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REVIEW ARTICLE

Considerations in the clinical use of amyloid PET and CSF biomarkers for Alzheimer's disease

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Abstract

Amyloid-β (Aβ) positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) biomarkers are now established tools in the diagnostic workup of patients with Alzheimer's disease (AD), and their use is anticipated to increase with the introduction of new disease-modifying therapies. Although these biomarkers are comparable alternatives in research settings to determine Aβ status, biomarker testing in clinical practice requires careful consideration of the strengths and limitations of each modality, as well as the specific clinical context, to identify which test is best suited for each patient. This article provides a comprehensive review of the pathologic processes reflected by Aβ-PET and CSF biomarkers, their performance, and their current

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and future applications and contexts of use. The primary aim is to assist clinicians in making better-informed decisions about the suitability of each biomarker in different clinical situations, thereby reducing the risk of misdiagnosis or incorrect interpretation of biomarker results.

KEYWORDS
Alzheimer, Aβ-PET, biomarkers, CSF, diagnosis

Highlights

- Recent advances have positioned Aβ PET and CSF biomarkers as pivotal in AD diagnosis.
- It is crucial to understand the differences in the clinical use of these biomarkers.
- A team of experts reviewed the state of Aβ PET and CSF markers in clinical settings.
- Differential features in the clinical application of these biomarkers were reviewed.
- We discussed the role of Aβ PET and CSF in the context of novel plasma biomarkers.

1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease clinically characterized by cognitive decline, memory loss, and behavioral changes.[1] AD is the leading cause of dementia, affecting more than 55 million people worldwide.[2] The pathophysiological hallmark of AD is the accumulation of amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the brain,[3] which precede clinical symptoms by years, if not decades.[4,5] Early and accurate diagnosis of AD is crucial for patient management, therapeutic intervention, and the development of disease-modifying treatments. Traditional diagnostic approaches, relying on clinical assessment including neuropsychological testing, often identify AD at a relatively late stage when significant neuronal damage has already occurred.[6] Moreover, neuropathological studies show that Aβ plaques and neurofibrillary tangles are found in only about 85% of cases who have a clinical diagnosis of AD dementia,[7–9] highlighting the limited specificity of clinical criteria in detecting AD neuropathology. Hence, there is an increasing emphasis on the clinical use of biomarkers to facilitate early and specific diagnosis of AD pathophysiology.[10–12]

Two biomarker modalities are now well-validated and approved components in the diagnostic workup of AD patients in specialized clinical settings: Aβ positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) biomarkers[10,13] These diagnostic tools allow for in vivo detection of cerebral Aβ pathology and have provided critical insights into the underlying disease mechanisms, enabling the identification of AD pathological changes even at the preclinical or mild cognitive impairment (MCI) stages of AD.[14–18]

Aβ-PET imaging uses radiolabeled tracers that bind selectively to fibrillar Aβ, allowing for visualization and quantification of these pathologic protein deposits.[19] This minimally invasive imaging technique thus offers direct visualization of regional cerebral Aβ deposition, which was previously only possible through histopathological examination.

CSF biomarkers reflect biochemical changes associated with AD pathology, providing an indirect measure of the presence of Aβ plaques.[20] Key CSF biomarkers for the detection of Aβ pathology in AD are $A\beta_{42}$ and the $A\beta_{42}/A\beta_{40}$ ratio, as well as hybrid ratios combining measures of phosphorylated tau or total tau with $A\beta_{42}$ (p-tau181/$A\beta_{42}$ and t-tau/$A\beta_{42}$).[12] A reduction in CSF $A\beta_{42}$ levels or the $A\beta_{42}/A\beta_{40}$ ratio, along with elevated t-tau and p-tau levels, constitute the biochemical signature of AD in CSF.[21–23] These biomarkers, though requiring a lumbar puncture, provide an accessible and cost-effective method for the in vivo detection of Aβ pathology.

Aβ-PET and CSF biomarkers have significantly transformed the diagnostic workup of AD in specialized memory clinics, improving the accuracy of the etiological diagnosis of dementia. These biomarkers have caused a shift from a clinical diagnosis based only on symptoms and cognitive testing to one that is increasingly supported by biomarkers.[10,11,24,25] Current clinical applications include aiding in the diagnosis of patients with cognitive impairment of uncertain etiology,[26,27] differential diagnosis,[28] prognosis,[16,17,29] and to establish the presence of abnormal Aβ required prior to the anti-Aβ therapy initiation,[30] among other uses.[31] Only Aβ-PET has thus far been used as the primary endpoint for the assessment of target engagement in pivotal clinical trials of anti-Aβ antibodies.[32,33] With the advent of novel disease-modifying therapies for AD, the use of these biomarkers is expected to increase,[34] as their assessment is critical for identifying suitable individuals for treatment. In the near future, AD biomarkers will be used for assessing treatment response and making decisions about ongoing therapeutic strategies.[35]

Here, we provide a comprehensive narrative review of Aβ-PET and CSF biomarkers, highlighting their commonalities but also their key differences with regard to the pathologic processes they reflect, the performance for detection of Aβ pathology, as well as their

interchangeability in current clinical practice. Additionally, we discuss the future role of these established biomarkers in the context of emerging blood-based tests for AD pathophysiology. The objective of this narrative review is to provide clinicians with a comprehensive understanding of the pathologic processes measured by Aβ-PET and CSF biomarkers, along with their strengths and limitations, enabling them to make more informed decisions on their appropriateness depending on the specific context of use.

RESEARCH IN CONTEXT

1. **Systematic review**: Using conventional search engines, we performed a comprehensive review of the published literature on clinically approved amyloid-β (Aβ) biomarkers, specifically Aβ positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers. We focused on available evidence on the pathological processes reflected by these markers, their diagnostic accuracy, as well as their current applications and potential future uses.
2. **Interpretation**: A strong body of literature supports the reliability of Aβ PET and CSF biomarkers in detecting Aβ pathology in clinical practice. However, careful selection based on clinical context is essential to minimize inaccuracies.
3. **Future directions**: Emerging clinical applications of Aβ biomarkers, including longitudinal monitoring of treatment effects, underscore the importance of further studying the unique features of each biomarker.

2 | NEUROPATHOLOGIC PROCESSES REFLECTED BY Aβ-PET AND CSF BIOMARKERS

Although the main purpose of both Aβ-PET and CSF biomarkers is to detect the presence of Aβ plaques, these markers reflect inherently different—yet closely related—neuropathologic processes. In this section, we review the specific biological changes measured by each biomarker and describe their relationship.

2.1 | Aβ PET

Despite being clinically used as a binary test, Aβ-PET is an imaging technique that can be used to quantify the regional deposition of fibrillar Aβ in the brain. The development of Aβ-specific radiotracers is based mostly on conjugated dyes such as Thioflavin-T and Congo red, which have been used by neuropathologists for the staining of Aβ fibrils.[36] Therefore, Aβ-PET imaging allows for the in vivo visualization and quantification of the accumulated burden of diffuse and neuritic plaques in gray matter[37–40] (Figure 1A), with the latter being one of the neuropathologic hallmarks of AD.[3] Given their more fibrillar structure, neuritic plaques contribute more than diffuse plaques to the overall magnitude of the Aβ-PET signal.[41]

Aβ-PET radiotracers also show affinity for vascular Aβ deposits characteristic of cerebral amyloid angiopathy (CAA).[42,43] The contribution from these deposits to the overall PET signal remains challenging to assess, but appears to be modest,[44] and the clinical utility of Aβ-PET in CAA remains unclear.[45] In addition, Aβ-PET tracers exhibit elevated uptake throughout white matter, regardless of the presence or absence of cortical Aβ (Figure 1A). This signal in the white matter does not reflect Aβ deposition. Although the mechanism of this nonspecific binding is not well understood, it has been hypothesized that Aβ-PET tracers bind to beta-sheets in the myelin basic protein.[46]

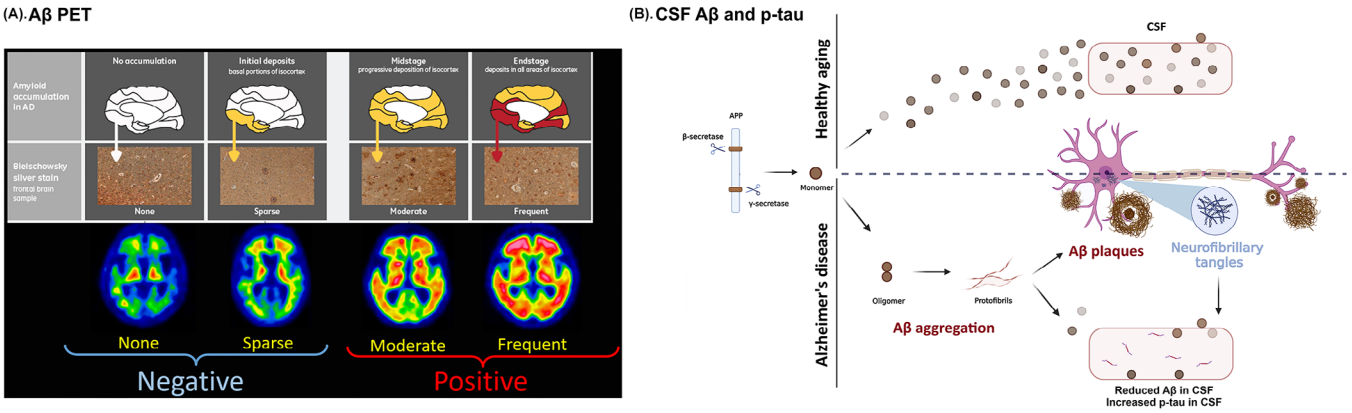

FIGURE 1 Schematic representation of the biological processes captured by Aβ-PET and CSF Aβ and p-tau. Panel (A) shows schematic representations of the spatial progression of Aβ pathology (upper panels) alongside the corresponding Bielschowsky silver staining (BSS) of neuritic plaques (mid panels) and exemplar Aβ-PET ([^{18}F]flutemetamol) scans (middle and bottom panels, respectively), across CERAD scores of "None," "Sparse," "Moderate," and "Frequent." A negative Aβ-PET scan reflects CERAD scores of "None" or "Sparse," while a positive Aβ-PET scan reflects CERAD scores of "Moderate" or "Frequent." Reprinted with permission from Dr. Christopher Rowe. Panel (B) represents the Aβ aggregation process in patients with AD, resulting in reduced Aβ and increased p-tau in the CSF (lower part of the figure, below the dashed line). This is contrasted with the process in normal aging (upper part of the figure, above the dashed line).

