IJHSR
ijhighschoolresearch.org
REVIEW ARTICLE

Relationship and Comparison between Plasma, Neuroimaging, and Digital Biomarkers in Alzheimer's Disease

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ABSTRACT: Alzheimer's disease (AD), the world's leading cause of dementia, presents significant diagnostic and therapeutic challenges due to its prolonged preclinical phase. This review critically examines three emerging biomarker modalities: plasma, neuroimaging, and digital biomarkers, evaluating their individual and combined utility in the detection and monitoring of AD. Plasma biomarkers provide minimally invasive, scalable measures of molecular pathology. Neuroimaging provides highly localized, anatomical detail necessary for diagnosis and monitoring of disease progression. Digital biomarkers from cognitive/behavioral measures via technological devices allow ecologically valid monitoring in real time. This comparative analysis weighs the respective strengths of each modality: accessibility (plasma), anatomic specificity (neuroimaging), and functionality (digital) against respective limitations. Within the ATN (Amyloid, Tau, Neurodegeneration) framework, this review synthesizes evidence to evaluate the rationale for an integrated biomarker approach for optimized early identification, personalized planning for therapeutics, and scalable mass-population screening.

KEYWORDS: Biomedical and Health Sciences, Pathophysiology, Alzheimer's Disease, Biomarkers, Plasma, Neuroimaging, Digital.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that impairs memory, cognition, and the capacity to perform everyday activities.[1] AD is the most common type of dementia, affecting over 55 million people worldwide as of 2024 and projected to exceed 139 million by 2050.[1] AD typically begins with an extended preclinical phase during which pathological changes occur without any obvious symptoms, marked by amyloid-β aggregation and tau pathology.[2,3] Once clinical symptoms become apparent, irreversible neurodegeneration has usually occurred by which point most therapeutic interventions are ineffective.[4]

These pathological mechanisms underlie the ATN framework (Amyloid, Tau, Neurodegeneration), which is now used extensively to stage AD biomarkers.[2] Amyloid deposition ('A') can be assessed using amyloid PET or plasma *Aβ42/40*; tau pathology ('T') can be quantified using tau PET or plasma phosphorylated tau (*p-tau181, p-tau217, p-tau231*); neurodegeneration ('N') is reflected in MRI-based brain atrophy or functional decline measured through digital cognitive tools.[5–7] This framework depicts how different biomarker modalities assess complementary facets of AD pathology.

However, although each biomarker class has been extensively studied in isolation, few investigations have systematically compared plasma, neuroimaging, and digital modalities within a unified ATN framework.[2,5,7,8] This gap constrains our ability to elucidate how molecular, structural, and functional measures interact across the AD continuum, thereby limiting the translational value of biomarker research. Consequently, a more integrated comparative approach is necessary to align biomarker discovery with clinical application, improve diagnostic precision, and guide multimodal trial design.[9]

In recent decades, biomarkers have become essential tools for early diagnosis, disease monitoring, and therapeutic planning in AD.[9–11] Plasma biomarkers provide noninvasive measures of molecular pathologies;[5] neuroimaging biomarkers provide information about changes in brain structure and function;[3,6] digital biomarkers capture cognitive and behavioral changes through continuous or task-based assessments enabled by modern technological devices.[7] Each type of biomarker reveals different aspects of disease development, yet together they enrich understanding of pathophysiological processes underlying AD.

The literature reviewed was identified through searches on PubMed, Google Scholar, and Scopus conducted between 2015 and 2024, focusing on peer-reviewed studies of plasma, neuroimaging, and digital biomarkers in AD. This review prioritized large cohort studies, systematic reviews, and clinical trial data to ensure robustness of evidence. Previous reviews have frequently considered plasma, neuroimaging, or digital modalities in isolation. However, few studies have systematically compared these modalities within a unified framework, even as the ATN model increasingly emphasises their complementarity to represent amyloid ('A'), tau ('T'), and neurodegeneration ('N').[5,7–9] This lack of integrated analysis creates uncertainty regarding how distinct biomarker classes should be positioned relative to one another in both research and clinical contexts. Accordingly, this review synthesizes recent evidence across plasma, neuroimaging, and digital biomarkers, evaluating their diagnostic performance, scalability, and translational readiness when interpreted through the ATN framework.

