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Clinical translation of fluid, imaging, and digital biomarkers for Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder, affecting millions worldwide. The clinical presentation of AD is heterogenous and often complicated by the presence of multiple co-pathologies, which can overlap with features of other neurodegenerative disorders, underscoring the need for tools to aid accurate and timely diagnosis. Biomarkers for AD span multiple modalities and are being increasingly used in clinical settings to aid diagnosis, monitor disease progression, and assess eligibility and response to disease-modifying therapies. Here, we provide an overview of current clinical applications of fluid, imaging, and digital biomarkers for AD. We also discuss biomarkers under development and challenges associated with the implementation of these modalities in clinical settings.

Keywords Alzheimer's disease, Fluid biomarkers, Neuroimaging, Digital biomarkers, Clinical implementation

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Background

Neurodegenerative diseases represent a significant global health challenge [1, 2]. Among these, Alzheimer's disease (AD) is the most prevalent, affecting millions worldwide [2, 3]. The most common initial clinical presentation of AD is progressive episodic memory impairment. However, symptoms can vary throughout the disease, affecting other cognitive processes, motor function, or behavior [4]. In clinical settings, AD diagnosis relies upon the detection of both clinical symptoms and pathological changes. However, a lengthy, preclinical stage of AD exists, where pathology is present in the absence of clinical symptoms. As such, parallel improvements in the detection of both clinical symptoms and pathologies represent a promising avenue for earlier diagnosis. Despite advances in understanding this disease, accurate and timely diagnosis remains challenging [5], particularly at early stages where clinical presentations overlap with other neurodegenerative diseases and definitive diagnostic tools are lacking [5]. This underscores the need for robust biomarkers to enhance diagnosis, monitor progression, and evaluate therapeutic efficacy [6].

Biomarkers are measurable indicators of biological processes or treatment responses [7] and serve diverse roles: identifying at-risk individuals; confirming clinical diagnosis; predicting disease progression and prognosis; and assessing treatment efficacy and safety, particularly of disease-modifying therapies (DMTs) [8]. As DMTs start to become approved for clinical use, biomarkers that stage disease severity and guide therapeutic decisions are essential for improving patient outcomes [9].

Biomarkers for AD span multiple modalities. Fluid biomarkers, derived from cerebrospinal fluid (CSF) and more recently blood, provide insights into pathobiological processes in vivo. While CSF biomarkers are considered gold-standard due to proximity to the central nervous system, their invasive collection limits widespread use [10]. Blood-based biomarkers (BBMs) are a less invasive, scalable, cost-effective alternative [11], with advances such as mass spectrometry (MS) and immunoassays improving their sensitivity and clinical reliability [12]. Imaging biomarkers, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), offer critical in vivo insights into brain structure, function, and pathology, with PET generally considered the gold standard against which fluid biomarkers are validated. Meanwhile, digital biomarkers, derived from wearable sensors, smartphone applications, and artificial intelligence (AI)-driven tools, may allow for passive and active continuous, real-world monitoring of cognitive, motor, and functional changes outside the clinic [13].

This review explores the clinical application of fluid, imaging, and digital biomarkers for AD. We evaluate biomarkers currently available to clinicians, examine those

under development, and highlight gaps yet to be targeted. By discussing their implementation, this review aims to shed light on their potential to advance early-stage screening, diagnosis and management, ultimately improving patient outcomes.

Fluid biomarkers

Key fluid biomarkers in Alzheimer's disease

Cerebrospinal fluid biomarkers

In AD, the most well-validated fluid biomarkers are derived from CSF [10]. First used in the 1990s to measure AD pathology in vivo, improved assay technology and standardization have significantly enhanced their utility [14, 15]. Current CSF biomarkers are crucial for differentiating AD from other dementias [16].

Key CSF biomarkers include amyloid-beta ($A\beta$), tau, and markers of neurodegeneration in clinical and research settings. $A\beta$ can be detected as $A\beta_{40}$, the most common isoform of $A\beta$, and $A\beta_{42}$, a fragment of the amyloid precursor protein [17]. Reduced CSF $A\beta_{42}$ levels indicate cortical $A\beta$ deposition in the brain, a hallmark of AD pathology. To increase diagnostic accuracy, CSF ratio $A\beta_{42}/40$ is used [18]. Tau protein, measured as total tau (t-tau) or specific phosphorylated isoforms (e.g., p-tau181, p-tau217, and p-tau231) [19], provides insights into AD-specific pathology [20]. Neurofilament light chain (NFL) is one of the most promising biomarkers for neurodegeneration; however, it is not specific to AD pathology and is elevated across other neurodegenerative diseases, including frontotemporal dementia (FTD) and amyotrophic lateral sclerosis [14].

Emerging CSF biomarkers under investigation for disease staging and prognostication include additional markers of tau pathology (p-tau205, microtubule binding region (MTBR)), astrocyte reactivity (glial fibrillary acid protein (GFAP)), synaptic dysfunction (neurogranin), and $A\beta$ metabolism (Beta-site Amyloid Precursor Protein Cleaving Enzyme 1 (BACE1)) [14, 19, 20]. Inflammatory markers, such as interleukins (IL-6, IL-12 and IL-10) [21] and chitinase 3-like (CHI3L1 or YKL-40), have also been explored, though findings remain inconsistent.

CSF biomarker quantification relies on a range of techniques with varying sensitivities and limitations. The enzyme-linked immunosorbent assay (ELISA) is a widely used, cost-effective technique for CSF biomarker quantification in clinical settings [22]; however, several limitations, including its singleplex capacity, moderate sensitivity, and the need for relatively high sample volumes [22] limit its scalability in clinical settings. Newer techniques, such as chemiluminescence and electrochemiluminescence (ECL), offer improved sensitivity and specificity compared to the ELISA and are increasingly used in clinical settings, despite higher costs [23]. The Ella instrument, a microfluidic immunoassay, is a

promising candidate for clinical implementation due to its automation, high sensitivity, single and multiplex capacity, and utilization of a small benchtop machine [22]. As techniques for fluid biomarker quantification continue to advance, it is critical to consider both their analytical performance and suitability for clinical implementation. Optimal methods should offer low turnaround times, high reproducibility, ease of use, and be easily integrated into existing clinical workflows.

Blood-based biomarkers (BBMs)

BBMs provide a minimally invasive, cost-effective approach for detecting and monitoring AD, enhancing accessibility for outpatient clinics and population-level screening [24]. While no single protein biomarker ensures a definitive diagnosis, multi-protein panels can potentially improve diagnostic accuracy and track disease progression [25]. BBMs hold promise as diagnostic tools for the early detection of AD in clinical settings [8, 26]. Their utility for monitoring and evaluating responses to disease modifying therapies is currently being explored in clinical trials [24].

The A β 42/40 ratio shows high diagnostic accuracy for detecting elevated cortical A β deposition [27, 28], although plasma reductions are significantly less pronounced than in CSF [29]. Importantly, the performance of this BBM varies by assay, with most A β -positive individuals exhibiting plasma levels close to the positive/negative cutoff, underscoring challenges in plasma-based A β detection [23, 26].

Plasma p-tau181 and p-tau217 are disease-specific biomarkers for AD, demonstrating high diagnostic accuracy in distinguishing AD from other neurodegenerative diseases [26]. Both p-tau181 and p-tau217 correlate with cortical A β and tau [30], although p-tau217 may offer increased accuracy [20]. Plasma p-tau231 has gained attention in recent years, as it correlates with imaging biomarkers and appears to increase in earlier disease stages [31].