2.2 | CSF biomarkers

The theoretical foundation for CSF biomarkers is that molecular changes in the brain's extracellular and interstitial environments are reflected through the communication of these spaces with CSF.[47] Thus, CSF biomarkers are not direct markers of either Aβ plaques or tau neurofibrillary tangles, but instead, measure dynamic biochemical correlates of these brain changes (Figure 1B). The CSF protein signature of AD shows whether Aβ plaque formation is actively ongoing but does not quantify the amount of plaques in the brain.[4, 48–51]

CSF in AD patients is characterized by a marked reduction in the concentration of the 42 amino acid-long and aggregation-prone form of Aβ ($A\beta_{42}$).[52] $A\beta_{42}$ is a fragment produced by the cleavage of the amyloid precursor protein (APP) that is usually released and transported from the brain's interstitial fluid into the CSF and blood.[53] One hypothesis for the decrease in CSF $A\beta_{42}$ observed in AD patients is that this hydrophobic peptide aggregates and becomes sequestered in neuritic plaques, leading to reduced amounts of soluble $A\beta_{42}$ being released in the brain interstitial fluid and CSF.[20] Thus, reductions in CSF $A\beta_{42}$ indirectly reflect the presence of Aβ plaques. An alternative theory is that lower CSF $A\beta_{42}$ levels are due to the propensity of $A\beta_{42}$ to form soluble oligomers and protofibrils that are stuck in the brain and not released into the CSF and blood.

Another relevant Aβ peptide species in CSF is $A\beta_{40}$. Although the concentration of $A\beta_{40}$ is reported to be unchanged in AD,[54] the ratio of $A\beta_{42}$ to $A\beta_{40}$ ($A\beta_{42/40}$) is more effective than the concentration of $A\beta_{42}$ alone in distinguishing between Aβ-positive and Aβ-negative individuals on PET.[55–57] The reason for the improved performance of the $A\beta_{42/40}$ ratio remains unclear but may relate in part to pre-analytical factors, blood-brain barrier permeability, and other interindividual variations in the transport of proteins from the brain into CSF as well as the volume and clearance of CSF.[58, 59]

In addition to the Aβ-related biomarkers CSF $A\beta_{42}$ and $A\beta_{42/40}$, the concentrations of total tau (t-tau) and phosphorylated tau at threonine residues 181 (p-tau181), 205, 217, and 231 in CSF are also increased in AD.[12, 52] Measurements of p-tau181 (also referred to as p-tau in previous publications) have been most frequently used in clinical assays, and while elevations in t-tau are believed to reflect neuronal damage,[60] elevations in phosphorylated tau may reflect secretion of truncated tau fragments that is more closely related to Aβ than neurofibrillary tangle pathology.[61–67] Further, increases in p-tau levels have been shown to mediate the relationship between Aβ plaques and tau tangles.[68–70] This led to the evaluation of the CSF p-tau181/$A\beta_{42}$ and t-tau/$A\beta_{42}$ ratios as biomarkers of Aβ pathology,[71, 72] which demonstrated superior concordance with Aβ-PET compared to $A\beta_{42}$ alone. Of note, clinical interpretation of these ratios, particularly t-tau/$A\beta_{42}$, may benefit from the evaluation in conjunction with the individual biomarker concentrations, as cerebrovascular insults, traumatic brain injury, and encephalitis may result in sharp increases in tau markers and their corresponding ratios in a non-Aβ-dependent manner.[73]

2.3 | Relationship between Aβ-PET and CSF biomarkers

Several autopsy studies have consistently demonstrated that the intensity of *ante mortem* Aβ-PET signal strongly correlates with the *post mortem* density of neuritic plaques.[40, 74, 75] Similarly, CSF $A\beta_{42}$ concentrations decrease rapidly with increasing Aβ-PET signal, but in contrast, there is a strong floor effect within the Aβ-positive range in which the correlation between these two biomarkers is almost non-existent (Figure 2).[76–78] In addition, longitudinal studies showed very weak correlations between longitudinal changes in CSF $A\beta_{42}$ levels and Aβ-PET signal over time.[79] These results highlight that variations in CSF $A\beta_{42}$ concentration within the abnormal range reflect aspects of Aβ pathology other than neuritic plaque density. Thus, CSF $A\beta_{42}$ represents a "state" marker[80] reflecting the presence or absence of Aβ pathology, rather than a marker of the amount of neuritic plaques. However, low levels of these biomarkers within the normal range are predictive of cognitive decline.[81, 82]

The associations of CSF p-tau181 and t-tau with Aβ-PET signal are weaker than those observed for CSF $A\beta_{42}$ or CSF $A\beta_{42/40}$,[83, 84] and these CSF tau markers showed no or minimal change over time in previous longitudinal studies.[85, 86] Similar to CSF $A\beta_{42}$, these results indicate that elevations in these CSF tau markers are associated with a pathologic state that is characterized by the presence of Aβ plaques but is not directly reflective of their cumulative amount.

Although several longitudinal studies have found that CSF $A\beta_{42}$ concentrations reach abnormal levels a few years before Aβ pathology is evident on Aβ-PET,[4, 48–51, 87] the timing of the biological processes measured by Aβ-PET and CSF biomarkers is similar (Figure 3).[11]

3 | PERFORMANCE FOR THE DETECTION OF CEREBRAL Aβ

In the following section, we provide an overview of the performance of Aβ-PET and CSF biomarkers for detecting Aβ pathology, reviewing the methods used to validate each biomarker as well as highlighting the factors that may influence their performance.

3.1 | Aβ-PET as predictor of Aβ at autopsy

Aβ-PET is a well-validated biomarker for AD. As required by regulatory agencies for clinical approval, the validation of Aβ-PET was based on "PET-to-autopsy" phase III studies, in which individuals underwent PET imaging within a short period before death (~1 year), and imaging findings were compared with Aβ burden at autopsy. These studies set the highest standard for biomarker validation in the field of AD, which resulted in the approval of several Aβ-PET radiotracers for clinical use by many regulatory agencies worldwide including the United States Food and Drug Administration (FDA), European Medicines Agency (EMA), as well as by several local agencies in Asia, North and South

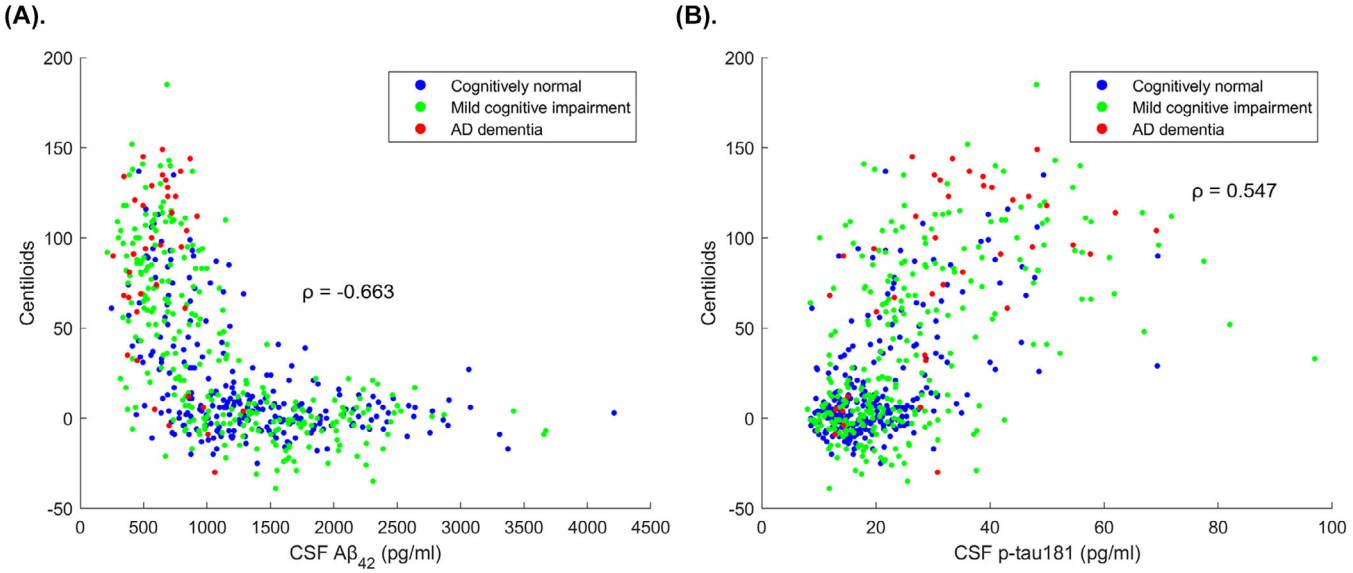

FIGURE 2 Relationship of Aβ-PET Centiloids with CSF Aβ_{42} and p-tau181. Data shown is from 562 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) with available Aβ-PET and CSF Aβ_{42} (A) and p-tau181 (B) (Elecsys) at the baseline visit. ρ represents Spearman correlations.

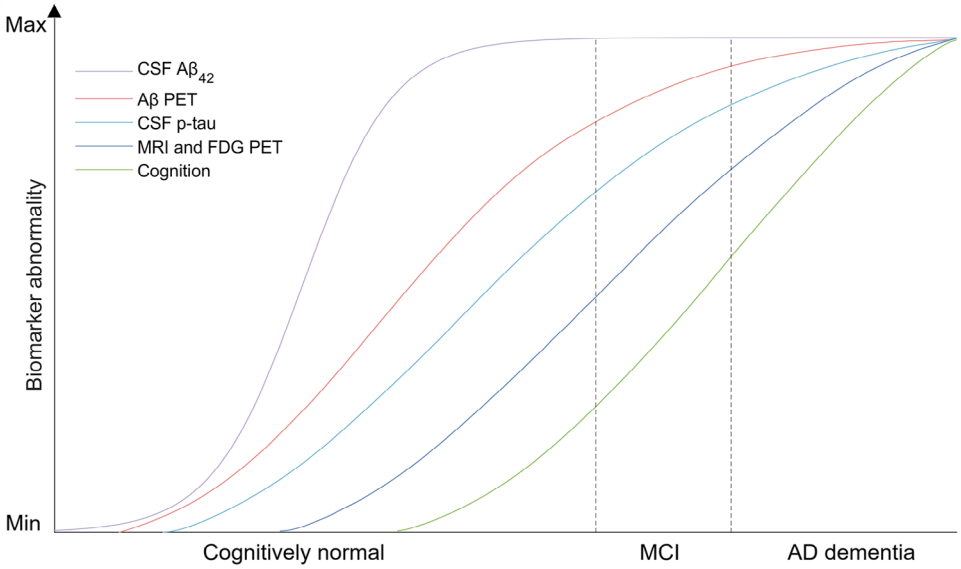

FIGURE 3 Schematic representation of the temporal course of Aβ-PET and CSF Aβ_{42} biomarker changes in AD. Shown are the hypothetical temporal trajectories of Aβ-PET and CSF Aβ_{42} changes, together with other AD biomarkers, and the corresponding clinical stages of AD, as proposed by Refs. 88, 89.