DOI: 10.36838/IJHSR87.80

■ Comparative Relationships Between Biomarker Modalities

While plasma, neuroimaging, and digital biomarkers provide valuable insights individually, their full diagnostic and translational potential emerges when evaluated together.[2]

Pairwise comparisons clarify whether less invasive and scalable modalities can effectively complement or, in certain cases, replace more established but costly techniques. These comparisons correspond to the ATN framework: amyloid and tau pathology ('A' and 'T') are measured by plasma and imaging biomarkers, and neurodegeneration ('N') by imaging and digital measures.[2,7] Evaluating these relationships reveals where modalities converge or differ, which informs diagnostic approach, trial planning, and multimodal biomarker integration in clinical care. The following sections discuss these pairwise relationships in detail, starting with that between plasma and neuroimaging biomarkers.

Plasma and Neuroimaging:

Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) are cornerstone neuroimaging techniques for AD, providing *in vivo* quantification of amyloid plaques, tau tangles, and neurodegenerative alterations.[3,6,8] These techniques, for example, amyloid-PET, have been shown to reveal Aβ accumulation up to two decades before the onset of clinical disease symptoms, while tau-PET provides regional specificity useful for disease staging, which in turn correlates with the severity of clinical presentations.[3,5,6,8] These modalities are, however, expensive, invasive, and less accessible in nonspecialized centers.[8] Within the ATN framework, imaging captures amyloid ('A'), tau ('T'), and neurodegeneration ('N') with high spatial precision, whereas plasma biomarkers provide scalable molecular proxies for amyloid and tau pathology.[2]

As a result, plasma biomarkers, such as phosphorylated tau isoforms *p-tau181, p-tau217,* and *p-tau231*, are emerging as more viable, scalable alternatives.[12–14] These phosphorylated tau proteins reflect AD pathology and can be measured in blood with increasing sensitivity and specificity.

Various research studies demonstrated a strong association between neuroimaging biomarkers and plasma tau concentrations in AD. Plasma *p-tau217* closely mirrors tau-PET signals in early tau-deposition regions such as the entorhinal cortex and inferior temporal lobe, suggesting strong potential as a surrogate marker even in preclinical disease stages.[13,15]

Consistent with this concordance, longitudinal studies showed that plasma *p-tau217* predicts future tau-PET positivity as well as medial temporal lobe atrophy.[13,15] The robust association suggests that plasma *p-tau217* can serve as a surrogate marker during the preclinical stage of disease. Overall, these results support the conclusion that plasma *p-tau217* tracks with PET signals and is a scalable surrogate for early diagnosis.

Plasma *p-tau217* demonstrates high specificity (≈96%) for distinguishing AD from other neurodegenerative disorders in research cohorts. Plasma *p-tau217* results stem from relatively small clinical cohorts and thus cannot be assumed to be generalizable until they are replicated in larger, more diverse groups. These results indicate the potential of plasma markers as early identifiers, especially in those with no evident clinical symptoms.[15] In addition to diagnostic discrimination, spatial correlation of plasma and imaging markers indicates their complementary value. Plasma *p-tau231* levels correlate with Braak stage I–II areas and earliest tau pathology in the transentorhinal cortex.[14] Such anatomical correlations indicate that plasma biomarkers can reflect neuroanatomical changes identified by imaging, though they lack spatial resolution. This overlap implies that plasma assays can partially replicate spatial patterns normally obtained using imaging. Plasma biomarkers have also been shown to predict subsequent changes detectable by neuroimaging in longitudinal studies.

Individuals with elevated plasma *p-tau181* levels, despite normal baseline tau-PET scans, became tau-PET positive within two years.[13] A 2023 long-term follow-up revealed that higher plasma *p-tau217* predicted increasing tau-PET binding and medial temporal atrophy.[16] These findings demonstrate that plasma biomarkers not only indicate current pathology but may also predict future disease progression, a valuable feature for longitudinal monitoring. These longitudinal results further bolster the argument in favor of plasma assays as not only reflective, but predictive measures in the ATN cascade, well before imaging-detectable alterations.

