosphorylated tau biomarkers by quantifying global neuroaxonal injury while p-Tau181 and p-Tau217 capture AD specific tau pathology [41]. Multi marker approaches integrating NfL, p-Tau species and GFAP significantly improve diagnostic accuracy, staging and patient stratification[42]. Recent precision neurology frameworks emphasize that combined biomarker panels provide comprehensive disease characterization by simultaneously capturing amyloid pathology, tau phosphorylation, astrocytic activation and neuroaxonal damage[43,47].

NfL demonstrates notable strengths as a blood-based biomarker including high sensitivity to neuroaxonal injury strong correlation with disease progression[39]. However, lack of disease specificity and variability in reported plasma thresholds (~18–34 pg/mL) highlight major limitations with assay harmonization, calibration and stage adjustment remaining critical challenges[40]. Biological variability and inconsistent reporting practices further hinder cross study comparability and clinical adoption[43]. Key research gaps include definition of normative values across the lifespan, the clarification of NfL dynamics in

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preclinical AD, the validation of multi marker panels in diagnostically complex cohorts and the establishment of standardized sample handling protocols[42]. Future directions should focus on large scale prospective validation, international consensus on assay reporting and integration of NfL in clinical practice guidelines[48]. In multi marker frameworks with p-Tau181, p-Tau217 and GFAP, NfL is a valuable complementary biomarker for the quantification of neurodegenerative burden and for monitoring disease progression in AD (Figure 2) [41].

Glial Fibrillary Acidic Protein (GFAP)

Glial fibrillary acidic protein (GFAP) is an intermediate filament protein expressed in astrocytes and is involved in maintenance of cytoskeletal integrity. Increased GFAP levels in AD are caused by astrocytic activation and can be detected in CSF and plasma. GFAP has been recently identified as an early, readily available biomarker that increases before the onset of cognitive decline and as a complement to neuronal markers such as tau and NfL[49-51].

GFAP is a marker of astroglial activation and reflects neuroinflammatory processes in AD. Astrocytes upregulate GFAP in response to amyloid deposition, which can be measured in CSF and blood. Studies have shown that plasma GFAP is associated with amyloid PET positivity, supporting its role in early detection of pathological changes[49,50]. Unlike tau biomarkers that indicate neuronal injury, GFAP offers a complementary perspective on disease mechanisms through the prism of glial responses. Its AD elevation relative to controls demonstrates its diagnostic potential. However, GFAP can also rise in other neurological conditions and therefore must be interpreted with caution[51,52].

One of the strengths of GFAP is that it is elevated early in preclinical Alzheimer's disease (AD), with plasma GFAP levels increasing in amyloid-positive individuals before overt cognitive symptoms or measurable cognitive decline[53]. Longitudinal studies have shown that GFAP increases prior to tau or NfL, indicating that it is a sensitive biomarker for early detection of disease[54]. This early elevation makes GFAP a useful screening tool for at-risk populations, especially when combined with amyloid PET or plasma tau assays[55]. Its ability to detect astrocytic activation in the prodromal phase makes it more useful for preventive strategies and for clinical trial recruitment[56].

Measurement of plasma GFAP is easy and promising as a screening biomarker for Alzheimer's disease (AD), with its diagnostic accuracy validated in real-world cohorts demonstrating a strong correlation with amyloid pathology[57]. GFAP provides a distinct sensitivity to astrocytic changes, adding to the range of biomarkers such as tau and NfL. In particular, its non-invasive measurement enables large scale screening, especially in primary care settings where CSF or PET imaging are not feasible[58]. However, GFAP specificity is still limited, since increases are also seen in traumatic brain injury and multiple sclerosis[59]. Thus, GFAP alone may not be sufficient, but its addition to biomarker panels improves screening accuracy[60].