America, and Australia.[90] Due to its ability to directly measure Aβ plaque burden and the extensive validation, Aβ-PET is being used as the gold standard for clinical validation of other biomarkers, including those from CSF.

Though Aβ-PET is an imaging technique that can quantify the amount of fibrillar Aβ in the brain, clinically approved methods for the assessment of Aβ-PET rely on the binary classification (negative/positive) of the scans using visual reads. In PET-to-autopsy studies, visual reads proved highly accurate in discriminating older adults with CERAD neuritic plaque scores of "absent" or "sparse" from those with "moderate" to "frequent" scores, exhibiting sensitivities of 88–98% and specificities of 88–100% (Table 1).[38–40] Importantly, quantitative measures (see Section 3.7) which are increasingly being used to supplement visual read methodology derived from Aβ-PET also demonstrated high accuracy discriminating between individuals with "absent/sparse" and "moderate/frequent" CERAD scores, as well as between "none-low" and "intermediate-high" AD neuropathologic change.[74, 91, 92]

TABLE 1 Performance of Aβ PET radiotracers in "PET-to-autopsy" studies for discriminating between "none/sparse" and "moderate/frequent" CERAD scores.

Radiotracer	Clinical approval by FDA, EMA, and other agencies	Method	Sensitivity (95% CI)	Specificity (95% CI)
[^{18}F]florbetapir (Amyvid)[38]	Yes	Visual read	92% (78% to 98%)	100% (80% to 100%)
[^{18}F]florbetaben (Neuraceq)[40]	Yes	Visual read	98% (94% to 100%)	89% (77% to 100%)
[^{18}F]flutemetamol (Vizamyl™)[39, 92]	Yes	Visual read	86% (72% to 95%)[39] and 91% (82% to 96%)[92]	92% (74% to 99%)[39] and 90% (74% to 98%)[92]
Pittsburgh Compound B (^{11}C-PiB)[74]	No	Quantification	89% (82% to 94%)	86% (75% to 94%)

3.2 | CSF biomarkers as predictors of Aβ at autopsy

A large number of research studies have reported high accuracy of CSF biomarkers for detecting Aβ pathology ("absent/sparse" vs. "moderate/frequent" CERAD scores) and relevant AD neuropathologic changes ("none-low" and "intermediate-high" AD neuropathologic change) at autopsy, supporting the validity of CSF biomarkers for AD.[93–101] Yet, no prospective phase III clinical study has validated the accuracy of *ante mortem* CSF biomarkers to predict Aβ plaque burden at autopsy. The primary limitation of these "CSF-to-autopsy" studies is the lack of prespecified cutoff values for establishing biomarker positivity, with most of the studies reporting sensitivities and specificities based on post-hoc research-driven values, which are generally not applicable in clinical settings. Furthermore, "CSF-to-autopsy" studies were usually not based on end-of-life cohorts, unlike "PET-to-autopsy" studies, leading to significantly longer intervals between CSF biomarker measurements and *post mortem* neuropathologic evaluations. For these reasons, clinical studies have primarily focused on the evaluation of the concordance between CSF biomarkers and Aβ-PET visual reads and, more recently, adjunct quantitative measures.

3.3 | CSF biomarkers versus Aβ-PET as predictors of Aβ at autopsy

There are only a few studies comparing head-to-head *ante mortem* CSF biomarkers with Aβ-PET as predictors of Aβ pathology at autopsy, reporting similar accuracies for both biomarkers.[99, 102–104] Concordance between both markers was also high (80–90%). A relatively small study (n = 21) comparing CSF biomarkers and Aβ-PET with neuropathology provided a detailed description of the biomarker-discordant cases.[99] The study reported three cases with discordant Aβ-PET and CSF biomarker results: two cases with non-AD neuropathological diagnosis and "none-low" AD neuropathologic change (A0B0C0 and A2B1C1)[3] exhibited positive CSF biomarkers but negative Aβ PET; the remaining discordant case had "high" AD neuropathologic change (A3B3C3) and displayed a positive Aβ-PET scan but negative CSF biomarkers. In addition, two cases had both positive CSF biomarkers and Aβ-PET but had a neuropathologic diagnosis of non-AD and exhibited "none-low" AD neuropathologic changes (A3B1C1 and A1B1C0). Together, these results demonstrate that several factors may account for discordant Aβ-PET and CSF biomarker results, and even positivity in both markers does not always indicate a neuropathological diagnosis of AD. This highlights the importance of considering comorbidities and the presence of other neurodegenerative disorders when interpreting Aβ biomarkers for clinical diagnosis. Larger head-to-head studies using a neuropathologically confirmed standard of truth would be valuable to better understand the differential performance of Aβ-PET and CSF biomarkers.

3.4 | CSF biomarkers as surrogates of Aβ PET

CSF biomarkers have proven accurate predictors of Aβ-PET results. Table 2 summarizes percent concordance metrics between Aβ-PET and CSF biomarkers measured using different fully automated platforms.[71, 72, 105–115] The reported sensitivities for CSF $A\beta_{42}$ were in general higher (from 79.5% to 100%) than the specificities (from 51% to 81%). This finding may be explained by the different timing in the onset of abnormal changes in soluble $A\beta_{42}$ and fibrillar Aβ, but also by the influence of other factors potentially leading to false positives on CSF markers (see Section 3.8). The use of the CSF biomarker ratios $A\beta_{42/40}$, p-tau181/$A\beta_{42}$, and t-tau/$A\beta_{42}$ resulted in generally better specificities than $A\beta_{42}$ alone (from 77% to 94% for $A\beta_{42/40}$, from 80% to 94% for p-tau181/$A\beta_{42}$, from 83% to 97% for t-tau/$A\beta_{42}$). Minimizing the number of false positive cases is important in the context of novel disease-modifying therapies, as a positive biomarker result may lead to inappropriate initiation of anti-Aβ therapy in patients who are Aβ-negative.

Overall, the reasonably high concordance between CSF biomarkers and Aβ-PET supports the use of both modalities in clinical practice to establish Aβ status. However, clinical interpretation of each individual biomarker modality should consider that a non-negligible fraction of cases may present with discordant biomarker results. When considering the clinical use of CSF biomarkers, clinicians must carefully assess each individual case to exclude the possibility of factors other than AD pathology potentially leading to positive CSF biomarker results (see Section 3.8). This is particularly important when these results could lead to significant changes in management or treatment decisions.[116]

TABLE 2 Reported performance of FDA- and EMA-approved fully automated CSF biomarker assays for predicting Aβ PET status.

Platform	Study	$A\beta_{42}$ (Sens/Spec)	p-tau181 (Sens/Spec)	t-tau (Sens/Spec)	$A\beta_{42/40}$ (Sens/Spec)	p-tau181/$A\beta_{42}$ (Sens/Spec)	t-tau/$A\beta_{42}$ (Sens/Spec)
Lumipulse G[a]	Alcolea et al.[105]	95/51	80/83	75/83	88/77	93/80	81/83
	Kaplow et al.[c], [106]	97/68	NA	74/84	NA	NA	92/85
	Moon et al.[107]	80/88	80/79	59/89	85/92	85/93	85/88
	Campbell et al.[108]	NA	NA	NA	77/98	79/99	NA
	Willemse et al.[109]	91/73	NA	NA	99/83	97/91	91/90
	Keshavan et al.[110]	74/100	66/100	82/54	94/100	94/100	90/92
	Nisenbaum et al.[111]	90/81	83/83	74/76	94/88	95/83	92/82
Elecsys[b]	Schindler et al.[72]	90/73	82/76	68/83	96/82	92/89	92/85
	Hansson et al.[c71]	86/81	NA	NA	NA	89/92	87/93
	Shaw et al.[112]	98/93	NA	NA	NA	97/100	97/100
	Doecke et al.[113]	81/81	81/77		90/90	90/91	83/97
	Campbell et al.[108]	NA	NA	NA	NA	77/98	NA
	Willemse et al.[109]	91/75	NA	NA	NA	96/89	89/90
	Amft et al.[114]	93/57	69/80	87/63	94/82	96/69	92/69
	Van Harten et al.[115]	86/76	NA	NA	NA	92/92	94/91

[a] *Note* that Aβ42/40 is the only clinically approved measure for the Lumipulse G platform.
[b] *Note* that p-tau181/$A\beta_{42}$ and t-tau/$A\beta_{42}$ are the only clinically approved for the Elecsys platform.
[c] Results were averaged (weighted average) across the different datasets presented in the study.

3.5 | Longitudinal Aβ-PET and CSF biomarkers

With the advent of novel anti-Aβ therapies, serial measurements of Aβ biomarkers will be necessary not only for identifying suitable candidates for these therapies but could also be valuable for monitoring Aβ clearance and determining when to discontinue therapy.