Yet measurements are not always concordant between modalities, and in a minority of cases, plasma-imaging discordance may be of clinical importance in and of itself. Some patients have elevated tau-PET signal with low plasma tau, which can reflect late disease stages, where tau production has slowed, but deposition continues.[13] This discordance actually serves to emphasize that plasma and imaging are not equivalent but rather sample different points along the trajectory of tau pathology with possible diagnostic utility in distinguishing the stage of disease.

Notwithstanding such heterogeneity, the complementary strengths of these modalities have been demonstrated in clinical research to reduce costs and optimize participant selection. For instance, plasma *p-tau217* was employed in the AHEAD 3–45 trial as a prescreening test for cognitively normal individuals prior to more expensive amyloid- and tau-PET imaging.[10] Likewise, the TRAILBLAZER-ALZ 2 study used plasma *Aβ42/40* and *p-tau217* assays for prescreening participants receiving anti-amyloid treatment.[11]

These examples illustrate how plasma biomarkers can function as a cost-effective adjunct to neuroimaging by enabling large-scale prescreening prior to confirmatory testing. Such trial designs demonstrate that combining plasma-based screening with confirmatory imaging maximizes cost-efficiency and recruitment efficiency in AD research.[17,18]

Although these encouraging correlations do exist, there are some important limitations. Plasma–imaging concordance studies have most often been performed in small, fairly homogeneous populations,[12,13] rendering generalizability difficult. Plasma assays are not yet globally standardized and show significant variability across laboratories and assay platforms, which detracts from clinical utility.[19] Finally, apparent discor-

dance among modalities emphasizes the value of multimodal assessment over dependence on any one class of biomarkers.

In total, these results emphasize the complementarity of imaging and plasma biomarkers. Imaging offers anatomical resolution and staging across the 'A,' 'T,' and 'N' domains, whereas plasma assays offer noninvasive, scalable measures of amyloid and tau. These results demonstrate the complementarity of plasma and imaging, where plasma allows for low-cost scalability and imaging offers anatomical resolution.

Neuroimaging and Digital:

Neuroimaging biomarkers, such as PET and MRI, have provided important information regarding the structural and functional changes related to AD. Structural MRI data show that hippocampal atrophy, an important marker of episodic memory decline, develops at a very early stage, while fMRI studies show disturbances within the default mode network (DMN), a set of brain regions including the posterior cingulate cortex and medial prefrontal cortex that support introspective cognition and memory-related processes.[6,20,21] As imaging technologies have advanced, digital biomarkers have demonstrated convergent validity with imaging-based measures, offering accessible tools for assessing real-world functional impairments.[22] Within the ATN framework, MRI and fMRI act as spatial markers of neurodegeneration ('N'), whereas digital biomarkers capture functional manifestations of this domain in ecologically valid contexts. This complementarity underscores their potential for integrated monitoring of disease progression.[2,7]

Memory deficits are among the earliest clinical manifestations of AD and are closely associated with hippocampal atrophy on MRI.[6,20] Performance on digital memory assessments, such as narrative recall and object-location tasks administered via tablets, is associated with subsequent left hippocampal volume loss in a region essential for encoding verbal material.[22] However, most such studies were conducted in highly educated, predominantly Western cohorts,[23] limiting the generalizability of digital testing across diverse cultural and socioeconomic groups. Furthermore, performance on digital episodic memory tasks also correlates with medial temporal lobe atrophy.[23,24] These results indicate that, despite lacking spatial resolution, digital cognitive assessments can effectively reflect the neurodegeneration detected by imaging modalities.