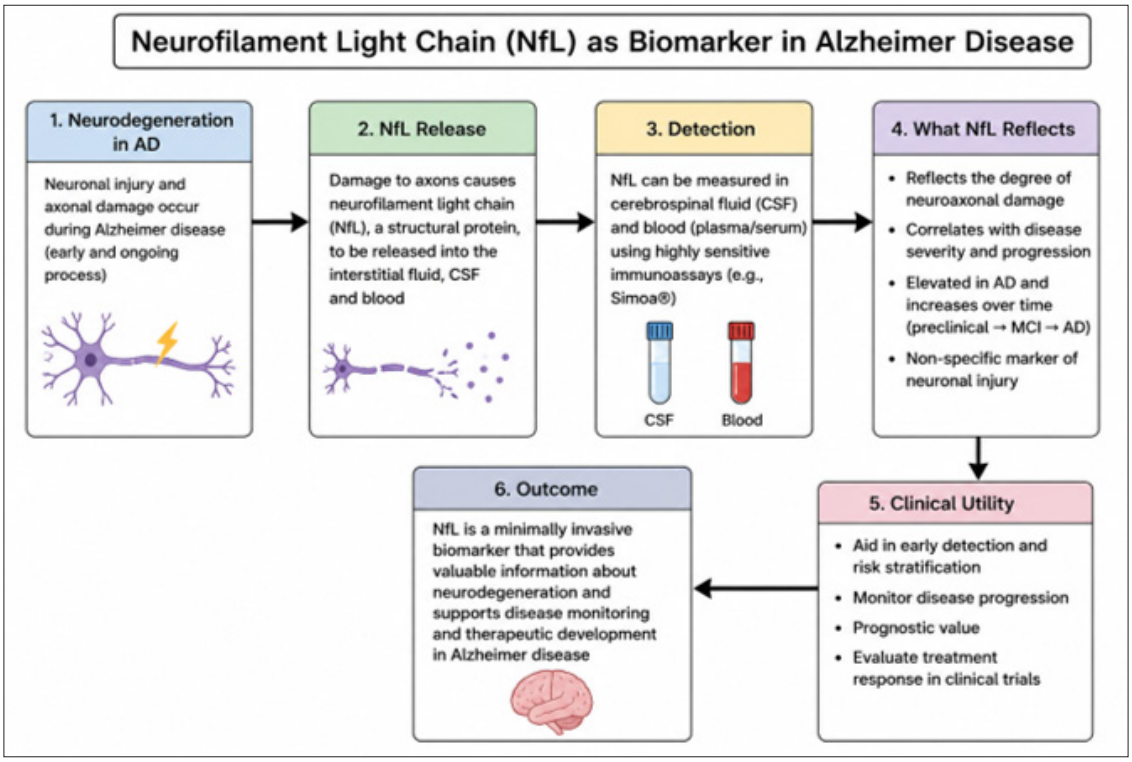

Figure 2.NfL as Biomarker in AD

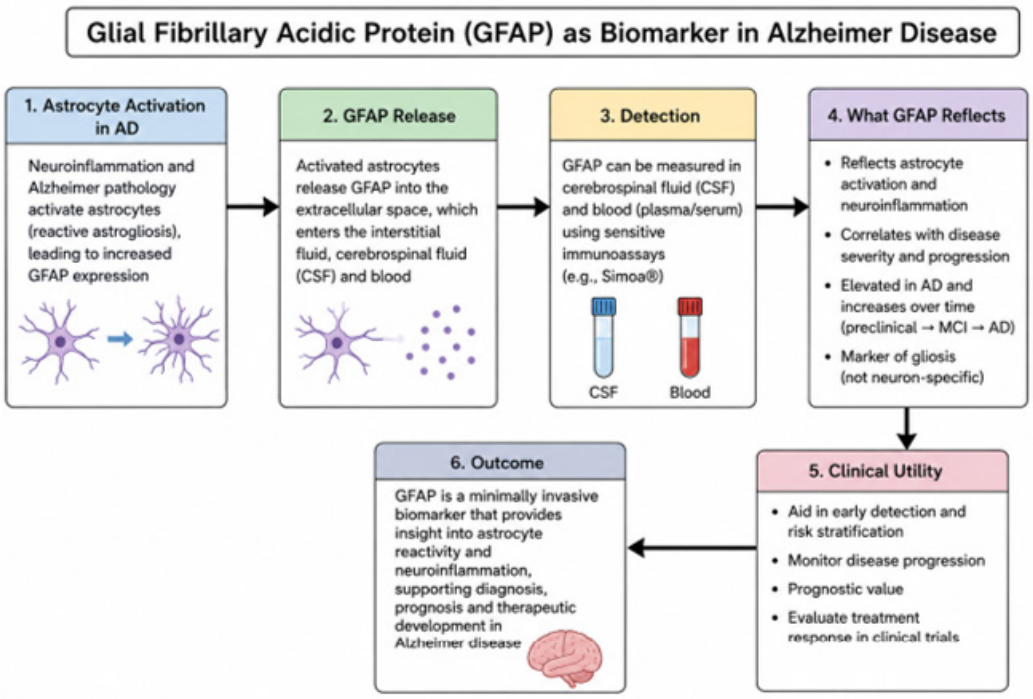

Figure 3.GFAP as Biomarker in AD

Table 1: Comparative Profile of Emerging Blood-Based Biomarkers in Alzheimer's Disease

Biomarker	Sensitivity	Specificity	Clinical Utility
Tau 181	Moderate	Moderate (less specific vs other tauopathies)	Early plasma marker; tracks amyloid pathology and cognitive decline
Tau 217	High	High (superior to Tau 181)	Strong correlation with amyloid PET; valuable in differential diagnosis
NfL	High	Low (elevated in multiple neurodegenerative diseases)	Marker of axonal injury; useful for disease progression
GFAP	Moderate	Moderate	Astrocytic activation marker; rises early in preclinical AD

GFAP demonstrates strong synergy with tau and NfL in multi-marker panels. Tau biomarkers are markers of neuronal injury, NfL is a marker of axonal degeneration, and GFAP is a marker of astrocytic activation. Taken together, these markers provide a complete picture of AD pathology[61]. Panels including GFAP showed improved diagnostic accuracy compared to single biomarkers[62]. Machine learning approaches combining GFAP, tau and NfL further increase the predictive power for disease progression[63]. This synergy highlights the role of GFAP not as a solitary marker, but rather as a complementary tool in the precision diagnostics of early detection, staging, and therapeutic monitoring (Figure 3)[64].

Comparative Insights

Blood-based AD biomarkers have varying sensitivity, specificity, and clinical applicability. Tau 217 is the strongest biomarker, followed by Tau 181. NfL and GFAP provide complementary readouts of axonal injury and astrocytic activation in the AD brain. Comparative studies stress the need to implement multi-marker panels and new multiplex strategies for improving diagnosis and disease staging (Table 1)[65-67].