As previously discussed, the intensity of the Aβ-PET signal in a cortical brain region provides a measure of the density of Aβ plaques therein.[75] Thus, Aβ-PET signal changes over time allow for monitoring the accumulation or removal of Aβ plaques. The ability of Aβ-PET signal intensity to track changes in Aβ plaque burden has been consistently demonstrated, showing increased rates of Aβ accumulation in individuals who were positive on their baseline Aβ-PET scan.[117–119] Moreover, a recent study demonstrated that individuals who are negative on their baseline scan but who will show significant Aβ accumulation over time (Aβ accumulators) can be reliably identified based on their baseline Aβ-PET levels, allowing for more efficient recruitment for secondary prevention trials.[120]

By contrast, the limited correlation between CSF biomarkers and Aβ-PET signal within the Aβ-positive range,[76–78, 121] indicative of limited correlation with the amount of Aβ plaques, together with the fact that CSF biomarker levels exhibit only small changes over time,[79, 122] makes these markers less useful for monitoring treatment-related reductions in cerebral Aβ burden. However, CSF biomarkers do change over time with several anti-Aβ and anti-tau therapies and, thus, can provide additional evidence of disease-modifying effects.[32, 123, 124]

3.6 | Variability in Aβ-PET measurements

Clinical use of Aβ-PET primarily relies on visual interpretation of the scans as negative or positive according to standardized procedures.[125–127] These visual interpretation methods have shown high inter-reader agreement, with Cohen's or Fleiss' κ values ranging from 0.63 to 0.94.[128–134] Of note, methodological factors such as the injected radiotracer dose and scan duration were found to have minimal impact on visual assessments of Aβ-PET images.[129, 134] These features indicate that visual interpretation methods for Aβ-PET represent a reliable and standardized way of assessing the presence of relevant Aβ pathology across different settings. This allowed the use of multiple tracers in several multicenter clinical trials that successfully enrolled participants on the basis of a visually positive Aβ-PET scan. Yet, it is also important to highlight factors that can reduce the robustness of visual reads to minimize the number of erroneous interpretations of an Aβ-PET scan in clinical practice. First, inter-rater variability appears to be correlated with the readers' experience interpreting Aβ-PET images[135]; second, in preclinical and prodromal stages, Aβ deposition may be emerging or focal,[136] complicating visual assessments, particularly for less experienced readers; third, partial volume effects due to either cortical atrophy or spill-in signal from the white matter, can result in false negative and false positive scans, respectively[137]; fourth, comorbidities such as normal pressure hydrocephalus, other neurodegenerative conditions and other brain abnormalities can complicate visual interpretation of Aβ-PET images[138–141]; fifth, the color scales and visual interpretation guidelines are different for each radiotracer,

which requires clinicians to be trained in the assessment of different tracers if switching between tracers is necessary.

Apart from visual reads, Aβ-PET can also be evaluated in a fully semi-quantitative manner. The advantage of a continuous rather than binary assessment of Aβ pathology, however, may be offset by an increased susceptibility of quantitative measures to variability. There are several biological and methodological factors that could influence the test-retest repeatability of PET-derived quantitative measurements.[142] An example of a common biological factor influencing Aβ-PET quantification is cortical atrophy. Severe cortical atrophy can result in relevant partial volume effects leading to an artificial decrease of the Aβ-PET signal in the affected cortical region.[143] This effect can have a significant impact on serial Aβ-PET measurements if severe atrophy develops over follow-up.[144] In addition, other biological factors, such as changes in cerebral blood flow, can also influence radiotracer delivery and uptake, resulting in signal variations and reducing the accuracy of longitudinal measurements[142, 145, 146] (see Ref. 120 for a detailed review).

In addition to these intra-subject sources of variability, several methodological factors can also affect quantitative PET measures. At the image acquisition level, these include the specific radiotracer used to image Aβ pathology, as well as differences in scanning time window,[147] delays between radiotracer injection and scan acquisition, patient motion in the scanner,[148] scanner resolution,[149] and image reconstruction parameters,[150] among others (see Refs. 137, 142 for a detailed review). The impact of other technical factors, such as scanner type and reconstruction algorithms, remains unclear. Given the significant changes in both hardware and software in the latest generation of digital PET/computed tomography (CT) scanners, these advancements could affect previous harmonization approaches, like the Centiloid[151] scale, which was primarily validated using older scanners. Additional studies are needed to investigate the impact of these recent developments on PET scanner performance. Another important source of variability across laboratories could be the specific quantification pipeline used, which typically involves different choices of reference regions, target regions of interest, cut-point values for establishing Aβ-PET positivity in a fully quantitative manner, and use (or not) of partial volume effects correction.[152] Overall, when consistently managing methodological factors, test-retest variabilities in quantitative Aβ-PET measures are relatively low, ranging from 1% to 8%,[117, 129, 153–155] allowing for the reliable detection of early treatment-related Aβ removal.[32, 33, 156, 157]

3.7 | Standardization of Aβ-PET measurements

A recent study has proposed a standardized visual interpretation method for all the available Aβ-PET radiotracers,[158] but this method has not yet been approved for clinical use. Despite the lack of a standardized visual method for all tracers, tracer-specific visual reads are generally considered highly interchangeable due to their high accuracy, robustness against methodological variations, and high reproducibility across different settings. Standardization is more important for quantitative measures derived from Aβ PET. Initial efforts focused on reducing between-scanner variability by applying a three-dimensional smoothing to achieve a uniform resolution, an approach that proved effective in large multicenter studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI)[159] or AMYPAD.[160] More recently, a novel methodology (PEACE) has shown better performance than three-dimensional smoothing,[161] though additional validation is needed in multicenter studies. In addition, the use of different quantification methods across laboratories did not allow for merging quantification results measured at different sites with varying tracers and quantification pipelines. This lack of standardization prevented the establishment of universal cut-points for clinically relevant normal/abnormal ranges and complicated the comparison of longitudinal changes in the Aβ-PET burden across laboratories. These limitations ultimately hinder the widespread use of quantification methods for Aβ-PET as an adjunct to visual reads in clinical practice and trials. For this reason, significant efforts have been made to develop a universal quantification scale, the Centiloid scale,[151] that harmonizes quantitative results across different radiotracers and quantification pipelines.

The Centiloid scale relies on reference data from a publicly available dataset from the Global Alzheimer Association Interactive Network (GAAIN) repository in which individuals were scanned with the Aβ-PET tracer Pittsburgh compound B ([^{11}C]PiB). Quantitative results are anchored from 0 (high certainty of the absence of Aβ based on the average Aβ burden of young healthy controls) to 100 (average Aβ burden of a group of patients with mild-moderate AD dementia), resulting in the Centiloid scale. By referencing additional Aβ-PET tracers and quantification methods to this reference data, any Aβ-PET quantitative measurement can be transformed to the Centiloid scale.[151] This scale has proven useful for establishing cut-points for Aβ-PET status, yielding sensitivities and specificities[74, 91] comparable to those in previous "PET-to-autopsy" studies using visual reads.[38–40] These Centiloid (CL) cut-points also showed high concordance with clinically approved visual reads,[162, 163] most of them ranging from 20 to 30 CL for distinguishing between visually positive and negative reads.[91, 162, 164–167] A detailed description of the Centiloid cut-points published in the literature can be found in.[168] In addition, the Centiloid scale has also proven robust against changes in effective image resolution and quantification pipelines.[152]

Though the Centiloid approach has significantly contributed to solve standardization problems, recent evidence suggests that the robustness of this method could be further enhanced by selecting methodological approaches that minimize bias and variability, such as specific reference and cortical regions of interest, quantification pipeline, or scanning time.[169–172] Adoption of these methodological guidelines will further increase the robustness and reliability of the Centiloid approach, but further studies are needed to determine the specific set of methods that allow for optimal reproducibility.

Previous studies have proposed alternative methods to the Centiloid approach for between-tracer harmonization of Aβ-PET scans.[173, 174] Despite results suggesting superior performance, none

of these methods have been further validated in external multicenter studies.

3.8 | Variability in CSF biomarkers measurements

The presence of comorbidities and other neurodegenerative disorders has been reported to be associated with abnormal levels of different CSF biomarkers. For instance, abnormal levels of CSF Aβ_{42} can be detected in a proportion of cases with Creutzfeldt-Jakob disease without Aβ plaques,[175] as well as in neuroinflammatory conditions[176, 177] and in CSF dynamics disorders such as normal pressure hydrocephalus.[178, 179] White matter hyperintensity burden is also associated with reduced CSF Aβ_{42} levels in both AD[180] and in non-demented individuals, independent of Aβ status.[181] Patients with neuroinflammatory conditions and subcortical small vessel disease also show reductions in CSF Aβ_{42} levels.[177, 182] However, as Aβ_{40} is similarly affected, the Aβ_{42}/$_{40}$ ratio results in fewer false-positives for Aβ plaques in these diseases.[58] CSF t-tau can be abnormally increased in conditions involving acute neuronal injury, such as stroke,[183] head trauma,[184] or Creutzfeldt-Jakob disease.[73] Even CSF p-tau181 levels, considered to be largely specific for AD,[185] have been reported to be elevated in patients with neuronal intranuclear inclusion disease and negative Aβ biomarkers.[186] The robustness of the CSF p-tau181/Aβ_{42} and t-tau/Aβ_{42} ratios against biological variations is less clear, although several studies suggest that the use of these ratios may result in improved performance.[59, 187] Further studies are needed to fully understand the impact of co-pathologies on the performance of CSF biomarker ratios.

In addition to the biological factors, there are a number of preanalytical and analytical factors that can influence CSF biomarker measurements. Preanalytical factors account for differences in the collection, handling, and storage of CSF, representing an important source of variability in CSF analyses of AD biomarkers.[188–190] Although a large number of factors influencing CSF measurements were previously studied, some factors have been consistently identified as relevant in several reports, which were the type of sampling tube, and aliquot tube volume,[191] among others (see Refs. 192–194 for detailed reviews). Of note, CSF biomarker measurements derived using clinically approved fully automated platforms are also sensitive to these preanalytical factors.[195] Analytical factors considered for manual assays were variations in technician expertise, local best practices, and lot-to-lot variability of kits and/or kit components.[196, 197]

3.9 | Standardization of CSF biomarkers measurements

The lack of standardized preanalytical and analytical procedures had hindered the use of universal cut-points for CSF biomarkers across different settings and impeded the decentralized analysis of CSF biomarkers in multicenter studies.[198] Therefore, the development of global strategies for the standardization of preanalytical and analytical factors was considered crucial for the successful implementation of CSF biomarkers in clinical settings and trials.

