WhitePaper

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# Emerging Alzheimer's Disease Care Pathways

## The Complementary Roles of Blood-Based Biomarkers and Positron Emission Tomography

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## Executive Summary

Alzheimer's disease (AD) is a rapidly growing global health crisis, affecting approximately 10% of individuals aged 65 years and older, with prevalence expected to double by 2050. The clinical landscape of AD is undergoing a fundamental transformation driven by the introduction of anti-amyloid disease-modifying therapies (DMTs) and the transition toward biologically defined diagnostic frameworks. Contemporary guidelines now emphasize the identification of AD based on in vivo biomarkers of amyloid and tau pathology rather than on syndromic clinical presentation alone.

As therapeutic options expand, early and accurate diagnosis has become a prerequisite for treatment eligibility. DMTs have demonstrated clinical efficacy in early-stage AD populations with confirmed amyloid pathology, reinforcing the need for timely and biologically validated diagnostic pathways.

In response, care pathways are being restructured to enable earlier identification of at-risk individuals and more efficient stratification for confirmatory testing and treatment of AD. This evolution is characterized by a shift toward initial screening and triage into primary care settings, supported by a progressive decentralization of confirmatory diagnostic infrastructure to neurology and memory clinics. The objective is to reduce diagnostic delay, increase patient throughput, and improve access to DMTs.

Within this evolving framework, blood-based biomarkers (BBMs), particularly plasma phosphorylated tau species (e.g., p-tau217), are emerging as scalable and minimally invasive tools for early detection and risk stratification in AD. In parallel, Positron Emission Tomography (PET) imaging and Cerebrospinal Fluid (CSF) testing remain the established biomarker standard for in vivo confirmation of AD pathology. PET imaging provides direct spatial visualization and quantification of aggregated protein deposition in the brain, enabling definitive biological classification of disease and supporting treatment decision-making in patients being considered for DMTs.

This white paper critically evaluates the complementary roles of BBMs and PET imaging in next-generation AD care pathways. It assesses their respective clinical utility, operational feasibility, and alignment with current guideline-based diagnostic frameworks. The analysis focuses on how these modalities can be integrated into scalable, efficient, and biologically grounded diagnostic pathways that balance equitable access, early detection, diagnostic accuracy, and healthcare system capacity. It is intended for neurologists, memory clinic leaders, healthcare administrators, and imaging specialists involved in the implementation of biomarker-driven AD care pathways, and aims to inform optimized, guideline-aligned implementation strategies for disease management in real-world clinical practice.

## Modern Alzheimer's Disease Care Pathways

Alzheimer's disease (AD) is the leading cause of dementia worldwide causing significant mortality and functional decline and its prevalence continues to rise with the increase of life expectancy. In the United States (U.S.), nearly 7 million people are living with AD, with projections approaching 13 million in the coming decades[1]. Historically, AD diagnosis was based primarily on clinical syndromic assessment, supported by structural imaging and neuropsychological testing, often at stages where neurodegeneration was already advanced[2]. This approach is no longer sufficient in the era of disease-modifying therapies (DMTs), where intervention is most effective in biologically defined early disease stages.

## From Syndromic to Biological Diagnosis of the Disease

AD is a progressive, neurodegenerative disease associated with cognitive, functional, and behavioral impairments[2]. Pathologically, AD is characterized by two hallmarks: the progressive accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular tau neurofibrillary tangles (NFTs) which cause progressive neuronal loss and synaptic dysfunction. These changes begin years or decades before clinical symptom onset, establishing AD as a continuum spanning from an asymptomatic preclinical phase with biomarker evidence of AD (preclinical AD), through mild cognitive impairment (MCI) to full-onset AD dementia (Figure 1)[3]. Importantly, AD is also a biologically heterogeneous disease. Diagnostic uncertainty often extends beyond amyloid status to include mixed vascular pathology, Lewy body disease, frontotemporal degeneration, and other co-pathologies.

Preclinical AD, the earliest stage in the AD continuum, is a prolonged asymptomatic phase characterized by the presence of AD pathology in the absence of detectable cognitive or functional impairment. Its duration varies widely and may extend over a decade, depending in part on age at onset. Progression to MCI due to AD is influenced by factors such as age, sex, and apolipoprotein E (APOE) status, and not all individuals with AD pathology will develop clinical symptoms. In those who progress, MCI due to AD typically presents with early short-term memory impairment followed by decline in additional cognitive domains, eventually leading to AD dementia with severe deficits that interfere with daily functioning and independence.