However, single biomarkers are often too unspecific or insensitive for clinical use, such as p-tau181 which correlates well with amyloid pathology but is not as specific for tau pathology as p-tau217, or neurofilament light chain (NfL) which reflects neurodegeneration across diseases[65,66]. Although the concentration of GFAP can increase earlier in non-AD, inclusion of GFAP in multi-markers such as tau (neuronal injury), NfL (axonal degeneration) and GFAP (astrocytic activation) panels has been shown by Antonioni et al. (2025) to improve accuracy for AD diagnosis, as all 3 concentrations in a panel were shown to be diagnostically complementary in differentiating AD and other dementias compared with a single marker[67]. Such panels might more accurately stage a patient's pathology and response to therapy than individual biomarkers.

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Emerging avenues for biomarker discovery such as multiplex assays and machine learning provide some hope for greater reliability in the measurement of biomarkers. For example, multiplex assays allow for parallel quantification of all tau isoforms, NfL and GFAP with low variability and increased throughput[68]. Machine learning models improve the prediction of amyloid positivity, cognitive decline and disease progression using multi-marker datasets. Machine learning models incorporating tau, NfL, and GFAP have the potential to improve Alzheimer's disease (AD) diagnosis beyond conventional cut-offs and enable tailored precision medicine based on individual biomarker profiles. Multiplexed/Computational approaches are the future of biomarker-based AD diagnostics as these provide more scalable, reproducible and clinically actionable approaches, despite the need for standardized and validated methods[69-71].