Attention deficits, measured by reaction time variability (RTV), demonstrate strong concordance with fMRI-based disruptions. Elevated RTV, an index of attentional instability, has been associated with reduced DMN interconnectivity, even among cognitively normal individuals at risk for AD.[21] A 2024 follow-up analysis demonstrated that computerized attention measures predicted early network decline, reaffirming the potential of digital attention testing in preclinical AD.[24]

Beyond formal cognitive testing, spontaneous speech has also been investigated as an indirect measure of background neuroanatomical change. Executive function, one of the initial domains affected by AD, has also been associated with structural changes in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex as observed on MRI.[20,23] Digital executive tests, such as the n-back and Stroop tasks, demonstrated sensitivity to dysfunction in affected brain regions. Digital administration of the Stroop test distinguished patients with MCI from controls and correlated with frontal lobe atrophy.[23] Speech-based digital biomarkers also demonstrate convergent validity with neuroimaging findings. A 2022 study found that increased silence duration in speech, a digital voice biomarker, correlated with early cognitive decline, and these speech patterns were associated with functional and structural brain changes in regions linked to AD.[25,26]

Longitudinal studies further strengthen evidence that digital biomarkers can predict neuroimaging outcomes. Earlier cognitive impairments detected by digital measures predicted subsequent hippocampal atrophy and tau deposition even when the baseline imaging was normal.[20,22] A 2024 validation study confirmed that digital memory impairments were associated with subsequent medial temporal lobe atrophy.[22] Together, these longitudinal findings suggest that digital tools may precede imaging-detectable decline by several years, reinforcing their utility as early screening instruments and continuous monitoring tools in at-risk populations.

Although findings are encouraging, several challenges persist. Digital biomarkers generally rely on heterogeneous platforms (e.g., tablets, smartphones, and wearable devices) and lack standardized protocols, complicating cross-study comparability. Wearable device integration into multimodal frameworks remains promising but underdeveloped, as wearable devices can provide continuous physiological measures that complement imaging and plasma-based markers. Test setting variability (home vs. clinic) and limited regulatory validation constrain translation to clinical trials or practice. Addressing these methodological and regulatory challenges will be essential for widespread clinical adoption.[7,27]

In summary, a substantial convergence of neuroimaging methods and digital cognitive biomarkers exists across many cognitive domains, particularly regarding memory, attention, and executive function. Neuroimaging tools provide accurate spatial representations of the brain, while digital tools track functional decline in ecologically valid settings at regular and economical intervals. This convergence supports combining both modalities for early detection and longitudinal monitoring of AD, with digital tools providing unique repeatability and ecological validity for both clinical trials and real-world applications.[7,27]

Digital and Plasma:

Plasma biomarkers such as phosphorylated tau isoforms (*p-tau181, p-tau217,* and *p-tau231*) and the amyloid-beta 42/40 ratio (*Aβ42/40*) are particularly effective in the identification of central pathological signs of AD.[12–14] Such biomarkers provide noninvasive tools that quantify molecular alterations indicative of amyloid deposition and tau pathology using scalable blood-based methods. Their clinical utility is greatly enhanced when linked with functional indicators from digital devices that record cognitive and behavioral performance.[7,22] Within the ATN framework, plasma biomarkers primarily reflect amyloid ('A') and tau ('T') pathology, whereas digital

DOI: 10.36838/IJHSR87.80

tools capture neurodegeneration ('N') through functional impairment. Integrating these modalities allows comprehensive assessment across all three domains.

Recent studies point to a rising correlation between plasma biomarker levels and performance deficits on digital cognitive tests. Plasma levels of *p-tau231* correlate with deficits in story recall and delayed recognition tests taken on tablet devices, even in cognitively healthy individuals.[22] These digital tests are found to be markers of medial temporal lobe function, an area that is the first to present tau pathology in AD. The presence of such a correlation suggests that functional deficits that are detected through digital means reflect underlying neurobiological processes, including elevated plasma tau levels.

Individuals with greater baseline plasma *p-tau217* levels declined more steeply in semantic fluency and learning ability over 18 months, according to web-based cognitive testing platforms.[15] These relationships were still significant after adjustment for possible confounding influences such as the APOE ε4 genotype and age, confirming the predictive validity of the plasma biomarker for functional decline. The findings also expand the role of internet-based testing in revealing subtle behavioral changes that result from molecular pathologies.