Early diagnosis enables proactive care planning, access to DMTs, and implementation of lifestyle and risk-reduction strategies that may help delay cognitive, functional, and behavioural decline. It may also reduce healthcare burden and system-level costs.

The dissociation between pathology and clinical presentation has fueled recent interest in biomarker-based diagnosis. The National Institute on Aging and Alzheimer's Association (NIA-AA) has recently created a research framework that shifts the definition and diagnosis of AD in living people from a syndromic to a biological construct[4]. In this framework biomarkers are grouped by A/T/N classification[4] based on:

**A** – the detection of Aβ through amyloid Positron Emission Tomography (PET) or Cerebrospinal fluid (CSF);

**T** – the detection of tau biomarkers through CSF p-tau, or tau PET;

**N** – neurodegeneration biomarkers through [18F]-fluorodeoxyglucose (FDG)–PET, structural Magnetic Resonance Imaging (MRI), or CSF total tau.

## The Alzheimer's Disease continuum

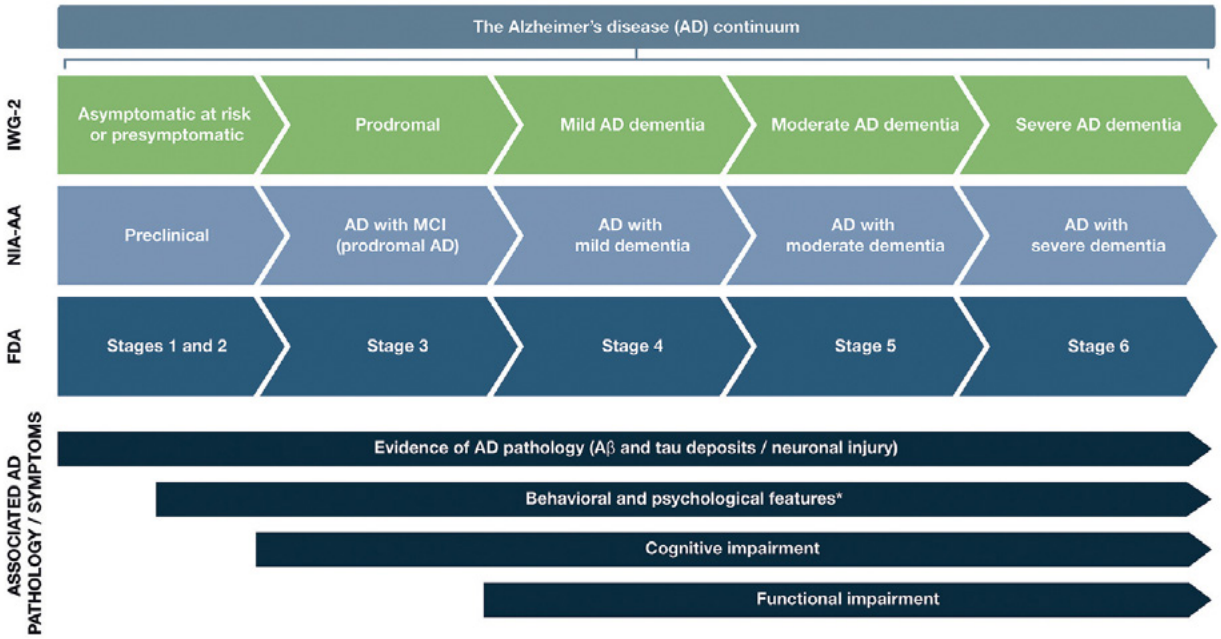


Figure 1: The AD continuum can be classified into different stages from preclinical AD to severe AD dementia; This figure provides a summary of the different naming conventions that are used within the AD community and the symptoms associated with each stage of the continuum. Abbreviations: Aβ, amyloid-beta. AD, Alzheimer's disease. FDA, Food and Drug Administration. IWG, International Working Group. MCI, mild cognitive impairment. NIA-AA, National Institute on Aging – Alzheimer's Association[3]

## Therapeutic Disruption: The Rise of Disease-Modifying Therapies

The growing body of evidence showing that accumulation of aggregated Aβ in early AD initiates pathological processes associated with AD led to the introduction of two anti-amyloid DMTs: Lecanemab (marketed as Leqembi)[6] and Donanemab (marketed as Kisunla)[7]. Both of these drugs are approved by the Food and Drug Administration (FDA) – in 2023 and 2024, respectively – for the treatment of early AD: MCI or mild dementia due to AD. The availability of these drugs has fundamentally altered diagnostic and therapeutic objectives in AD by shifting the focus from symptomatic management to disease modification through the reduction of Aβ.