To minimize variability due to preanalytical factors, a simplified and standardized preanalytical protocol for CSF collection and handling before analysis in clinical settings was developed.[191, 194] This protocol includes specific recommendations on the materials and methods employed for CSF extraction, handling of contaminated samples, transport, and storage. Given that commercially available assays explicitly prescribe this preanalytical protocol, adherence to it in clinical practice is important to minimize the rate of patients with false positive/negative results.

Significant progress has also been made in reducing variability attributable to analytic factors. The International Federation of Clinical Chemistry and Laboratory Medicine Working Group for Biomarkers for Neurodegenerative Diseases (WG-BND), together with the Alzheimer's Association Global Biomarker Standardization Consortium (GBSC), has developed certified reference materials and methods for CSF Aβ_{42}, which has significantly reduced batch-to-batch variability and bias between results from different assays.[199] Similar work is in progress for CSF t-tau and p-tau markers. In addition, the development of fully automated assays has resulted in significant reductions in across-laboratory analytical variation by providing highly accurate measurements together with increased reliability and reproducibility due to its automation.[200]

The use of fully automated platforms, together with the standardization initiatives for AD CSF biomarkers, has successfully reduced the degree of variability in CSF biomarker measurements across laboratories. As reported by the Alzheimer's Association quality control program for CSF biomarkers, an external quality control program involving more than 85 laboratories across 20 countries, between-laboratory variability in clinically approved CSF biomarkers was lower than 5%.[201] These results support the reliability of these markers when used in clinical practice.

3.10 | Performance in underrepresented populations

The study of the performance of Aβ biomarkers in underrepresented populations is currently a focus of active research efforts. Recent studies have found that dementia prevalence is higher among self-identified Black or African American and Hispanic adults compared to non-Hispanic White individuals.[202–204] This observation has motivated further AD biomarker studies to determine whether the increased prevalence in these groups reflects a higher rate of positive Aβ biomarkers or is driven by conditions other than AD, such as cerebrovascular disease. Interestingly, the majority of these studies reported lower levels of abnormal CSF biomarkers and Aβ-PET findings in Black adults compared to Non-Hispanic White adults,[205–211] while other studies have found no significant differences[212] or have observed an increase in Aβ-PET signal.[213] These results may indicate differences in the etiology of dementia among underrepresented groups, such as underlying cerebrovascular disease, but also social

factors that can impact health and worsen dementia symptoms. In line with this hypothesis, Black[214–217] and Hispanic[214,218] individuals exhibit higher rates of hypertension and diabetes, both of which are associated with white matter pathology and cortical and lacunar infarcts.[219–222]

A previous study reported weaker associations of CSF $A\beta_{42/40}$ with CSF tau markers, Aβ PET, and cognitive decline in Black compared to Non-Hispanic White participants.[211] Notably, the associations of Aβ-PET with cognition were consistent across the studied racial groups. Further clinical studies comparing the performance of Aβ-PET and CSF biomarkers are necessary to understand whether these biomarker modalities perform differently in underrepresented groups.

4 | INTERPRETATION OF BIOMARKER FINDINGS

In this section, we review the interpretation and applications of Aβ biomarkers as binary and continuous measures of cerebral Aβ burden.

4.1 | Binary versus continuous measures of Aβ burden

Binary assessment of the presence or absence of cerebral Aβ is the most used method for interpreting Aβ biomarkers in clinical practice. However, continuous measures of Aβ burden are valuable for detecting intermediate levels (the so-called "gray-" or "indeterminant" zone[11,223]) and monitoring changes over time. This might be relevant for early intervention, as individuals who are negative on an Aβ biomarker may nevertheless have incipient Aβ pathology that has not progressed enough to yield a positive biomarker result. Cognitively normal individuals with emerging levels of Aβ have been shown to have higher rates of Aβ accumulation over time and a higher risk of cognitive decline[224–226] compared to individuals without Aβ, which highlights the relevance of detecting these early pathologic changes (e.g., for possible future early therapeutic intervention).

An advantage of a continuous rather than binary assessment of Aβ pathology is that it provides a more detailed picture of the pathologic course of the disease. Previous studies have identified a set of CL values associated with relevant biological stages of AD: Aβ levels < 12 CL are indicative of the absence of Aβ plaques[74,227]; Aβ levels > 24 CL reflect the presence of moderate or frequent Aβ plaques (according to the CERAD scale) and therefore represents the common definition of Aβ positivity[74]; Aβ levels > 60 CL were found to be associated with significantly faster rates of aggregated tau accumulation as measured with tau PET.[228] Furthermore, although the associations between Aβ and cognition are generally weak, previous studies have derived minimum Centiloid values associated with the onset of cognitive decline in both preclinical[229] and symptomatic[167] stages of AD.

Aβ-PET quantification has also allowed for the establishment of a window of Centiloid values around the definition of Aβ positivity, known as the gray zone,[223] which represents the transition from the absence of pathologic changes to fully established pathology. This gray zone, typically defined as the range between 10 and 30 CL (EMADOC-1700519818-1200791[230]), includes individuals who may not be detected using the standard definition of Aβ positivity but who have intermediate levels of Aβ pathology. These intermediate levels could be relevant for identifying Aβ accumulators in the earliest stages of the disease (range between 10 and 20 CL[120]) or to detect the presence of established Aβ pathology with high confidence (Aβ > 40 CL).[74]

The value of CSF biomarkers beyond the binary classification of Aβ status remains uncertain. As discussed previously (see Section 2.3), CSF biomarkers concentrations exhibit poor associations with continuous Aβ-PET within the Aβ-positive range, which indicates that variations in this range do not reflect changes in the amount of Aβ plaques in the brain. This, together with the lack of standardized metrics across CSF assays, has prevented the derivation of a "gray-zone" or other cut-point values associated with biologically or clinically relevant endpoints. However, recent studies point toward the feasibility of implementing a "gray-zone" for CSF biomarkers.[231–234] In addition, previous evidence indicates that CSF p-tau181 concentrations are associated with longitudinal tau deposition as measured with tau PET in Aβ-positive, tau-PET-negative individuals,[69,70,235] suggesting that p-tau181 elevations in CSF could be reflective of early tau deposition not detectable on PET. Further studies are needed to understand the utility of CSF biomarkers beyond binary classification. Centiloid-like approaches for harmonized CSF biomarker interpretation are now being explored.[236]

4.2 | Discordance between Aβ-PET and CSF biomarkers

Although Aβ-PET and CSF biomarkers generally show good correspondence with each other, discordant results occur in approximately 10%–20% of patients in clinical settings.[232,237] Identifying the biological and methodological factors that contribute to discrepancies between CSF and PET Aβ has been a key objective of numerous comparative studies[237–239] and is important for the correct interpretation of conflicting results. One of the biological factors that could lead to discordant results is the temporal offset between Aβ-PET and CSF biomarker changes. As discussed in Section 2.3, changes in CSF $A\beta_{42}$ concentrations appear to precede PET-detectable fibrillar Aβ deposition and neuritic plaques, thus a fraction of discordant cases could be reflecting early stages of Aβ deposition. This hypothesis is supported by previous studies showing a larger proportion of individuals with a CSF-positive/Aβ-PET-negative profile than those with a CSF-negative/Aβ-PET-positive profile,[105,232,237] as well as by longitudinal studies indicating faster rates of Aβ accumulation on PET among those with a CSF-positive/Aβ-PET-negative profile.[50,239,240] Another potential biological explanation for isolated positivity in CSF biomarkers could be the presence of concomitant neurological disorders as discussed in Section 3.8. In addition, although relatively rare, some genetic forms of AD can present with negative Aβ-PET scans but clearly abnormal CSF biomarkers.[241,242] Finally, analytical and preanalytical factors

in CSF biomarker measurements (Section 3.8), together with variability in the visual assessment or quantification of Aβ PET, may also account for a fraction of the discordant cases.

While discordant results in the form of abnormal CSF $A\beta_{42}$ levels together with normal p-tau181 can be expected due to the different temporal offset between abnormalities in these markers (Section 2.3), high CSF p-tau181 concentrations in combination with normal CSF $A\beta_{42}$ are more difficult to interpret.[243] This is because CSF p-tau181 elevations are believed to be relatively specific for AD[244,245] and therefore would not be expected in the absence of Aβ. The frequency of CSF p-tau181 levels with normal $A\beta_{42}$ is approximately 4%–5% in real-world clinical settings, with increasing prevalence for older age groups.[246] To date, the aetiology of this biomarker profile is unclear. Previous data suggest that p-tau elevations in the absence of Aβ could be driven by non-AD conditions that present with AD-like tau pathology, such as tangle-dominant dementia or primary age-related tauopathy (PART),[247–249] but other studies do not support this hypothesis.[68,250] As discussed previously (Section 3.8), other potential causes of discordant CSF $A\beta_{42}$ and p-tau181 results might be the presence of age-related comorbidities or methodological variability. Further studies are needed to understand the aetiologic substrate of the CSF p-tau181-positive/$A\beta_{42}$-negative profile.

The clinical outcomes associated with discordant biomarker profiles are not particularly clear. While previous studies report that the presence of a positive Aβ-PET scan with normal CSF biomarkers is associated with faster rates of clinical decline,[239] others found no significant differences.[238,246] Similarly, discordance between CSF $A\beta_{42}$ and p-tau181 does not seem to indicate a higher risk of clinical progression, leading to recommendations to interpret this biomarker profile in the same way as fully negative CSF biomarker results.[246,251]

5 | CONTEXT OF USE

In this section, we review the current and future contexts of use of Aβ-PET and CSF biomarkers in clinical practice and trials.

5.1 | Regulations and current practices for Aβ PET

To date, three Aβ-PET radiotracers, [^{18}F]florbetapir (Amyvid; Eli Lilly and Company), [^{18}F]florbetaben (NeuraCeq; Life Molecular Imaging), and [^{18}F]flutemetamol (Vizamyl; GE HealthCare) have been approved for clinical use by the US FDA, the EMA, and other regulatory agencies around the globe.[90,252] For clinical use in the United States, current Aβ-PET radiotracers are required to be evaluated using radiotracer-specific visual interpretation methods. Quantification of Aβ-PET can be used to support visual reads in clinical practice in Europe. A Biomarker Qualification Opinion (BQO) issued by the EMA for the use of the Centiloid scale in clinical practice was also recently adopted by the EMA reinforcing the value of quantification to supplement image interpretation (EMADOC-1700519818-1200791[230]). However, widespread access to reliable quantification pipelines in clinical settings remains limited. This may change in the coming years with the emergence of new commercially available Centiloid pipelines certified for clinical use.[162,253–255] Centiloid quantification is presently not approved for clinical use in the United States.