Beyond cognitive testing, speech-derived digital biomarkers offer a noninvasive alternative means of capturing the early molecular alterations. In a recent cohort study, poorer digital executive function performance predicted subsequent increases in plasma *p-tau181* and decreases in the *Aβ42/40* ratio.[22] This suggests that, in some preclinical cohorts, functional alterations may precede or coincide with peripheral biomarker changes, particularly in preclinical AD cohorts.

For instance, amyloid-positive status exhibited significantly more silent pauses and altered auditory parameters in remote speech recordings, demonstrating an association between speech-based digital biomarkers and underlying AD pathology.[26] However, most speech-derived digital biomarkers are still developed on prototype platforms, and standardized methods for integrating these tools into clinical practice have yet to be developed or validated.

In addition, remote digital cognitive testing, including working memory and semantic classification tasks, has shown promise as an early predictor of AD risk. Impaired performance on these tests predicted pathological plasma biomarker profiles one to two years later, particularly in cohorts with preclinical amyloid positivity.[28] These findings illustrate how digital performance can precede molecular change, rendering it amenable to risk stratification. Collectively, these studies suggest that digitally measured functional decline may foreshadow, and in some cases outpace, molecular alterations detected in plasma, highlighting the potential of digital tools for risk stratification in preclinical AD.

Despite encouraging results, key challenges remain. Most studies are limited by small, demographically homogeneous cohorts, raising concerns about generalizability. Digital tools also differ across platforms, complicating standardization, and few have yet been validated as regulatory endpoints. These limitations must be addressed before plasma and digital integration can be routinely implemented in clinical trials or practice.[7,22,27]

Collectively, current evidence confirms a bidirectional relationship between molecular and behavioral indicators, reinforcing the value of multimodal integration. When used together, these modalities enhance diagnostic precision, disease monitoring, and participant stratification in AD research. Importantly, integrating digital and plasma biomarkers offers a practical approach for prescreening and participant enrichment in large-scale clinical trials and remote longitudinal monitoring in real-world settings.

■ Comparison between Plasma, Neuroimaging, and Digital Biomarkers

The preceding paragraphs outlined the interaction of plasma, neuroimaging, and digital biomarkers and their molecular, structural, and functional qualities. Equally important is a systematic evaluation of each modality's comparative strengths. Each biomarker class offers distinct advantages and limitations depending on its use in presymptomatic detection, staging, therapeutic monitoring, or trial design. This section compares the three modalities on seven dimensions: diagnostic precision, temporal sensitivity, invasiveness, cost and scalability, clinical readiness, ecological validity, and primary limitations. This dimensional comparison highlights the usefulness of each modality in its domain and demonstrates how their differences allow for an integrated and complementary diagnostic framework. In the ATN framework, plasma biomarkers mainly index amyloid ('A') and tau ('T'), neuroimaging spans the three domains ('A', 'T', and 'N'), and digital biomarkers capture functional expressions of neurodegeneration ('N'). This comparative perspective illustrates how the three modalities align with distinct layers of the disease process. The following table summarizes these relationships, followed by a detailed analysis of each dimension.

Table 1: Comparison between plasma, neuroimaging, and digital biomarkers across different domains.