Markers of neurodegeneration, such as NfL and t-tau, reflect neuroaxonal injury. NfL, though a robust marker of neurodegeneration, lacks specificity for AD as it is elevated in various neurodegenerative, infective, and inflammatory diseases, such as multiple sclerosis and amyotrophic lateral sclerosis [23, 26]. Neuroinflammatory markers, including triggering receptor expressed on myeloid cells 2 (TREM2), CHI3L1, and monocyte chemoattractive protein 1, indicate glial activation, a rapid response to A β pathology. These biomarkers hold potential for understanding the inflammatory processes driving disease progression.

Compared to CSF biomarkers, the quantification of BBMs requires highly sensitive techniques due to the lower concentrations of A β and p-tau in the periphery

[32]. Recently, the single molecule array (Simoa) technology was developed, significantly enhancing the detection of these low concentration proteins [33]. Additional techniques for measuring A β have also been developed, including immunoprecipitation-liquid chromatography-mass spectrometry and immunoprecipitation-matrix-assisted laser desorption/ionization [34, 35]. These mass spectrometry methods outperform the Simoa for quantification of A β [28]; however, the widespread implementation of these methods in clinical settings is limited by the high cost and low throughput. Emerging alternative AD biomarkers, such as dried plasma spots, enable remote measurements of biomarkers like p-tau181, p-tau217, and NfL [36, 37], and can be analyzed using full-automated platforms already available in clinical settings; however, further research is required to validate their diagnostic effectiveness.

Clinical translation and application of fluid biomarkers

Diagnostic utility and standardization

CSF biomarkers are well-established for diagnosing AD and are included in diagnostic criteria for mild cognitive impairment (MCI) due to AD and AD itself [38–40]. Three hybrid ratio biomarkers are available as in vitro diagnostics: Fujirebio Lumipulse G β -Amyloid Ratio (A β 42/40) [41], Roche Elecsys p-tau181/A β 42 ratio [42], and Roche Elecsys t-tau/A β 42 [43] (Table 1). These biomarkers detect brain A β deposition and are recommended within a broader diagnostic evaluation in clinical practice when AD is suspected [44]. A meta-analysis showed they improve diagnostic confidence and changes in patient management in 31% of cases [45]. However, their routine use remains limited due to the invasive nature of lumbar punctures and accessibility challenges.

BBMs have recently emerged as minimally invasive tools for diagnosing AD (Table 1). The Alzheimer's Association 2024 guidelines recommended BBMs demonstrating an accuracy of 90% be considered equivalent to CSF or PET scans for diagnosing AD [40]. Since then, BBMs have gained traction in specialty care settings as part of the AD diagnostic workup, with the Lumipulse p-tau217/A β 42 ratio recently becoming available as an in vitro diagnostic [46]. Several other BBMs are clinically available as laboratory-developed tests (LDT) or having received breakthrough device designations [47–50]. Precivity AD (C2N Diagnostics) was the first BBM available as a LDT, utilizing immunoprecipitation mass spectrometry (IP-MS) to quantify the A β 42/40 ratio and apolipoprotein E (APOE) proteotype [51]. Other notable LDTs include the Precivity AD2 test [52] and ALZPath p-tau217 kit [53]. The clinical availability, utility, and interpretation of these BBMs will evolve as more research becomes available. Currently, the A β 42/40 ratio, p-tau181

Table 1 Clinical use of Fluid, Imaging, and digital biomarkers

Biomarker Modality	Biomarker	FDA/EMA approved or LDT/RUO	Current Utility in Clinical Setting	Emerging Utility
Fluid Biomarkers				
CSF	A β 42/40 Ratio [80]	FDA/EMA approved	Diagnostic	-
	p-tau181/A β 42 Ratio [81]		Diagnostic	-
	t-tau/A β 42 Ratio [82]		Diagnostic	-
	NfL*	RUO	-	Prognostic
	Microtubule binding region		-	Prognostic
	CHI3L1 or YKL-40		-	Prognostic
	GFAP		-	Prognostic
	Neurogranin		-	Prognostic
	BACE1		-	Prognostic
	Plasma/Blood		p-tau217/A β 42 Ratio [46]	FDA/EMA approved
A β 42/40 ratio [83]		LDT	-	Diagnostic
A β 42/40 ratio + %p-tau217 [84]		-	-	Diagnostic
p-tau181 [49]		-	-	Diagnostic
p-tau217 [50]		-	-	Diagnostic/Prognostic
NfL*		-	-	Prognostic
Imaging Biomarkers				
MRI	Atrophy	FDA/EMA approved	Diagnostic/Prognostic	-
PET	A β -PET ([¹⁸ F]-flutemetamol, [¹⁸ F]-florbetapir, [¹⁸ F]-florbetaben)	-	Diagnostic/Prognostic	-
	Tau-PET ([¹⁸ F]-flortaucipir)	-	Diagnostic/Prognostic	-
	FDG-PET	-	Diagnostic/Prognostic	-
	SV2A-PET	RUO	-	Prognostic
DWI	WM changes	RUO	-	Prognostic
Digital Biomarkers				
Watch/Wristband	Gait and movement	RUO	-	Early detection
Smartphone/Tablet	Classical cognitive concepts/functions	-	-	Screening and diagnosis
	Speech and language patterns	-	-	Early detection
	Gait and movement	-	-	Early detection
Handheld/Fixed	Classical cognitive concepts/functions	-	-	Early detection
Microphone	Speech and language patterns	-	-	Early detection

Note. CSF NfL and plasma NfL (LDT) are used for prognostic purposes in some specialized clinics in the US and UK, supported by validated protocols and growing clinical evidence, despite lacking FDA/EMA approval

Abbreviations: A β , Amyloid-beta; BACE1, Beta-site amyloid precursor protein cleaving enzyme 1; CHI3L1 or YKL-40, Chitinase 3-like; CSF, Cerebrospinal fluid; DWI, Diffusion weighted imaging; EMA, European Medicines Agency; FDA, Food and Drug Administration; GFAP, Glial fibrillary acidic protein; LDT, Laboratory developed test; MRI, Magnetic resonance imaging; NfL, Neurofilament light chain; PET, Positron emission tomography; p-tau, phosphorylated tau; RUO, Research use only; SV2A, Synaptic vesicle protein 2a; t-tau, total tau; WM, White matter

and p-tau217 are increasingly used to detect elevated A β -levels [54], though the interpretation of A β 42/40 ratio benefits from being paired with additional measures [55]. Negative plasma p-tau181 or p-tau217 results are indicative of a low likelihood of cognitive decline resulting from AD, whereas positive p-tau181 or p-tau217 results warrant further evaluations with AD biomarkers (i.e., CSF or PET) [54].

Predictive value and prognostic significance

CSF A β 42/40, p-tau181/A β 42, and t-tau/A β 42 ratios are predictive of conversion to AD and facilitate early diagnosis [56, 57]. These biomarkers remain highly reliable for staging and tracking AD pathology, particularly in research settings.