Current use of Aβ-PET in clinical settings in the United States is largely consistent with the Appropriate Use Criteria (AUC) published in 2013 and updated in 2024.[31] These guidelines recommend the use of Aβ-PET for patients with cognitive impairment of uncertain etiology confirmed by a dementia specialist, and when Aβ-PET results are expected to increase diagnostic certainty and influence patient management. Clinical scenarios in which amyloid PET would typically be considered appropriate include: patients of any age presenting with MCI or dementia in whom AD is suspected (including amnestic and non-amnestic phenotypes associated with underlying AD neuropathology), to inform prognosis in patients with MCI due to clinically suspected AD, patients with MCI/dementia with inconclusive CSF biomarkers, and to determine eligibility and monitor response to approved anti-Aβ therapies. Aβ-PET is considered to have uncertain value in patients with subjective cognitive decline who are deemed at heightened risk of AD based on age, known APOE4 genotype, or multi-generational family history. Aβ-PET is also of uncertain value for informing prognosis of patients with dementia due to suspected AD. Inappropriate scenarios include the use of Aβ-PET in cognitively unimpaired individuals and individuals with subjective cognitive decline who are at low risk for AD, for assessing the severity of dementia or tracking disease progression in patients with biomarker-confirmed AD, for patients presenting with prodromal Lewy body dementia (LBD) or dementia with Lewy bodies (DLB), for patients with recent conclusive CSF biomarkers (positive or negative), for nonmedical use (e.g., insurance coverage, employment screening) and in lieu of genotyping for suspected autosomal dominant mutation carriers.[256]

Other patient-centered guidelines for the appropriate use of biomarkers in diagnosing neurodegenerative disorders have recently been proposed and endorsed by a majority of experts across various European scientific societies.[24] Panelists recommended using Aβ-PET as a second-line test following inconclusive CSF biomarker results, prioritizing CSF biomarkers as the first-line test for detecting Aβ and soluble tau pathology. Of note, AD biomarker testing is only recommended in patients with an AD-typical or atypical phenotype. In this proposed diagnostic workflow, CSF biomarkers and Aβ-PET are deemed appropriate only for individuals with objective evidence of cognitive impairment suspected to be caused by AD.[10] A positive Aβ-PET scan is considered sufficient for the establishment of a final causal diagnosis of AD in this patient population.

5.2 | Contraindications, adverse events, and patient-clinician experience with Aβ PET

Current limitations that hamper the use of Aβ-PET in clinical settings include limited availability, relatively high costs, and radiation exposure. PET is only contraindicated in a few patients with known hypersensitivity to the radiotracer or other excipients (specific to

[^{18}F]flutemetamol). Adverse events are rare and mild, and include injection site pain, increased blood pressure, and headache. Although PET imaging sessions are generally well tolerated by patients, some individuals may be unable to undergo PET imaging due to severe claustrophobia, particularly when scanned using PET/MR cameras.[257] Other patients may be reluctant to undergo PET imaging due to radiation exposure, although some studies indicate that radiation exposure could be significantly reduced.[258] Aβ-PET imaging is restricted to centers equipped with a PET scanner that have access to a cyclotron facility capable of producing and shipping the required radiotracer on the same day. Additionally, tracer production failures are common and often lead to significant delays in PET imaging, thereby increasing the burden on patients. Differences in reimbursement policies across different countries have created additional barriers to the use of this imaging technique. The approval of new anti-Aβ therapies may have prompted a change in this situation, as the US Centers for Medicare and Medicaid Services (CMS) revised their non-coverage policy in October 2023 and started reimbursing for Aβ PET, contributing to increased accessibility of this imaging technique.[259] However, current reimbursement rates do not fully compensate for the actual costs of Aβ-PET imaging, resulting in additional barriers to the use of this biomarker and disincentivizing its use by healthcare providers.

5.3 | Regulations and current practices for CSF biomarkers

Several CSF assays have been approved for clinical use in Europe over the last two decades, and CSF biomarkers have been routinely used in European memory clinics to aid in the diagnostic workup of AD patients for more than a decade.[116, 260, 261] Approval in the United States has come more recently with the introduction of fully automated CSF assays.[252] To date, only two of these automated assays have been approved by both the FDA and the EMA, namely the Lumipulse G (Fujirebio, Tokyo, Tapan) and the Elecsys (Roche Diagnostics, Rotkreuz, Switzerland) platforms. In clinical practice, CSF biomarker results are categorized as positive/negative using prespecified cut-points provided by the vendor. These cut-points were derived by maximizing concordance with Aβ-PET visual reads in independent cohorts.[262–264] Thus, positive/negative CSF biomarker results must be interpreted as proxies of positive/negative Aβ-PET visual reads. Of note, the Lumipulse assay provides a range of intermediate CSF A$\beta_{42/40}$ ratio values (0.058 to 0.073) in which a positive Aβ-PET scan is the most likely result but the uncertainty increases, thus results falling in this gray zone should be interpreted with caution.[264] This is not the case for the Elecsys assay that provides a single cut-point for the p-tau181/Aβ_{42} and t-tau/Aβ_{42} ratios for the definition of positive/negative results.[262, 263] Interpretation of continuous levels of CSF biomarkers is currently not recommended for the diagnostic workup of patients with AD.

Current use cases for CSF biomarkers in clinical practice in the United States are similar to those for Aβ-PET and also reflect previously published AUC.[265] A notable difference between the AUC for CSF biomarkers and the 2013 AUC for Aβ-PET was the indication for CSF biomarker testing in patients meeting core clinical criteria for probable AD with a typical age of onset, which is now recognized as appropriate in the 2024 update of the AUC for Aβ-PET.[256]

In Europe, several guidelines for the clinical use of CSF biomarkers have been proposed over the last decade.[261, 266, 267] The most recent European consensus guidelines recommend, whenever possible, prioritizing the use of CSF biomarkers as a first-line test in patients with objective evidence of cognitive impairment suspected to be caused by AD.[10, 24] Of note, a diagnosis of AD can be concluded in these patients if CSF biomarker results are unequivocally indicative of brain Aβ (based on either CSF Aβ_{42} or the CSF A$\beta_{42/40}$ ratio) and tau pathology (based on elevated CSF p-tau), thus incorporating the notion that AD is a clinical-biological disorder defined by the presence of both Aβ and tau.[10] Evidence of isolated abnormal CSF Aβ in the absence of elevated CSF p-tau is generally not sufficient for establishing an AD diagnosis and would require second-line biomarker testing.

5.4 | Contraindications, adverse events, and patient-clinician experience with CSF biomarkers

Despite the increased accessibility and lower costs of CSF biomarkers, there are also a number of limitations that can complicate its use in clinical practice. Lumbar punctures are contraindicated in patients with an intracranial space-occupying lesion or Arnold-Chiari malformation. Additionally, patients on anticoagulation medications must have therapy temporarily discontinued (as for other procedures), and patients with coagulopathies, other bleeding diatheses, certain spine abnormalities, spinal cord compression, or local skin diseases at the puncture site may not be eligible for CSF extraction.[268] Apart from these contraindications, a fraction of eligible individuals might be unwilling to undergo a lumbar puncture due to a lack of familiarity with the procedure, especially in certain countries such as the United States.[269] Side effects, principally post lumbar puncture headache syndrome, have been reported as occurring in 2% to 30% of patients[270–275]; use of atraumatic needles, as well as smaller needle diameters, result in much lower side effects, but not all practitioners are trained in their use; overall there are fewer side-effects in elderly individuals.[260] Rare side-effects include bleeding or infection.[268] CSF extraction requires qualified and trained clinicians to minimize the risk of complications. Although CSF biomarkers are covered by insurance in the United States, the rate of reimbursement for these tests may not match the actual costs.[276] As a result, healthcare providers may be disincentivized to perform lumbar punctures, resulting in reduced accessibility to CSF biomarker testing and potential delays in treatment initiation with anti-Aβ drugs.

5.5 | Diagnostic guidelines and recommendations

Although the previously discussed AUC for Aβ-PET and CSF biomarkers currently guide the appropriate use and interpretation of these

biomarkers in clinical settings, new criteria for the diagnosis of AD based on biomarkers have been recently proposed.[11] The 2024 Revised Criteria for Diagnosis and Staging of AD (2024 Revised Criteria for short), developed by a workgroup convened by the Alzheimer's Association, represent the most recent efforts to update the previous 2018 National Institute on Aging (NIA) and Alzheimer's Association (AA) Research Framework for AD.[13] The core principle of the 2018 NIA-AA Research Framework is the definition of AD as a biological rather than a syndromic construct. The disease is conceptualized as a continuum that manifests with the first detectable neuropathologic changes in asymptomatic individuals and progresses with incremental neuropathologic changes, finally leading to neurodegeneration and the onset of clinical symptoms. AD can, therefore, be diagnosed in vivo, independent of the presence of symptoms, through the use of biomarkers that detect its hallmark biological features, namely Aβ plaques and neurofibrillary tangles.[3] The 2018 NIA-AA Research Framework was intended for use in research settings, not in clinical practice. Its main aim was to provide a common framework for guiding biomarker research. However, the 2024 Revised Criteria aims to advance the clinical implementation of the framework, providing criteria that inform the diagnosis and staging of AD based on available knowledge, but it is not meant to replace specific clinical practice guidelines. We also note that a biological definition of AD, independent of clinical symptoms as proposed in the 2024 Revised Criteria, is not universally accepted by the scientific community. Alternative criteria based on biomarkers and clinical symptoms have also been proposed.[10]