Dimension	Plasma Biomarkers (A/T)	Neuroimaging Biomarkers (A/T/N)	Digital Biomarkers (N)
Diagnostic Accuracy	High for *p-tau217* and *Aβ42/40* (AUC > 0.90) in research cohorts; real-world accuracy under validation	Gold standard for anatomical specificity and disease staging (amyloid/tau PET, MRI)	Moderate at present; improving with task diversity, AI, and multimodal tests
Temporal Sensitivity	Become abnormal ~7–10 years before symptom onset	Amyloid PET abnormal 15–20 years before onset; tau PET and MRI closer to symptoms	May detect very early functional changes (e.g., subtle speech, executive dysfunction), but less validated and temporally uncertain
Invasiveness & Burden	Minimally invasive (venipuncture)	Moderately to highly invasive; radiation exposure (PET), long scans	Noninvasive, home-based, frequent data capture
Cost & Scalability	Lower cost; scalable; increasingly feasible in primary care, though assays are not standardized	High cost, limited scalability; mainly tertiary centers or trials	Very low cost; highly scalable with consumer devices, but equity/digital divide issues limit reach
Clinical Readiness	Increasing adoption in trials; clinical uptake growing, but assay harmonization is lacking	Already established and regulatory-approved for diagnosis/staging	Experimental; platforms in pilot/validation stage; regulatory pathways emerging
Ecological Validity	Low; snapshot of molecular pathology in clinic setting	Moderate; in-clinic brain state measures	High; reflects real-world cognitive and behavioral function in daily life
Limitations	Affected by systemic factors; assay variability across labs, and standardization needed	Costly, centralized, logistically burdensome	Susceptible to device bias, environmental noise, and digital literacy/access variability

Diagnostic Accuracy:

Plasma *p-tau217* and *Aβ42/40* display excellent diagnostic accuracy (AUC > 0.90) in distinguishing AD from other dementias in large multicenter cohorts such as Janelidze *et al*. (n ≈ 1,200) and Palmqvist *et al*. (n ≈ 600).[5,15] Real-world accuracy may be reduced because such estimates are often derived from highly selected research cohorts.[29,30] Their accuracy, nonetheless, makes plasma assays promising candidates for large-scale early detection. Neuroimaging, especially tau-PET, remains the gold standard for anatomical staging, supplemented by longitudinal imaging studies of several hundred individuals across multisite consortia such as ADNI.[6,20] Digital biomarkers currently demonstrate modest accuracy (AUC ≈ 0.70–0.80) in small pilot groups of 100–300 subjects but are being refined at a high rate by multimodal assessments enhanced by machine learning.[7,24] AI approaches increasingly enable detection of subtle behavioral patterns such as reduced speech fluency or slowed response latency that may signal preclinical decline.[25,26] While imaging offers regional specificity and plasma biomarkers capture molecular signatures, digital technologies capture behavioral correlates that mirror more pervasive, early-stage cognitive disruptions that may precede discrete molecular or anatomical abnormalities. These accuracy differences reflect each modality's unique biological target rather than implying a diagnostic hierarchy.[2,9] In clinical practice, this means plasma assays are most promising for scalable early detection, imaging remains essential for staging and differential diagnosis, and digital tools may act as continuous functional readouts to track intervention response.[30] Together, these modalities demonstrate complementary accuracy profiles. Neuroimaging defines anatomical localization, plasma assays detect biochemical pathology, and digital tools capture functional impact.

Temporal Sensitivity:

Neuroimaging modalities such as amyloid PET document pathological deviations 15–20 years prior to symptom onset and hence serve as the earliest measurable indicators of pathological change.[3] Plasma tau biomarkers appear several years before clinical onset (estimated 7–10 years in longitudinal modeling).[13,29] Digital biomarkers, though still in early development, may detect subtle cognitive and functional changes even before measurable molecular abnormalities emerge.[7,21] Subtle impairments such as minor speech delays or executive dysfunction detected via digital tools may reflect compensatory neural responses that precede measurable pathological changes.[24,25] These signals remain less validated than molecular or imaging markers, and their temporal positioning within the ATN cascade is still under investigation. This temporal progression suggests a continuum of biomarker evolution: imaging often captures the earliest detectable deposition, while plasma assays reflect downstream molecular changes.

Invasiveness and Patient Burden:

The level of invasiveness itself is an important determinant of follow-up and longitudinal screening adherence. Plasma biomarkers are accessed by venipuncture alone and thus are convenient to sample repeatedly.[19] Neuroimaging, particularly PET, entails radiation exposure, prolonged scanning time, and clinical equipment with logistical inconveniences.[8,18] Digital biomarkers are remotely administered and completely noninvasive, permitting frequent data capture outside clinical settings.[27] These differences illustrate how plasma and digital approaches improve compliance in longitudinal research, while neuroimaging is still needed for definitive, multifactorial diagnosis.