In research settings, plasma p-tau181 and p-tau217 are predictive of conversion to AD in cognitively unimpaired (CU) participants and those with MCI [58, 59]. Further, p-tau217 has demonstrated dynamic longitudinal trajectories, highlighting its potential efficacy for disease staging and predicting disease progression [53, 60]. While the positive predictive value (PPV) of p-tau181 and p-tau217 remains limited, particularly among CU participants, their negative predictive value (NPV) is generally high [53, 59, 61, 62], supporting their use as tools to rule out AD pathology as a potential cause of cognitive decline. NfL is a nonspecific biomarker increased across multiple neurodegenerative diseases and should not be used alone to diagnose AD [63, 64]. However, NfL correlates more strongly with cognitive symptoms and cortical atrophy

than plasma A β or p-tau [65–67] and enhances predictions of cognitive decline when used in combination with other biomarkers and cognitive examinations [68].

Monitoring disease progression and treatment efficacy

BBMs are playing a growing role in clinical trials for DMTs for AD, where they are being used to enrich trial populations by identifying A β -positive individuals prior to enrollment, thereby reducing the number of CSF or PET tests needed. For example BBMs are being incorporated as preliminary screening tools to identify participants who should undergo further testing (i.e., CSF or PET), to confirm their biomarker status [69]. Clinical trials of AD DMTs are also including BBMs as outcome measures to evaluate the pharmacodynamic effects of DMTs [20].

Challenges translating BBMs into the clinic

Before the widespread implementation of BBMs in clinical practice, a number of considerations must be addressed. For an in-depth discussion of these considerations, the authors refer the readers to Mielke et al. (2024) [70]. Briefly, much of the research on BBMs has been conducted in samples recruited from specialty care settings or academic research centers. These populations tend to consist of individuals who are more likely to be White, be of higher socioeconomic status, have fewer comorbidities, and are, on average, younger than typical patients seeking care for cognitive concerns. Thus, to support the widespread implementation of BBMs in clinical practice, further studies are needed to validate these biomarkers in more diverse, representative cohorts, considering the effects of age, sex, race/ethnicity, and socioeconomic status [71]. In addition, it will be critical to evaluate the diagnostic performance (i.e., sensitivity and specificity) of each BBM among these diverse cohorts and across a range of clinical settings.

Moreover, the effect of various chronic conditions on BBMs will need to be better characterized prior to their widespread clinical implementation. For example, chronic kidney disease has been shown to affect levels of A β 40, A β 42, p-tau181, p-tau217, and NFL in the blood, which could lead to erroneous interpretations of these biomarkers [72–74]. Cardiovascular comorbidities, including diabetes, hypertension, dyslipidemia, heart disease, and stroke have also been shown to affect levels of A β 40, A β 42, p-tau181, p-tau217, and NFL [72, 75, 76]. Additionally, the effect of medications for chronic conditions will need to be characterized prior to their implementation, as it has been reported that medication combining sacubitril/valsartan, a medication used to manage chronic heart failure, affects A β 42/40 ratios [77].

Standardization is also essential for the implementation of BBMs in clinical practice. Variability in

pre-analytical and analytical procedures can lead to differences in the levels of BBMs across batches and laboratories. For example, pre-analytical factors, such as sample collection, transport, and storage, have been shown to affect levels of A β 42, A β 40, A β 42/40 ratio, p-tau181, and GFAP [78]. Implementing standardized operating procedures, such as the one developed by the Standardization of Alzheimer's Blood Biomarkers working group and the Global Biomarker Standardization Consortium [79], and rigorous internal and external quality control procedures are essential to standardize measurements of BBMs. Together, these efforts will enhance the comparison and validation of BBMs across different laboratories and studies.

Longitudinal prospective studies, such as REAL AD, are being conducted to validate the diagnostic and prognostic utility of BBMs for AD in the general population [71]. While prior research has highlighted the potential value of BBMs, studies such as REAL AD provide the opportunity to replicate these findings in more diverse populations and examine phenotypic differences, particularly in relation to factors that influence the onset and progression of clinical symptoms, such as age and *APOE* genotype [19]. The results from these studies will inform our understanding of the capabilities and limitations of BBMs at the population level, ultimately facilitating a more widespread implementation of these biomarkers in clinical settings. Furthermore, while BBMs are more accessible and cost-effective compared to CSF biomarkers, their reliance on centralized locations for the collection, storage, and analysis of samples will continue to limit the populations in which BBMs will be available. However, emerging tests, such as ones that utilize dried plasma spots [36], could eliminate these barriers, significantly improving the accessibility of biomarker testing.

Imaging biomarkers

Key imaging biomarkers in neurodegenerative diseases

Imaging biomarkers

Structural magnetic resonance imaging (sMRI) is a widely used imaging modality in AD research and practice [85], detecting atrophy, gray and white matter loss, and cortical thinning [86]. Key biomarkers, including medial temporal lobe atrophy (e.g., hippocampus and entorhinal cortex) and white matter hyperintensities are associated with cognitive decline and AD progression [87–89]. Beyond biomarker detection, MRI is routinely recommended in clinical guidelines (e.g., NICE) as a critical step in excluding alternative pathologies—such as tumors or vascular lesions—before confirming an AD diagnosis. MRI also aids differential dementia diagnosis by revealing distinct atrophy and cortical thinning patterns [90–92], supporting the characterization of phenotypic variants and their neurobiological underpinnings.

As neuroimaging captures structural and functional deviations across brain systems, it offers a powerful framework for linking clinical heterogeneity to underlying circuit-level dysfunction. In clinical trials, MRI supports participant selection and safety monitoring by identifying amyloid-related imaging abnormalities (ARIA) [93–95].

High-resolution imaging, such as 7 Tesla (T) MRI, has enhanced hippocampal subregional volume quantification and the assessment of perivascular spaces in AD [96, 97]. Although its higher accuracy comes with limitations like high installation costs and specialized training [98], it shows potential for advancing AD biomarkers. In contrast, portable MRIs, though limited by lower field strength, are being explored for applications like treatment monitoring and improving accessibility in remote areas [99–104]. Rapid structural imaging techniques have been developed to reduce scan times while maintaining comparable image quality [105]. These advancements may enhance the accessibility and tolerability of MRI and

are currently under investigation for applications such as treatment monitoring [106].

Quantitative MRI techniques, including T1-, T2-, and T2*-relaxation times, diffusion-weighted imaging and quantitative susceptibility mapping (QSM), provide advanced measures of neurodegeneration and biomarkers like iron accumulation linked to A β deposition [107–116].

A β -PET imaging enables visualization and quantification of A β plaques, supporting AD diagnosis [117] (Fig. 1). Increased binding is observed in temporal, parietal, and frontal lobes in AD, and alongside tauopathy and neurodegeneration, is associated with cognitive deterioration [86, 118, 119]. Clinically approved tracers include [¹⁸F]-flutemetamol, [¹⁸F]-florbetapir (AV45), and [¹⁸F]-florbetaben (FBB), while Pittsburgh compound B (PiB) and [¹⁸F]-flutafuranol (NAV4694) are used in research [117, 120–122].