In the 2024 Revised Criteria, biomarkers are grouped into three categories, namely Core AD biomarkers, non-specific biomarkers that reflect AD-related neuropathologic process, and biomarkers of non-AD pathologies typically associated with aging. An important concept is that Core AD biomarkers are further classified into Core 1 and Core 2 based on the timing of abnormal changes. Core 1 biomarkers become abnormal approximately at the same time as Aβ PET, and include CSF Aβ_{42} and p-tau181, as well as p-tau217 and p-tau231, together with their plasma counterparts. Thus, in this framework, Aβ-PET and these fluid biomarkers are considered interchangeable with regard to the type of biomarker (Core 1). An abnormality in specific Core 1 biomarkers (Aβ-PET or CSF A$\beta_{42/40}$, p-tau181/Aβ_{42}, t-tau/Aβ_{42}, or their equivalent plasma biomarkers) is considered sufficient for a diagnosis of AD. This is a major change compared to the 2018 NIA-AA Research Framework, which required the presence of abnormal levels in both Aβ and tau biomarkers.[3] The rationale for this change is that a positive Aβ biomarker is reflective not only of Aβ plaques but is also strongly associated with the presence of tau neurofibrillary tangles (Braak stages $\geq$ III) and thus with "moderate/frequent" AD neuropathologic changes.[11] It is important to note that the association between Aβ positivity and "moderate/frequent" AD neuropathologic changes is stronger in symptomatic individuals, while a fraction of asymptomatic individuals with a positive Aβ biomarker will not have "moderate/frequent" AD neuropathologic change (13%–26%). Although a positive Core 1 biomarker confirms a diagnosis of AD, clinical judgment, together with other biomarker information, is essential to determine whether AD pathology is a dominant contributor to a patient's clinical symptoms. Core 2 biomarkers include tau PET and novel CSF tau biomarkers, namely, p-tau205, microtubule-binding region- (MTBR) tau 243, and non-phosphorylated mid-region tau fragments.[277, 278] These biomarkers become abnormal later in the disease process representing tau proteinopathy and are more closely associated with neurodegeneration and clinical symptoms than Core 1 biomarkers. Therefore, the intended use of Core 2 biomarkers is to stage AD progression after a positive Core 1 biomarker has confirmed the presence of AD pathology. A positive Core 2 biomarker would, for instance, support that a patient's clinical syndrome is caused by AD pathology. Currently, Core 2 biomarkers are not meant to be used as standalone tests for AD.

To date, the 2024 Revised Criteria do not specify how to interpret biomarker findings that are not uncommon in clinical practice, such as discordant results between Aβ-PET and CSF biomarkers. For additional details on non-core biomarkers and clinical staging, we refer the reader to the publication of the Revised Criteria.[11]

It should be noted that the biomarker-centric approach proposed in the Revised Criteria is not universally accepted by the AD scientific community. The 2021 report from the International Working Group (IWG)[10] highlights the limitations of using a purely biological definition of AD in clinical practice and suggests that a clinical-biological approach, rather than a strictly biological one, offers a more useful diagnostic framework. Another key difference between the two frameworks is that the IWG requires biomarker evidence of both Aβ and tau pathology for an AD diagnosis, whereas the Revised Criteria allow a diagnosis based on a positive Aβ biomarker alone.[11] A 2024 response from the IWG to the Revised Criteria further emphasized their position that AD should be interpreted as a clinical-biological entity, where individuals with an established clinical phenotype are tested for biomarkers of AD pathology, including now also newly-developed plasma biomarkers.[279]

It is also important to emphasize that, in clinical practice, a biomarker-based diagnosis of AD should not be restricted to identifying individuals eligible for anti-Aβ therapies. Knowledge of Aβ status can be relevant in many clinical scenarios independent of the patient's eligibility for anti-Aβ therapies. Approximately 15%–20% of older patients with clinically diagnosed AD dementia exhibit negative Aβ-PET scans, and this proportion increases up to 50% for persons with MCI. A negative Aβ-PET scan allows clinicians to confidently rule out AD pathology as the cause of the patient's cognitive symptoms, even when the patient presents with a typical AD clinical syndrome, thus directing clinicians to focus additional diagnostic efforts on non-AD aetiologies. Moreover, although Aβ-PET or CSF Aβ biomarker positivity is prevalent in cognitively normal older individuals[14] and those with non-AD dementias (particularly in dementia with Lewy bodies),[280] a positive Aβ-PET scan in patients with MCI or AD dementia can strengthen diagnostic certainty and influence management options, as demonstrated in large studies evaluating the clinical utility of Aβ-PET in the United States and Europe.[26, 281] In patients with MCI due to suspected AD pathology, a positive Aβ-PET scan can inform the risk of incident AD dementia. Knowledge of Aβ status can also be valuable in the diagnostic workup of complex dementia cases presenting with atypical features. Overall, these findings highlight the utility of

TABLE 3 Use of Aβ-PET and CSF biomarkers in current phase 3 clinical trials of disease-modifying drugs in patients with symptomatic AD.[282]

Agent	Aβ PET for inclusion	CSF biomarkers for inclusion	Aβ PET as endpoint	CSF biomarkers as endpoint
Aducanumab (NCT05310071)	Yes	Yes	Yes	No
Lecanemab (NCT03887455)	Yes	Yes	Yes	No
Donanemab (NCT04437511, NCT05738486, and NCT05508789)	Yes	No	Yes	No
AR1001 (NCT05531526)	Yes	Yes	No	Yes
Buntanetap (NCT05686044)	No	No	No	No
Fosgonimeton (NCT04488419 and NCT04886063)	No	No	No	No
Levetiracetam (NCT05986721)	Yes	No	No	No
Masitinib (NCT05564169)	Yes	Yes	No	No
Metformin (NCT04098666)	No	No	Yes	No
Nilotinib BE (NCT05143528)	Yes	Yes	Yes	Yes
Piromelatine (NCT05267535)	No	No	No	No
Remternetug (NCT05463731)	Yes	No	Yes	No
Semaglutide (NCT04777396 and NCT04777409)	Yes	Yes	No	No
Simufilam (NCT04994483 and NCT05026177)	Yes	Yes	Yes	Yes
Valiltramiprosate (NCT04770220)	No	No	No	Yes

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positron emission tomography

Aβ biomarkers beyond identifying candidates for anti-Aβ therapies, indicating their potential clinical value even among those who do not qualify for these treatments.

5.6 | Clinical trials

Aβ-PET and CSF biomarkers have played a pivotal role in the design and implementation of clinical trials for AD. These markers have been successfully used to select participants for trials using disease-modifying drugs, including the approved drugs aducanumab, lecanemab, and donanemab, allowing for the exclusion of patients with clinical AD but who do not have biomarker evidence for Aβ pathology, and thus would not benefit from interventions targeting AD pathology. Participant selection is typically based on Aβ-PET visual reads, and some trials consider visual reads interchangeable with CSF biomarkers (for instance, the lecanemab CLARITY AD trial[32]) (Table 3).

Aβ-PET quantification has also proven useful in clinical trials. Recruitment in trials such as donanemab trials TRAILBLAZER-ALZ,[157] TRAILBLAZER-ALZ 2,[33] and lecanemab trial AHEAD 3-45[283] have been based on a specific set of Centiloid values (37 CL for TRAILBLAZER trials and 20 and 40 CL for the prevention-based AHEAD 3-45 studies), which differed from the standard definition of Aβ positivity and better aligned with the goals of each trial. In addition, quantitative measures in the Centiloid scale have been successfully used to monitor treatment-related changes in Aβ burden and assess target engagement.[33, 123, 156, 157, 284, 285] As discussed previously, direct monitoring of changes in Aβ plaque burden is challenging with CSF biomarkers (Section 3.5), although clinical trials have used CSF or plasma biomarkers to investigate disease-modifying effects of anti-Aβ therapies on these markers.[32, 33, 123]

In clinical settings, Aβ-PET quantification may become relevant for the objective assessment of Aβ clearance in AD patients undergoing anti-Aβ therapies, supporting treatment discontinuation decisions particularly for therapies which are thought to be effective only against neuritic plaque forms of Aβ.[35, 286] This novel potential application is motivated by recent findings from donanemab's TRAILBLAZER-ALZ 2 trial, which demonstrate a sustained benefit throughout the trial duration after treatment completion.[287] Treatment completion was defined based on quantitative measures from Aβ-PET as either (1) a follow-up Aβ-PET scan (performed every 6 months) showing a value lower than 11 CL, or (2) two consecutive Aβ-PET scans with values between 11 and 25 CL.[33] After 12 months of treatment with donanemab, approximately 66% of the participants had Centiloid values consistent with a negative Aβ-PET scan (<24.1 CL).[287] Yet, additional research is needed to confirm the appropriateness of this approach in clinical practice, as well as to study the feasibility of implementing this approach in memory clinics, which currently have limited access to Aβ-PET quantification pipelines. Additionally, baseline Centiloid values were predictive of the time required to achieve a negative Aβ-PET scan (<24.1 CL), which may help clinicians determine the timing of follow-up Aβ-PET scans to confirm Aβ plaque clearance.[287] Baseline Centiloid values may also be useful to predict long-term progression to dementia in patients attending memory clinics.[167]

6 | FUTURE ROLE OF PLASMA BIOMARKERS FOR AD

Recent advances have been made in the development and clinical validation of blood-based biomarkers (BBMs) for AD. $Aβ_{42/40}$ can be quantified with mass-spectrometry and immunoassay techniques,[288–290]

the former being the only method that has proven sufficiently accurate for determining Aβ positivity on PET.[291] Several plasma p-tau immunoassays were also developed, targeting p-tau181, p-tau217, and p-tau231, with somewhat higher accuracies for detecting Aβ status.[292–298] Among these, p-tau217 has emerged as the most promising for clinical implementation due to the large effect size in mean levels measured in cognitively impaired Aβ-positive patients versus Aβ-negative controls,[250, 299] where certain p-tau217 blood tests exhibit similar or even superior performance to clinically approved CSF tests in research settings.[231] Such a blood test has recently been shown to have excellent performance even in primary care, showing a great potential to improve the diagnostic work-up of AD also in this context.[300]

Head-to-head studies comparing different BBM assays have been performed. In one study, a comparison of eight plasma $A\beta_{42/40}$ assays showed that mass spectrometry-based assays were the best performing, with discriminative abilities of around 85% for detecting Aβ-positivity determined by CSF or PET and mean reductions ranging from ~8% to 14% in Aβ-positive versus Aβ-negative groups.[291] Similar results were observed in another head-to-head study comparing six different assays in participants from the ADNI.[301] In head-to-head studies comparing plasma p-tau biomarkers to detect Aβ-positivity determined by either CSF or PET, the best-performing assays were usually those targeting p-tau217, with discriminative abilities reaching 90%–95% or higher, and their mean increases in Aβ-positive groups were around 100%–300%.[302, 303] Contrary to $A\beta_{42/40}$, both mass spectrometry-based methods and immunoassays for p-tau217 demonstrated high performance. The superior agreement with gold-standard Aβ-positivity for p-tau217 biomarkers, compared to the lower-magnitude reductions of plasma $A\beta_{42/40}$ motivated a debate on whether p-tau variants would have better performance properties to withstand biological and analytical sources of variation frequently seen in clinical chemistry laboratories.[304, 305] Furthermore, it was previously shown that plasma p-tau exhibit less problems than $A\beta_{42/40}$ with test-retest variability affecting the biomarker classification of the patients.[306]