Cost and Scalability:

Cost remains a decisive constraint in AD diagnostics. Neuroimaging is resource-intensive, with a single PET scan typically costing several thousand dollars when performed using state-of-the-art technology.[18,31] Plasma biomarkers, although still undergoing validation, represent a substantially more affordable option and are increasingly suited for deployment in primary care settings.[30,32] Digital biomarkers offer the highest scalability, as they require minimal infrastructure and enable passive, high-frequency measurement through consumer devices.[7,21] Formal cost-effectiveness modeling demonstrates that the use of blood-based or digital prescreening prior to PET imaging substantially reduces trial recruitment costs and participant burden.[18,31] These findings have broader health-economic implications, suggesting that plasma and digital biomarkers can reduce both trial-related and healthcare expenditures by decreasing reliance on high-cost imaging. Collectively, these cost differentials position plasma and digital biomarkers as promising first-line tools for scalable screening across diverse healthcare systems, supporting the adoption of tiered diagnostic models in AD.

Clinical Readiness:

Neuroimaging modalities are already being utilized via regulatory approval and integration into diagnostic criteria.[2] Plasma biomarkers are nearing clinical utility as they become integrated into trial designs and diagnostic algorithms, though the lack of assay standardization remains a major barrier to implementation.[30,32] Digital biomarkers are largely at the validation and preclinical research stages, with ongoing pilot studies in progress and unresolved regulatory questions.[27] The relative paucity of clinical readiness in digital biomarkers is a reflection of their recent discovery and continuing regulatory assessment.[27,33] Policy framework development and regulatory concordance will be needed to propel these devices from pilot trials to regular use in healthcare practice.[27,33] In summary, neuroimaging is clinically established, plasma biomarkers are undergoing translational adoption, and digital metrics remain pre-regulatory, reflecting the developmental gradient across modalities.

Ecological Validity:

Ecological validity has been conceptualized as the degree to which a biomarker captures daily functioning.[33] Digital biomarkers uniquely quantify behavior in real-world conditions, such as everyday speech or response latency.[25,27] Plasma and neuroimaging biomarkers, however, quantify biological processes under controlled conditions, providing precise but static

DOI: 10.36838/IJHSR87.80

snapshots of disease.[2,6] Digital tests should therefore be considered adjunctive tests that complement, rather than substitute for, traditional diagnostic tests.[7,27] Their use also raises equity concerns because access to smartphones, tablets, or stable internet may differ across age groups, socioeconomic groups, and cultural backgrounds. These synergistic strengths emphasize the need for integration of biological and behavioral data in minimizing access disparities to promote equitable clinical translation.

Modality Limitations:

Despite their promise, each biomarker modality faces distinct limitations. Plasma tests, while accurate and minimally invasive, lack global standardization and therefore limit the reproducibility of findings across populations.[5,19] Neuroimaging provides gold-standard anatomical precision but is constrained by cost, radiation exposure (in PET), and limited accessibility, which limits its utility to specialty centers and trials rather than broad clinical practice.[8,18] Digital biomarkers, though scalable and ecologically valid, suffer from heterogeneity in platforms and protocols, as well as disparities in digital literacy and device access that raise equity concerns.[21] Collectively, these limitations reinforce the complementary value of the three biomarker classes: plasma detects molecular pathology, imaging defines anatomical context, and digital tools capture functional consequences.