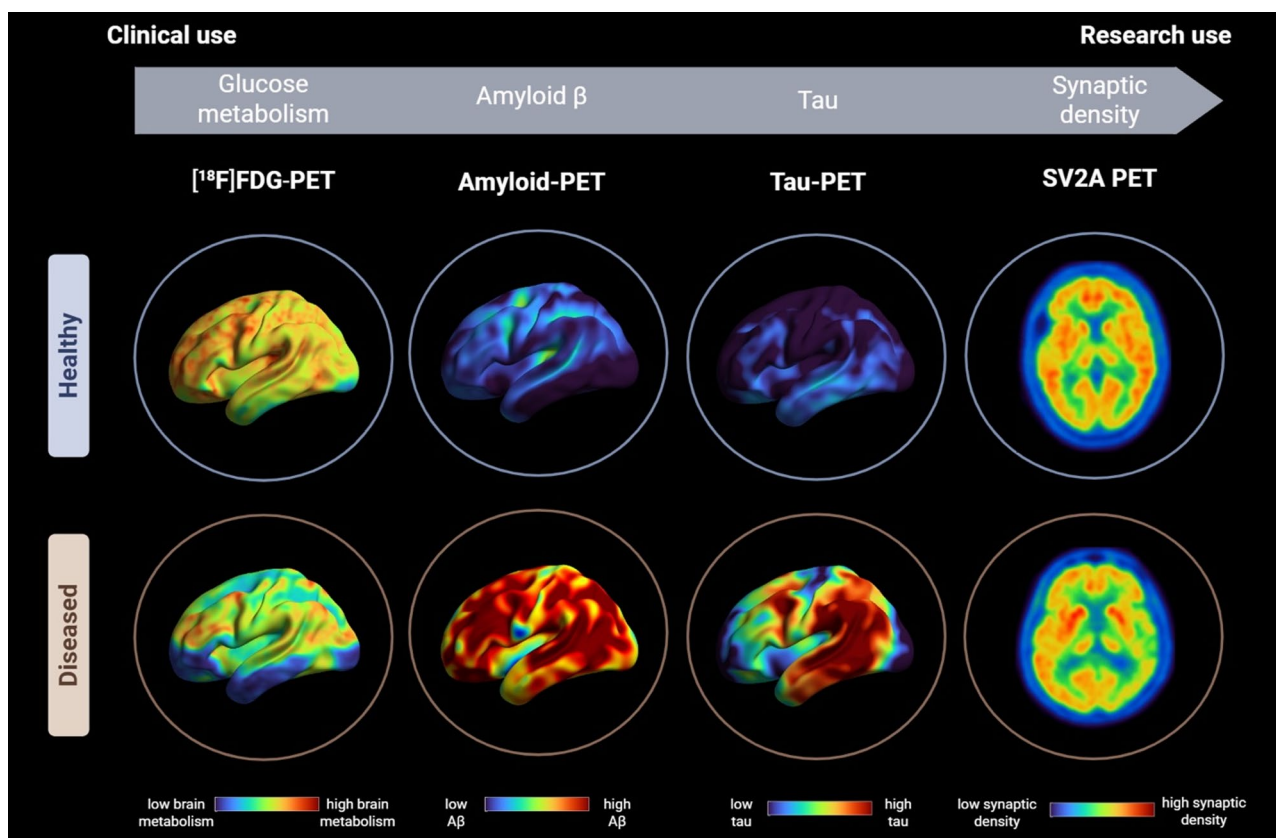


Fig. 1 PET neuroimaging across multiple modalities in healthy and disease-associated brain patterns. The top row (blue circles) displays representative images from individuals with healthy brain patterns, and the bottom row (orange circles) shows cases with abnormal findings. Imaging modalities are arranged from left to right, progressing from those most commonly used in clinical practice to those primarily applied in research. Modalities include [¹⁸F]-FDG-PET for glucose metabolism, [¹⁸F]-AV45 PET (florbetapir) for amyloid deposition, [¹⁸F]-AV1451 PET (flortaucipir) for tau pathology, and [¹¹C]-UCB-J PET for synaptic density (SV2A). FDG-, amyloid-, and tau-PET images are shown as 3D-surface projections of the left hemisphere, while SV2A PET images are displayed as axial slices (caudal aspect, frontal at the top). FDG-, amyloid-, and tau-PET data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and subsequently analysed; SV2A-PET images were provided by Prof. Matthias Brendel (LMU Munich, Germany), illustrating a pattern observed in primary progressive aphasia. All images are included solely for illustrative purposes and were not subjected to any additional analysis within this work

Quantitative scales such as the Centiloid (CL) [123–125] standardize A β -PET measures across tracers and centers [126–128], with thresholds of 24–30 CL indicating A β -positivity [129]. Semi-quantitative methods such as standardized uptake value ratio (SUVR) are commonly used, despite being sensitive to tracer dynamics and instrumentation. The growing demand for precise A β -PET quantification, driven by A β -removing therapies, highlights its role in identifying candidates and monitoring treatment efficacy. Despite its limitations, the CL scale has proven valuable in supporting visual assessments in clinical and research settings [130–132]. A β -PET has been a central tool in DMT trials [133, 134].

Tau-PET, using the FDA/EMA-approved tracer [^{18}F]-florotau (TAUVID[™]), is the only clinical biomarker for in vivo detection of neurofibrillary tau tangles in symptomatic individuals (Braak V-VI) [135–137] (Fig. 1). Other Tau-PET tracers, including [^{18}F]-MK-6240 and [^{18}F]-PI-2620, have demonstrated greater selectivity for tau tangles and have received Fast Track Designations from the FDA [138–141]. Tau-PET is more closely associated with cognitive changes in AD than A β -PET [142–145], making it a valuable tool for clinical trials, diagnosis, and disease monitoring [126, 133, 144, 146–148]. However, high costs and limited availability and reimbursement by most health systems or insurances currently restrict its routine clinical use.

Tau-PET quantification faces challenges due to variability in tau aggregation, tracer differences, and complex dynamics [149–151]. Current methods often target regions with high tau uptake, risking oversight of spatial variability [152]. Standardized efforts like the Cent-TauR scale aim to improve consistency but may overlook early-stage or spatially diverse regional tau accumulation detectable by the FDA/EMA-approved visual method [152–155].

[^{18}F]fluorodeoxyglucose (FDG)-PET assesses brain glucose metabolism, with hypometabolism in temporoparietal and posterior cingulate regions [156, 157] indicating AD-related neuronal dysfunction and faster cognitive decline (Fig. 1). FDG-PET is widely available in clinical practice and is particularly valuable for predicting MCI-to-AD conversion [158]. It also aids in distinguishing AD from other dementias [159] and monitoring disease progression [160, 161].

Clinical translation and applications of cross-sectional imaging biomarkers

Diagnostic utility and standardization

sMRI helps exclude other causes of cognitive decline, assess comorbidities like vascular lesions [162], and detect progressive atrophy indicative of neuronal loss [163]. Recommended as a first diagnostic step [162], sMRI has high sensitivity [164], while computed

tomography (CT) offers quicker results [165]. MRI is preferred for prognosis and therapy monitoring.

A β - and FDG-PET show high sensitivity and specificity for AD and other dementias [166], altering diagnoses in 30–44% of cases [167, 168] and management in ~60% [167, 169]. FDG-PET enhances diagnostic accuracy, especially in AD and FTD, though it performs better in dementia than MCI [170]. Tau-PET helps differentiate AD from other diseases and supports clinical decisions, as individuals with low tau levels respond better to anti-amyloid therapies [171, 172].

The growing recognition of phenotypic diversity in neurodegenerative disorders—reflected in new diagnostic frameworks that emphasize variant presentations—further underscores the value of imaging biomarkers. Tools like PET and MRI help capture distinct biological signatures that align with clinical subtypes, enabling more personalized diagnostic pathways.