Clinical Applications

Blood biomarkers can detect AD pathology years before cognitive decline. Strong correlations between plasma p-Tau217 and p-Tau181 with amyloid and tau load were observed with the diagnostic accuracy of p-Tau217 being superior (AUC = 0.94) than p-Tau181 (AUC = 0.88) [72,73]. GFAP as a marker of astrocytic activation and NfL as a marker of axonal injury provide complementary information about neuroinflammation and neurodegeneration[74,75]. Blood assays are less invasive than lumbar puncture or PET imaging and are more feasible for large-scale screening in primary care[75]. In older adults, higher plasma p-Tau217 concentrations are predictive of global cognitive decline, indicating the potential for preclinical detection[73]. These biomarkers are able to stratify disease severity across the AD continuum p-Tau217 and p-Tau181 are associated with tau burden and cognitive impairment, while NfL levels increase in a progressive manner with neuronal loss reflecting the clinical transition from mild cognitive impairment to dementia[72,74]. GFAP elevations are a marker for astrocytic reactivity and amyloid pathology. Multi marker panels combining p-tau, NfL and GFAP provide better accuracy in separating cognitively unimpaired individuals from prodromal AD[73,75]. Higher NfL predicted faster clinical dementia rating progression in Aβ-positive individuals[74].

Blood biomarkers are used to monitor biological responses to disease modifying therapies. Anti-amyloid interventions resulted in normalized decreases in plasma p-tau181[76,77]. Reductions in NfL could indicate neuroprotective effects[78]. Blood assays are more feasible and cost-effective 1.5–3.9 times than repeated PET or CSF sampling[75]. Biomarkers were included as inclusion criteria or outcomes in 84% of disease-targeting trials[7], transforming AD clinical trial design with blood-based biomarkers. They serve to screen and to enrich, thus lessening the need for PET. Biomarker-guided stratification enhances the precision medicine[78,79]. Challenges include assay standardization and regulatory acceptance, addressed by WHO's 2024 preferred product characteristics[80].

Future Directions

Large-scale validation remains a key priority. Current evidence demonstrates strong associations between plasma p-Tau217, p-Tau181, NfL and GFAP with Alzheimer's pathology and progression, but most studies have been restricted to relatively homogeneous cohorts. Future research should be focused on multi center, multiethnic and longitudinal studies to establish generalizable cut-off values that can be generalized and reproducibility across assay platforms. For clinical use, it will be critical to harmonize analytical methods and reach regulatory consensus on biomarker cut-offs. Without such standardization, comparability of results across studies and equitable implementation will be limited[81-84].

Integration of blood biomarkers with digital biomarkers is equally important. Advances in smartphone based cognitive testing, wearable sensors and remote monitoring platforms provide the opportunities to combine molecular signatures with real world functional data. AI and machine learning models can utilize multimodal inputs to improve risk prediction, detect subtle preclinical changes and personalize monitoring trajectories. This convergence of biological and digital data could enable scalable, cost-effective surveillance of at-risk populations, while reducing reliance on invasive or expensive modalities[81,84].

Future implementation must also address ethical and accessibility considerations. Disclosure of biomarker results in asymptomatic individuals raises complex issues of informed consent, psychological burden and potential stigmatization. Data privacy and secure handling of digital health records are paramount, particularly as biomarker data are increasingly linked with personal devices. Moreover, equitable access is still a major concern, and biomarker-based screening must be tailored to low- and middle-income countries, where healthcare infrastructure and affordability may create further obstacles to care and worsen current inequalities[85]. Ultimately, the path is paved toward personalized medicine. Multi marker panels including Tau181, Tau217, NfL, GFAP are likely to outperform single biomarkers to stratify risk, stage disease and guide therapeutic interventions. These profiles can enhance patient selection and help direct individualized treatment strategies. The convergence of validated blood-based biomarkers with digital health technologies and precision medicine frameworks holds the potential to fundamentally transform AD diagnosis, monitoring and management in the coming decade[81,84,86,87].

Conclusion

Tau 217 is considered the preferred biomarker in AD

because of its higher specificity and correlation with the presence of AD-specific amyloid pathology. NfL and GFAP remain complementary biomarkers of axonal damage and astrocytic activation, and correlate with disease severity. Collectively these blood-based biomarkers can provide a multidimensional picture of disease pathology, and if implemented in routine clinical practice they could transform both the accessibility and affordability of AD diagnosis and management through improved early diagnosis, differential diagnosis, and periodic monitoring of disease progression and treatment response.

Conflict of Interest

The authors do not have any conflicts of interest.

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