Synthesis and Implications:

This comparative analysis underscores the strategic complementarity of the three biomarker classes. Plasma assays allow for large-scale molecular screening;[19] neuroimaging provides spatial resolution for staging and diagnosis[6]; and digital technologies enable continuous, ecologically valid monitoring of cognitive and behavioral function.[27] While each modality has inherent limitations when used alone, together they align molecular, structural, and functional domains to a coherent diagnostic framework that encompasses the full trajectory of AD. In practice, recent prevention and treatment trials increasingly adopt this tiered model: plasma assays for prescreening, neuroimaging for confirmation and staging, and digital tests for longitudinal follow-up and monitoring of treatment.[7,10,11] This combined approach maximizes diagnostic specificity and enables patient-tailored therapeutic strategies, particularly as studies increasingly target presymptomatic intervention and long-term disease monitoring in heterogeneous populations.[2,32] Future research should prioritize the development of multimodal integration platforms that balance plasma, imaging, and digital biomarkers in integrated diagnostic algorithms for optimal analytical sensitivity, specificity, and scalability. Furthermore, standardized assay procedures, interoperable digital platforms, and shared data governance structures will be key to the translation of multimodal biomarkers from proof-of-concept studies into routine clinical practice.[19,32]

■ Conclusion

The clinical picture of AD is being transformed rapidly by advances in plasma, neuroimaging, and digital biomarkers. Each modality provides a unique, complementary perspective. Plasma biomarkers allow for minimally invasive, affordable identification of amyloid and tau pathology. Neuroimaging, and particularly PET and structural MRI, remains critical for anatomical accuracy and disease staging. Digital biomarkers provide ecologically valid assessments of cognition and behavior, documenting fine functional impairment in real-world settings. Within the ATN framework, the modalities provide a comprehensive picture of progression of the AD: plasma assays index ATN A (amyloid) and ATN T (tau), neuroimaging spans all sub-domains of ATN, and digital measures capture functional correlates of neurodegeneration.

Integration enables recruitment of participants for clinical studies and for individualized, adaptive monitoring and therapeutic approaches. Yet, translation of standardized diagnostic models to everyday clinical practice is still challenged by several difficulties, such as inter-assay variation between heterogeneous plasma platforms, the absence of complete international standardization of digital devices, and unanswered regulatory and validation dilemmas. For primary and community care, scalable plasma and digital biomarkers might be used as prescreening devices, thereby reducing the high costs of neuroimaging and enabling prospective clinical intervention at a shorter disease stage. At the clinical-trial level, multimodal prescreening approaches can reduce recruitment costs, expedite enrollment timelines, and enhance demographic diversity of study cohorts. At the health-system level, low-cost prescreening approaches can diminish economic burden while enhancing equitable access to evaluative diagnostic exploration for both high- and low-resource settings. Continued advances in wearable sensors and artificial intelligence will further expand the reach of biomarker-based monitoring, yet successful implementation will require investment in digital infrastructure, method standardization, and harmonized regulatory policies.

Despite rapid development, a number of challenges must be addressed before multimodal biomarker approaches are widely adopted for routine use in the clinical setting. Neuroimaging will continue to provide essential staging information despite its prohibitive cost and limited availability, which are current constraints for its universal adoption. Plasma biomarkers currently demonstrate the highest level of clinical readiness, but overarching large-scale harmonization of assays and convergent regulatory approaches must occur for routine adoption. Digital biomarkers, while highly scalable, remain the most investigational class. Device heterogeneity, scarce standardization, data protection concerns, and cultural variations continue to constrain their generalizability and regulatory approval.

Future research should emphasize large, multiethnic validation study cohorts across a variety of groups, globalization of assay harmonization, and regulatory framework development for digital endpoints. Real-world integration will also require the development of simplified clinical guidelines and reimbursement models to ease biomarkers' transition from

the research setting into everyday clinical practice. Of the three biomarker modalities, plasma biomarkers have by far the strongest evidence base for short-term clinical translation. Digital biomarkers, also derived from artificial intelligence and wearable sensor technologies, are investigational but extremely promising, assuming issues of privacy, interoperability, and data stewardship are appropriately managed. Together, these patterns indicate that plasma biomarkers are the most immediately translatable to clinical practice, neuroimaging will continue to serve as a foundation of disease confirmation and staging, and digital biomarkers have tremendous potential for changing continuous monitoring and patient engagement as soon as standardization, privacy, and equity concerns are appropriately overcome.

Acknowledgments

I would like to thank Dr. Bahaa Attaallah for all the support, mentorship, and guidance provided throughout my research journey.

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