Because of their temporal biomarker sequence, A β -PET, followed by tau-PET, can predict early abnormalities, whereas FDG-PET and volumetric MRI (vMRI) abnormalities appear closer to the prodromal stage [40, 163]. However, A β load is affected by age and *APOE* genotype even in individuals without dementia, and it can accumulate in the brain decades before symptom onset [173, 174]. Although challenging to interpret, an A β -negative PET scan effectively rules out AD [136] whereas A β -positive results place the individual on the AD continuum, even if amyloid might not be the major etiology underlying symptoms [175]. Moreover, A β -positivity can be a deciding factor in early-onset dementia [162].

A β - and tau-PET have been highlighted in the updated diagnostic guidelines, requiring biomarker abnormality of both for an in vivo AD diagnosis [40]. In essence, combining A β -PET with a topographic biomarker (e.g., tau-PET) can improve specificity [176, 177] but often poses significant limitations.

Predictive value and prognostic significance

Hippocampal atrophy measured by sMRI correlates with clinical decline and is a prognostic biomarker for disease progression [178–180]. However, MRI alone appears insufficient to predict the MCI-to-dementia conversion [181].

A β -PET offers higher predictive accuracy than sMRI [182], but has limitations. Elevated A β -levels are found in 30% of CU elderly individuals, do not correlate with symptom severity, and plateau in later disease stages [162, 182]. These challenges can be mitigated by using CL scale quantification [132, 183] or by combining A β -PET with FDG-PET, which enhances predictive value [184].

FDG-PET outperforms clinical measurements for MCI and AD prognosis [185], early hypometabolism in the left posterior cingulate cortex and precuneus predicting

conversion to AD [186]. However, its predictive accuracy remains inconsistent [187, 188]. Recent approaches combining FDG-PET with MRI have shown promise, but require refinement [189], particularly through AI-driven advancements [190].

Tau-PET correlates more strongly with symptom severity and hypometabolism than A β -PET [191–193]. Tau accumulation often precedes cognitive symptoms [194], with its spread coinciding with A β deposition and cognitive decline [195, 196], making it highly effective for staging disease severity and predicting progression in early stages [147]. In essence, PET-based staging accommodates heterogeneous disease patterns, enabling personalized treatment approaches [197], while combined with A β -PET enhances predictions of cognitive decline in preclinical AD [198].

Monitoring disease progression and treatment efficacy

The A β cascade hypothesis has guided AD research and the development of amyloid-targeting immunotherapies [199, 200], though their clinical efficacy remains mixed [126, 201], often showing modest cognitive improvements compared to conventional therapies [202]. Safety concerns, particularly ARIA, necessitate cautious evaluation using A β -PET [203]. The recent FDA/EMA-approved monoclonal antibody lecanemab has increased demand for regular MRI scans, particularly in patients with early-stage AD who may benefit most from DMTs [204].

Advanced imaging, especially FDG-PET, is crucial for assessing AD therapies, as it has alternatively been proposed [205]. While A β -PET raises concerns about non-specificity, with A β tracers accumulating in inflammatory areas and producing signals unrelated to A β pathology [206–210], FDG-PET provides critical insights into cerebral metabolism and neuronal function [211], potentially better reflecting cognitive benefits [212]. MRI complements this by monitoring ARIA and brain volume changes, which are critical for patient safety and understanding therapeutic impact [205].

Recent findings suggest that accelerated volume loss following A β clearance may represent “amyloid-removal related pseudo-atrophy” (ARPA), where reduced cortical volume reflects plaque clearance rather than neurodegeneration [213, 214]. This does not correlate with neurodegenerative markers like tau, indicating a potentially protective effect, with preserved hippocampal volume suggesting potential benefits [213].

The EMERGE and ENGAGE trials of aducanumab showcased the complexities of linking clinical outcomes to biomarker changes, with EMERGE indicating significant clinical benefits in slowing decline [215]. However, both trials highlighted ARIA as a common adverse event, underscoring the necessity for periodic imaging

assessments, while utilizing statistical region-of-interest (sROI) analyses could improve detection of treatment effects with smaller sample sizes [216].

Imaging challenges

Despite significant advancements, the clinical implementation of advanced imaging technologies remains challenging. High costs, lengthy protocols, and limited accessibility are major barriers, particularly in resource-constrained settings [217]. To address these, government subsidies must implement cost-effective alternatives like portable devices [218], ultra-fast PET sequences, and expanded insurance coverage are essential to make these technologies more accessible [162].

Standardization is another critical challenge. Variability in imaging protocols, acquisition parameters, and analysis methods leads to inconsistent results across institutions. PET imaging, particularly tau-PET, faces additional hurdles in achieving robust quantification [150, 152] and defining clinically meaningful cut points. Unified protocols are vital for improving reproducibility and clinical utility. On the other hand, biomarker specificity remains a concern. Improved PET tracers, fluid biomarkers integration, and the AI applications, such as FDG-PET [219] or MRI-based models [220], can enhance the accuracy and disease state differentiation.

Emerging PET modalities, including tau-PET, synaptic vesicle protein 2a (SV2A)-PET, and neuroinflammation-targeting tracers such as translocator protein (TSPO)-PET, show promise for capturing molecular aspects of AD beyond A β but face issues like off-target binding [221, 222] and limited validation [223] (Fig. 1). TSPO-PET, in particular, enables *in vivo* assessment of glial activation—a hallmark of early and sustained neuroinflammatory responses—although challenges such as genetic variability in TSPO affinity limit clinical validation. Increased research funding and global collaboration are essential for overcoming these challenges and enabling application across diverse populations.

Magnetoencephalography (MEG) is also gaining attention for its capacity to capture millisecond-level neuronal dynamics, offering insight into large-scale brain network activity and functional disconnection in AD. By measuring real-time circuit activity, MEG complements structural and molecular imaging and may help bridge the gap between observed cognitive symptoms and disrupted connectivity patterns. Lastly, a shortage of trained professionals limits the effective use of advanced imaging. Expanding education and training programs, alongside telemedicine platforms for remote consultations, can help bridge this gap.