While fluid measures of p-tau were initially placed within the tau biomarker category in the NIA-AA Research Framework,[13] it was later suggested that they could be more reflective of biomarker-confirmed Aβ pathology due to the higher correlations with Aβ-PET and high diagnostic accuracy for Aβ-positivity.[61, 302, 303] Studies with *post mortem* data indicated that plasma p-tau231 and p-tau181 indeed showed a higher association with Aβ plaques, but p-tau217, the most clinically promising biomarker, seemed to reflect both Aβ plaques and neurofibrillary tangle (NFT) burden.[68, 231, 297] This further raised the need for NFT-specific biofluid-based biomarkers. Candidates such as CSF p-tau205, ptau217 occupancy ratio, and other forms of tau such as assays for MTBR such as MTBR-tau 243, or truncated tau368/t-tau ratio have been proposed in CSF.[277, 278, 307, 308] Although some of these candidate fluid biomarkers appear more closely associated with tau PET, they have not yet been validated across multiple cohorts, compared with *post mortem* NFT pathology, or assayable in plasma. Thus, there remains a significant need for validated NFT-specific BBMs.

Despite these advances, practical aspects of BBMs' use, including sources of significant inter-laboratory variability, need to be addressed before widespread clinical implementation. Blood is a more complex fluid in composition than CSF, and, except for some mass-spectrometry methods,[231] the accuracy of plasma biomarkers and robustness against comorbidities may be lower compared to that provided by CSF biomarkers or Aβ-PET.[309, 310] Thus, although some plasma biomarkers have shown promising performance,[231] it is still unclear whether they can be used as standalone biomarkers, completely replacing CSF biomarkers and PET, in clinical practice. Given the currently available evidence, it is likely that the immediate clinical utility of BBMs will lie in screening for Aβ-positivity patients with cognitive impairment, where those with equivocal results may especially benefit from further CSF or PET testing.[251]

Importantly, BBMs may also have utility in clinical trials. One of their logical applications involves optimizing the cost-efficiency of trial recruitment.[311] For example, the TRAILBLAZER-ALZ 2 donanemab trial demonstrated that pre-screening with plasma p-tau181 before Aβ- and tau-PET scans could effectively identify candidates with both proteinopathies, improving recruitment efficiency. Based on this, TRAILBLAZER-ALZ 3 adopted plasma p-tau217 as the sole enrollment criterion for asymptomatic older adults, bypassing Aβ-PET. This approach, while innovative, raises concerns of potentially including an undesirable rate of Aβ-negative patients in the trial. Results from these and future trials will aid in determining the role of BBMs in trial recruitment and enrollment. Additionally, BBMs may be useful in monitoring treatment effects.[312] Recent anti-Aβ trials indicated substantial and early reductions in plasma levels of p-tau181 and p-tau217 in the treatment arms.[156, 313] However, these reductions were evident at the group level, and it is still unknown whether BBM changes associate, at the individual-patient level, with Aβ clearance or with clinical benefits. For example, plasma p-tau217 did not prove to be accurate in monitoring Aβ plaque clearance in donanemab's TRAILBLAZER-ALZ 2 trial.[287]

Currently, there are no BBMs fully approved for clinical use by the FDA. In the United States, C2N Diagnostics and Roche have obtained a Breakthrough Device Designation from the FDA and are currently validating their BBMs and associated algorithms with promising results.[314–319]

A recent position paper proposed that BBMs used in clinical practice need to have accuracies for the classification of Aβ-PET status similar to that of CSF biomarkers.[320] This concept prompts interest in comparisons between BBMs and CSF biomarkers in research and real-world clinical cohorts. In addition, potential factors influencing or confounding BBM results have already been identified. Plasma p-tau levels have been associated with chronic kidney disease (CKD), though its clinical relevance remains uncertain.[251, 321–323] Plasma $A\beta_{42/40}$ levels have been suggested to be more vulnerable to analytical sources of variation and are substantially affected by a commonly used cardiovascular drug.[304, 305, 324] Additionally, a serial-sampling study evaluating BBMs weekly over 10 weeks indicated that biological fluctuations must be considered, as unexpectedly high BBM values can yield false-positive results.[325] Most importantly, studies prospectively evaluating

TABLE 4 Summary of factors potentially influencing selection between Aβ PET and CSF biomarkers.

Factors affecting biomarker selection	Aβ PET	CSF biomarkers
Clinical use		
• Direct measure of the target pathology	Yes	No
• Tau-related biomarkers available with the same test	Not available	CSF p-tau isoforms
• Neuronal injury biomarkers available with the same test	Possible with early phase imaging but unclear value	CSF t-tau and Neurofilament light chain
• Differential diagnosis	Can be useful for the differential diagnosis of frontotemporal dementia[28]	Different CSF biomarker measurements can support the diagnosis of a non-AD disorder[326]
• Interpretation of biomarker results beyond binary classification	Possible with quantification	Not possible
• Longitudinal assessment of treatment-related changes in Aβ burden	Possible with quantification	Not possible
• Use for inclusion in clinical trials	Yes, allowing for inclusion with different Aβ burden levels	Yes, but only possible with standard Aβ positivity
• Use as endpoint in clinical trials	Yes, allowing for the assessment of target engagement	Yes, for the assessment of downstream therapeutic effects on different pathologic markers.
Patient-driven factors		
• Presence of comorbidities	CAA may result in small elevation in Aβ PET signal	A number of comorbidities may lead to a positive CSF biomarker result (see Section 3.8).
• Contraindications	Hypersensitivity to the radiotracer of any other excipient (only for [^{18}F]flutemetamol[125])	Treatment with anticoagulants, spinal defects, intracranial masses, among others (see Section 5.4)
• Adverse events	Rare events include injection site pain, increased blood pressure, and headache	1 out of 3 patients report headache and/or back pain. Severe headache is more rare. Other rare events include infection and bleeding.
• Patient concerns about the procedure	Severe claustrophobia. Radiation exposure.	A fraction of the patients refuses lumbar puncture.
Region-specific factors		
• Costs	High	Relatively low, but requires highly trained clinicians
• Availability	Limited to centers with convenient access to a cyclotron	Widely available
• Reimbursement	Limited reimbursement in some countries.	Typically reimbursed in most countries, but reimbursement rated do not match costs in the United States (see Section 5.4)
• Preference in current practice	Preferred in the United States due to patients' reluctance to lumbar punctures	Preferred in Europe due to higher availability and reduced costs

Abbreviations: CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; PET, positron emission tomography.

pre-defined cut-points considering real-world analytical variations (e.g., different instruments, batch-to-batch variations) are still needed.

7 | CONCLUSIONS

Despite reflecting different aspects of Aβ, converging evidence indicates that both Aβ-PET and CSF biomarkers have excellent performance for the detection of Aβ pathology. Standardization efforts have resulted in a high degree of repeatability across different settings, which allowed the reliable implementation of these diagnostic tools in clinical settings. Aβ-PET and CSF biomarkers will be even more important in clinical practice as new disease-modifying therapies become available. Current evidence suggests that plasma biomarkers for AD could also play an important role as an adjunct to these markers, rather than completely replace them.

The increased use of Aβ-PET and CSF biomarkers in clinical practice underscores the need for a thorough understanding of their strengths, but also their key differences and limitations. Prompted by their excellent accuracy for detecting Aβ and high concordance, some researchers have suggested that Aβ-PET and CSF biomarkers could be considered fully interchangeable biomarkers. Although this assumption can

be reasonably valid in conceptual frameworks or to address specific research questions, the situation is likely more complex in clinical practice. The present narrative review highlights a number of situations that, although relatively infrequent, can result in a significant number of misdiagnosed patients, particularly if the use of these biomarkers escalates. Persistent issues such as discordant biomarker results, occurring in approximately 10%–20% of the patients, false positives driven by comorbidities, or practical limitations emphasize the necessity for careful selection of the most appropriate biomarker for each clinical scenario, rather than assuming complete interchangeability (Table 4),[28, 125, 326] The accuracy of biomarker results is now even more critical, as inaccuracies can lead to the inappropriate initiation of disease-modifying therapies for AD in individuals who do not have AD pathology. Currently, the public health consequences of inaccurate biomarker results in persons treated with disease-modifying therapies remain unclear.

The advent of anti-Aβ therapies is likely to expand the clinical applications of Aβ biomarkers beyond the traditional binary assessment of Aβ for treatment eligibility. Previous clinical trials (TRAILBLAZER-ALZ 2) have based treatment discontinuation decisions on quantitative Aβ-PET measurements of changes in Aβ burden and are now included in the FDA-approved donanemab therapy. Therefore, it is plausible that, when these drugs become widely available, clinicians will also request repeat Aβ-PET scans to confirm Aβ removal and decide on treatment discontinuation. It is important to note that, currently, reliable assessment of treatment-related Aβ plaque clearance is only possible with Aβ PET, which again underscores the differential applications of Aβ-PET compared to fluid biomarkers.

In summary, this narrative review provides substantial evidence demonstrating the high reliability of Aβ-PET and CSF biomarkers for detecting Aβ pathology in clinical practice. However, rather than being fully interchangeable, current evidence suggests that careful consideration of the specific clinical context is necessary to select the most appropriate biomarker and minimize inaccurate results. New clinical applications of Aβ biomarkers beyond binary classification, such as longitudinal monitoring of treatment-related effects, further highlight the need to delineate the specific capabilities of each biomarker. The field of fluid biomarkers, particularly BBMs, is rapidly evolving, likely resulting in novel applications of these markers as standalone tools or in synergy with Aβ-PET imaging. Overall, current literature suggests that both Aβ-PET and CSF biomarkers will continue to play an increasingly important role in the diagnostic workup of patients with AD.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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