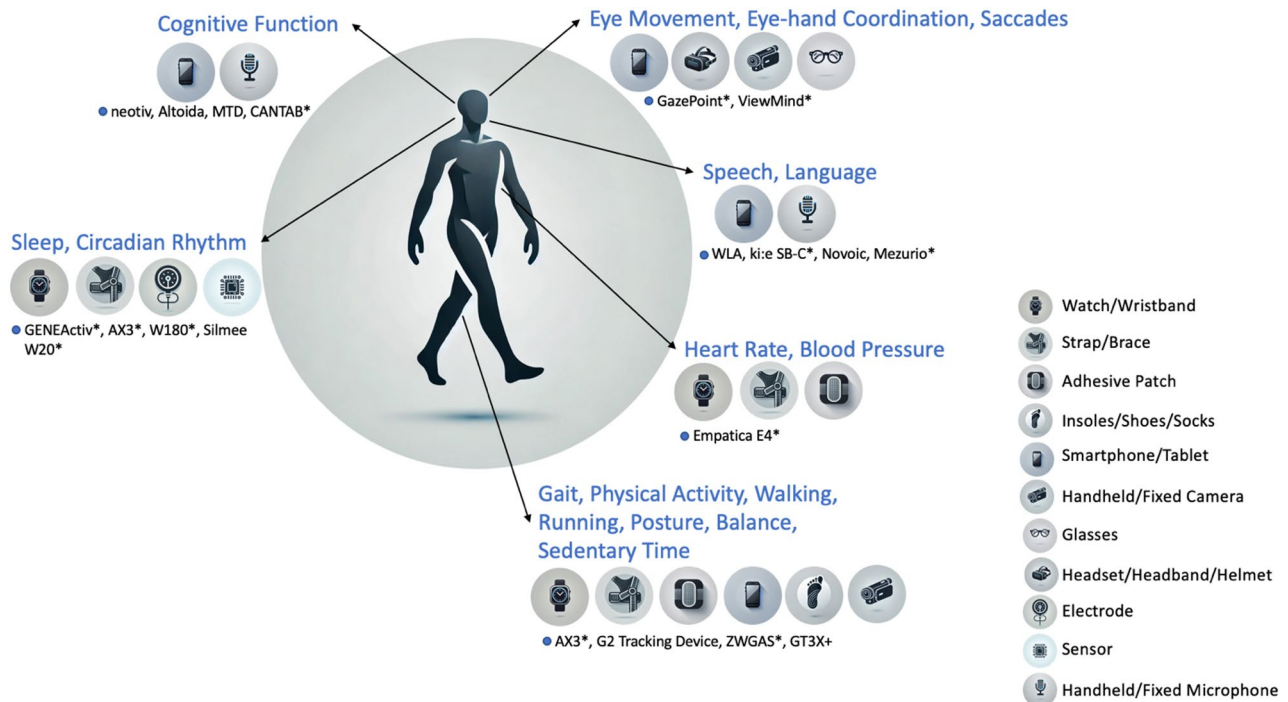


Fig. 2 Non-exhaustive overview of types of digital tools and concepts measured. Per health concept, most common measurement methods and technology types are shown, as well as indicative examples of validated tools. MTD: Mayo Test Drive; CANTAB: Cambridge Neuropsychological Test Automated Battery; GENEActive: Wristband manufactured by Activinsights, UK; AX3: Wearables manufactured by Axivity; W180: Wristwatch manufactured by Shenzhen Fitfaith Technology Co., Ltd.; Silmee W20: Wristband sensor manufactured by TDK Corporation; WLA: Winterlight Assessment by Winterlight Labs/Cambridge Cognition; ki: e SB-C: Speech-based biomarker by ki: elements; Mezurio: Smartphone-based assessment by Digital Phenotyping Laboratory, Oxford University Big Data Institute; G2 Tracking Device: GPS data logger manufactured by Azuga Inc, CA; ZWGAS: Zeno Walkway Gait Analysis System manufactured by Protokinetics; GT3X+: Accelerometer manufactured by ActiGraph. The figure was originally created by the authors using a combination of AI-assisted design (ChatGPT's image generation capabilities) and manual editing in PowerPoint. *Tools currently undergoing validation in preclinical AD [226]

Digital biomarkers

Key digital biomarkers in neurodegenerative diseases

The ongoing technological advancements and health-care digitalization [224] have led to the development of “digital biomarkers,” which can be collected either within-clinic or remotely, with or without supervision, and can involve both active and/or passive data collection. Digital assessments capture a wide variety of measures, including cognition, behavior and functionality (Fig. 2). Despite variability in definitions, digital biomarkers share three key elements: (a) they are objective, physiological and/or behavioral measures; (b) they are collected and measured via digital tools; and (c) they aim to detect or capture, predict and/or influence health-related outcomes [225].

Digital data collection provides numerous advantages, enhancing the sensitivity of gold-standard biomarkers for screening and monitoring across neurodegenerative diseases [227]. Automated assessments enable cost-effective, time-efficient, and frequent data collection, improving both sensitivity and reliability. Advanced tools capture fine-grained information alongside conventional metrics, enabling timely detection of changes in cognition, behavior, and function, especially at early stages [226, 228, 229].

Additionally, passive data collection in natural environments boosts ecological validity, although it is important to take into consideration privacy and ethical issues raised.

Gait and movement

Gait disturbances are sensitive, non-invasive biomarkers for early detection and monitoring of neurodegenerative diseases [230, 231], serving as a surrogate for underlying motor, cognitive, and spatial orientation impairments linked to affected brain networks [232]. Gait measures like speed, rhythm, and variability can distinguish asymptomatic individuals at-risk for dementia from healthy controls and predict clinical symptom onset with moderate to high accuracy [233–242]. Specific measures like gait asymmetry, truncal mobility, and balance are useful in identifying Lewy body dementia (LBD), while pace impairments appear more severe in vascular dementia compared to AD or FTD [233, 243–246].

Cognition

Numerous digital tools have been developed to assess traditional neuropsychological cognitive constructs

such as (working) memory, processing speed and executive functioning. Particularly for preclinical AD, these have already demonstrated adequate construct and criterion validity. Specifically, significant associations are observed between the digital assessments and global cognitive measures (i.e., PACC5, MMSE) [247–250], as well as domain-specific neuropsychological tests [251–253]. More importantly, cognition, as captured by digital assessments, has been associated with imaging and gold-standard A β and tau biomarkers related to AD pathology [254–256]. Digital tests are administered either in a supervised setting or remotely, utilizing computers, smartphones, or tablets, and can be conducted on personal or provided devices [257]. Digital assessments have also paved the way toward high-frequency burst designs of cognitive testing enhancing sensitivity to intra-individual variability and refining cognitive profiling [248, 258, 259].

Speech and language patterns

Speech production is a highly complex human function integrating cognitive and linguistic planning, motor control and execution, making it susceptible to underlying pathogenic processes. Therefore, speech-based biomarkers offer a novel promising approach for detecting early cognitive decline in neurodegenerative diseases. Speech-based assessments incorporate tasks within a spectrum from low cognitive load (i.e., free speech) to high (i.e., story recall) and from very constrained (i.e., word list learning) to free speech [260]. Novel methods of speech analysis, including automatic speech recognition and feature extraction technologies, can then capture fine-grained features reflecting underlying pathology [261, 262].

AD specifically and MCI present a distinct speech profile reflected both by what is said (linguistic features) and how it is said (acoustic features). Linguistically, word finding difficulties are a core characteristic [263, 264] along with simplified syntax [265] and reduced grammatical complexity [266]. Altered acoustic features are also observed, including temporal features such as the number and duration of pauses [267], energy features (i.e., jitter or shimmer) as well as lower frequency modulations [262, 268] even at preclinical stages. Recently studies have also associated speech-based features and A β biomarkers, further validating their sensitivity [269, 270].

Data collection and analysis

Use of sensors, apps, and online platforms

Digitization of cognitive tests in neurodegenerative diseases simplifies data collection compared to classical paper-and-pencil tests. Web- and app-based platforms on computers, tablets, and smartphones offer integrated data collection and automatic scoring [271]. Eye

movement can be tracked via eye-tracking cameras or the same devices for memory tests [272], while speech data is captured through microphones during free speech or speech-based cognitive assessments [273] (Fig. 2).

Gait and movement are captured by wearable sensors and devices like smartphone applications and research-grade technologies [230], balancing usability and data quality. Multi-sensor systems offer high accuracy but are cumbersome for real-world deployment, while smartphone-based solutions show promising scalability but lack validation against gold-standard tools. Challenges remain in standardizing gait metrics across neurodegenerative diseases and validating tools for clinical use. Expanding research into passive monitoring and scalable technologies is crucial to establish gait analysis as a biomarker for early detection, differential diagnosis, and disease progression.

Data integration and interpretation using AI and machine learning

The rise of digital health technologies has accelerated data generation, necessitating advanced tools for integrating and processing diverse datasets. Centralized cloud-based repositories such those proposed by the National Neuropsychological Network [274], enable seamless data transfer, collaboration, and large-scale innovations, data mining, deep learning analytics, and algorithm development for automating performance validity assessments [275]. Complex datasets require advanced preprocessing and statistical methods. Machine learning [260, 276, 277] and deep learning models [278], combined with traditional statistical methods [279], enhance fine-grained feature extraction from raw digital data, detection accuracy and refine assessments based on cognitive phenotypes and bioinformatics.

Clinical translation and applications of digital biomarkers

Diagnostic utility and standardization

Digital biomarkers have emerged as promising tools for the earlier detection of AD, particularly in preclinical stages. Although not yet widely implemented in clinical settings, these biomarkers have demonstrated high feasibility and scalability in large-scale community-based studies. Digital cognitive tests can be self-initiated by asymptomatic individuals at-risk for AD (e.g., APOE4 carriers), by those with cognitive concerns, or by healthcare providers as part of an AD diagnostic evaluation. Additionally, web-based pre-screening can enhance community engagement by identifying at-risk patients often missing in traditional memory clinics [280]. Digital biomarkers hold promise for improving early detection and diagnosis of AD in both supervised and remote, unsupervised settings.

Digital measures offer the advantage of capturing fine-grained, real-life changes in cognition, behavior, and function that are often overlooked in traditional clinic-based testing. Continuous, ecologically valid monitoring in naturalistic environments may enable earlier detection of functional changes or impairment, particularly in individuals with preclinical AD. For example, ongoing validation studies of unsupervised digital cognitive tests with BBMs for AD diagnosis in real-world clinical settings aim to refine their screening and diagnostic utility [71].

The concept of a “Digitized Memory Clinic” [281] recently highlighted that certain digital health technologies are already at the implementation stage (e.g., digital cognitive testing, digital decision support tools). The authors described how the traditional “brick-and-mortar” memory clinic can be enhanced with the introduction of digital health technologies. More sensitive digital assessment methods can help identify patients at the earliest stages (i.e., subjective memory complaints or with preclinical risk factors), enhancing preventative and detection efforts. As the complexity and number of digital technologies grow, the Digital Medicine Society (DiMe) has compiled an extensive list of validated tools that capture clinically meaningful constructs and can be applied in clinical trials and research [282].

Predictive value and prognostic significance

Digital biomarkers offer a unique opportunity to refine phenotypic characterization, even in CU individuals. For example, differences between $A\beta^-$ and $A\beta^+$ groups have been found based on subtle characteristics such as acoustic speech features, learning curves and a combination of physiological parameters [250, 269, 283]. Ultimately, when incorporated into frameworks, such as the “Digitized Memory Clinic”, digital biomarkers may facilitate individualized prognostication.

Monitoring disease progression and treatment efficacy

Major pharmaceutical companies have incorporated digital assessments in studies evaluating their feasibility, validity and sensitivity [284–286], particularly for cost-effective pre-screening before invasive procedures [257]. Digital biomarkers can be also used for cognitive and functional monitoring of MCI and symptomatic AD patients. This continuous monitoring can be used to improve the tracking of disease progression and evaluate an individual’s response to treatment.

Challenges translating digital biomarkers into the clinic

Before digital biomarkers are widely implemented in clinical practice, there are several challenges that must be addressed, including regulatory approval, validation, and standardization. Regulatory considerations for digital biomarkers align with those for other digital health

technologies, emphasizing effectiveness and economic impact [287]. Major regulatory bodies such as the FDA (USA), the EMA (EU), and the MHRA (UK) have published relevant documents outlining important guidelines on the regulatory aspects of digital health technologies.

To ensure proper standardization, DiMe has established the V3 framework for the evaluation of digital health technologies for their fit-of-use in clinical trials [288]. The framework outlines three steps: verification, analytical validation, and clinical validation. Verification assesses whether sensors accurately capture data and generate appropriate outputs. Analytical validation evaluates whether the tool reliably measures cognitive or behavioral function. Clinical validation evaluates the utility of the digital biomarker in the intended population and context-of-use.

Prior to widespread implementation in clinical settings, digital biomarkers must demonstrate high validity and reliability for the assessment of the intended cognitive or behavioral functions (e.g., memory). For the monitoring of disease progression and treatment efficacy, it is critical that digital biomarkers demonstrate test-retest reliability and sensitivity to longitudinal changes. Importantly, these metrics must be demonstrated within the relevant target population. Further, the implementation of digital biomarkers in clinical settings is reliant upon the interpretability and actionability of the data. This requires the summarization of data in clear, accessible readouts that are accompanied by educational resources that promote the understanding and effective application of the results in both healthcare provider and patient populations.

Future directions

Evolving diagnostic frameworks in AD

Historically, a definitive diagnosis of AD could only be made postmortem based on neuropathological evidence of $A\beta$ plaques and neurofibrillary tau tangles. During this period, clinical diagnoses were limited to probable or possible AD, based on clinical symptoms and medical histories. The development of CSF and PET biomarkers enabled the in vivo assessment of AD pathologies, facilitating the development of a clinico-biological diagnostic framework that incorporates both clinical symptoms and biomarker evidence [289].

More recently, The Alzheimer’s Association published revised criteria for the diagnosis and staging of AD that distinguishes between clinico-biological and biological diagnoses [40]. This shift reflects the growing recognition that AD pathologies can begin accumulating decades prior to the onset of clinical symptoms. As such, there is an increasing emphasis on identifying individuals in the preclinical stage of AD for earlier intervention.

Within this evolving diagnostic framework, BBMs are increasingly being recognized as tools that can detect the

presence of AD pathology. The accessibility and scalability of these biomarkers can support the wider application of biological diagnosis of AD in research settings, and the clinico-biological diagnosis of AD in clinical settings, thus enhancing earlier detection and monitoring of AD across both participant and patient populations. In parallel, digital biomarkers are increasingly recognized as clinical or functional measures that can enhance preventative and detection efforts for AD. Emerging evidence supports an association between digital biomarkers and A β biomarkers, highlighting the potential of digital biomarkers for the screening and detection of individuals who may be eligible for further biomarker testing (i.e., fluid or imaging) to support a clinico-biological or biological diagnosis.

Together, these biomarkers are contributing to the most recent shift in the AD diagnostic framework, where an increasing emphasis is being placed on earlier detection and intervention. While current diagnostic pathways still primarily rely upon traditional biomarkers (i.e., CSF and neuroimaging), emerging evidence supports an association between digital biomarkers and AD pathologies, even among CU older adults. In the future, combining different biomarker modalities, such as BBM and digital biomarkers, in the AD diagnostic pathway could significantly expand the accessibility of early AD detection.

Combining fluid, imaging, and digital biomarkers

As we move towards a personalized patient centered approach in routine clinical practice, different biomarker modalities will need to be combined, synthesized, and presented in a meaningful way to the individual. Even after all these outstanding technological advancements in AD biomarkers research, an 'elevated p-tau217' result in isolation doesn't really provide meaningful information to the patient and their family. Moving forward, personalized approaches will require more than just the detection of pathologies; it will depend on subtyping, specifying pathological pathways, and contextual interpretations that account for symptom heterogeneity and multiple comorbidities, such as hypertension, diabetes, and depression that frequently accompany AD [290, 291].

Moreover, the pathophysiology of AD is impacted by a combination of polygenic, epigenetic, and environmental influences that can exacerbate or mitigate these pathological accumulations. As such, a shift towards more patient-oriented strategies in the clinic requires the use of clinically meaningful cut-points and intermediate zones that reflect uncertainty and consider individual differences. Algorithms could be used to classify participants based on biomarkers, clinical symptoms, risk factors, and comorbidities to inform diagnosis and prevention/treatment strategies. This personalized approach (i.e., precision medicine) has already been widely adopted

in oncology, where treatment strategies are tailored to an individual, considering their specific genetic, environmental, and lifestyle factors. With the increasing availability of multimodal biomarkers and refined phenotypic characterizations, precision medicine holds promise for advancing AD diagnostic and therapeutic strategies. Further, novel biomarkers, such as BBMs and digital biomarkers, will enhance the capabilities of clinicians and researchers for the longitudinal monitoring of disease progression and treatment response.

As we move towards these personalized approaches for AD, healthcare providers will play a pivotal role in synthesizing and transforming multimodal biomarker data into care strategies tailored to specific individuals. Integrating fluid, imaging, and digital biomarkers will generate large, complex data that must be interpreted with respect to an individual's genetic, environmental, and lifestyle factors. It will be critical for clinicians to be equipped with an understanding of these different biomarker modalities and their interpretations, and the skills necessary to synthesize the results into patient-centered approaches. These approaches will require training to be available to ensure that clinicians have the expertise to contextualize findings and guide therapeutic decisions. Within this evolving care pathway, clinical expertise remains indispensable for both the integration of biomarkers and the support of patients and their families.

AD research currently finds itself at a juncture: while numerous biomarkers are available, targeting different disease stages and goals, their implementation into daily clinical use remains the biggest hurdle. Recent efforts of a few studies are trying to bridge the gap between translational and personalized medicine, like AD-RIDDLE [292], where plasma biomarkers and clinical implementation protocols will be live, so that they can be evaluated realistically, outside of fixed and overfitted research terms. In this way, cut points will be assessed, as well as the real value of biomarkers at each stage. For instance, in REAL AD [71], digital biomarkers accompanied by plasma assessment will be used as the first stage of ongoing pathological changes to evaluate when a plasma score is alerting and whether this will be aligned with digital testing.

Over the next decade, we anticipate increased clinical implementation of multimodal biomarkers in AD. Integrating fluid, imaging and digital biomarkers is relevant across the disease spectrum, fulfilling distinct, yet complementary, purposes. In the initial preclinical stages, the low cost and accessibility of digital biomarkers and BBMs can support initial screening and risk stratification. Abnormal findings can be followed up with additional biomarker testing (i.e., CSF or PET), while MRI can guide treatment strategies.

In symptomatic patients, particularly at the MCI stage, a combinatorial biomarker approach can enhance diagnostic accuracy and patient monitoring. Notably, digital biomarkers enable the collection of fine-grained physiological, cognitive and behavioral data across different timescales, and can be initiated by the patient or healthcare provider. The accessibility and scalability of digital biomarkers facilitates high-frequency, longitudinal data collection, allowing for earlier detection of subtle changes and enhanced monitoring of disease progression and treatment response.

Importantly, scalable and low-threshold digital biomarkers can be employed in a sequential and complementary manner to support a more efficient and accessible patient pathway in AD. The diagnostic process may begin with automated, resource-light and non-invasive modalities (i.e., digital cognitive testing, passive monitoring), followed by more resource-intensive procedures (advanced imaging, laboratory testing) for confirmation and further evaluation. Each of these modalities has its own limitations. BBMs can be influenced by peripheral factors, medications, or comorbidities; imaging biomarkers remain costly with limited accessibility; and digital biomarkers yield complex datasets, requiring advanced statistics and raising privacy and ethical considerations. However, by implementing multimodal biomarkers in AD, the strengths of one modality can be used to address the weaknesses of another.

Conclusions

Integrating fluid, imaging, and digital biomarkers into clinical care could substantially enhance the detection, diagnosis, monitoring, and management of neurodegenerative diseases. BBMs are increasingly accessible tools, now incorporated into clinical trials and care. Imaging biomarkers offer precise quantification for better diagnostic accuracy, enhanced by technological advances that improve standardization and applicability. Digital biomarkers, including digital assessments and speech-based features, show promise for earlier detection of cognitive changes. Together, these biomarkers could enable precision medicine in neurodegenerative diseases.

However, challenges remain. First, biomarker performance in research settings may not translate directly to clinical settings due to diverse patient populations. Large-scale validation and standardization studies are needed in primary and secondary care. Meanwhile, established biomarkers like CSF and PET can complement emerging tools. Second, the accessibility and cost of biomarkers may impact their clinical care, alongside regulatory and ethical considerations regarding implementation, result disclosure, and data storage.

Biomarkers hold immense potential to transform clinical outcomes and advance disease understanding.

Continued research and collaboration are key to overcoming these challenges and realizing their full benefits.

Abbreviations

AD	Alzheimer's disease
DMTs	Disease-modifying therapies
CSF	Cerebrospinal fluid
BBMs	Blood-based biomarkers
MS	Mass spectrometry
PET	Positron emission tomography
MRI	Magnetic resonance imaging
AI	Artificial intelligence
A β	Amyloid-beta
t-tau	Total tau
p-tau	Phosphorylated tau
NfL	Neurofilament light chain
FTD	Frontotemporal dementia
MTBR	Microtubule binding region
GFAP	Glial fibrillary acid protein
BACE1	Beta-site amyloid precursor protein cleaving enzyme 1
IL	Interleukin
CH13L1 or YKL-40	Chitinase 3-like protein 1
ELISA	Enzyme-linked immunosorbent assay
ECL	Electrochemiluminescence
TREM2	Triggering receptor expressed on myeloid cells 2
Simoa	Single molecule array
MCI	Mild cognitive impairment
LDT	Laboratory-developed tests
IP-MS	Immunoprecipitation mass spectrometry
APOE	Apolipoprotein E
CU	Cognitively unimpaired
PPV	Positive predictive value
NPV	Negative predictive value
sMRI	Structural magnetic resonance imaging
TSPO	Translocator protein
MEG	Magnetoencephalography
NICE	National Institute for Health and Care Excellence
ARIA	Amyloid-related imaging abnormalities
T	Tesla
QSM	Quantitative susceptibility mapping
AV45	Florbetapir
FBB	Florbetaben
PIB	Pittsburgh compound B
CL	Centiloid
SUVR	Standardized uptake value ratio
FDG	Fluorodeoxyglucose
CT	Computed tomography
vMRI	Volumetric MRI
ARPA	Amyloid-removal related pseudo-atrophy
sROI	Statistical region-of-interest
SV2A	Synaptic vesicle protein 2a
LBD	Lewy body dementia
DiMe	Digital Medicine Society

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Authors' contributions

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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