Early-stage biological confirmation of amyloid pathology has become a prerequisite for DMT eligibility, transforming diagnosis of AD from a descriptive exercise to a gating step for access to therapy, with direct clinical and economic consequences.

Discovery and development of new therapies for AD has a growing number of trials with a diverse array of AD pathophysiological processes being addressed by drugs in trials. On the Index Date of January 1, 2026, there are 192 clinical trials for AD assessing 158 drugs (Figure 2)[5]. 70% of current trials are developing new disease targeted therapies for AD.

## Agents in clinical trials for treatment of Alzheimer's Disease

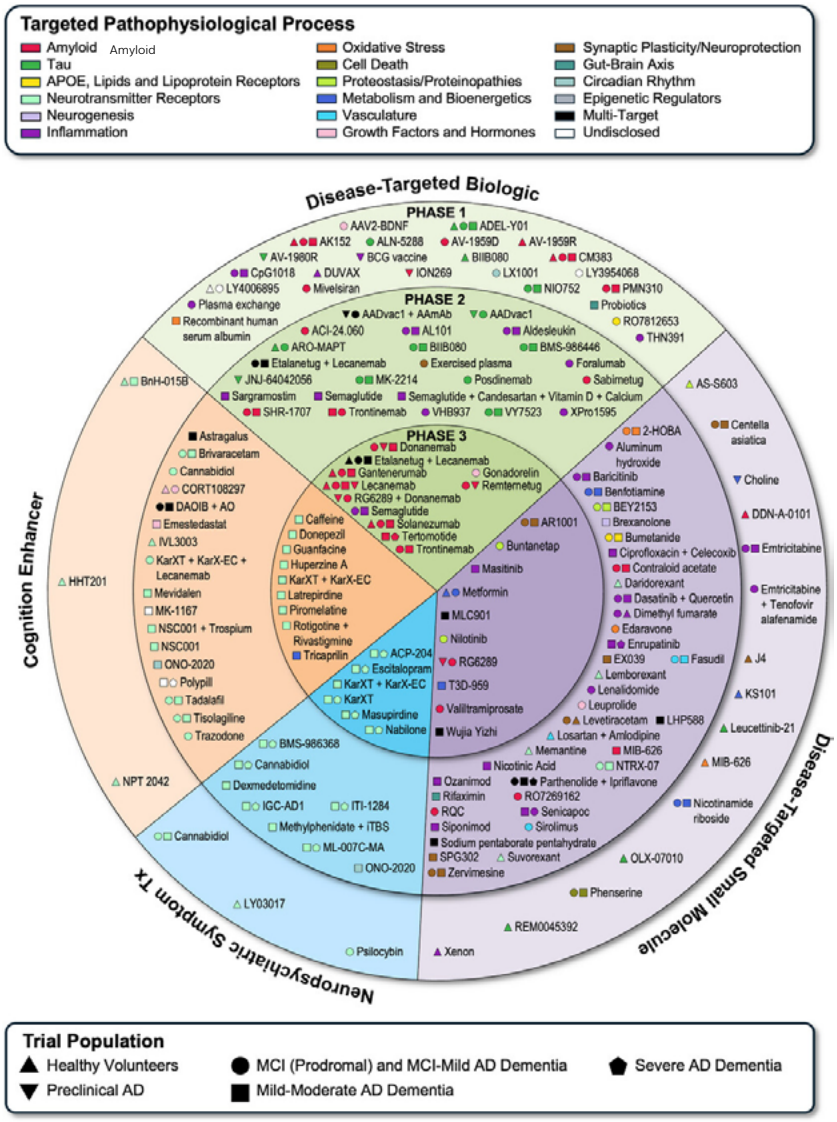


Figure 2: Agents in clinical trials for treatment of AD on the Index Date of January 1, 2026, as recorded on clinicaltrials.gov. The inner ring shows Phase 3 agents; the middle ring includes Phase 2 agents; the outer ring presents Phase 1 therapies. Agents in green areas are biologics; those in purple areas are disease modifying small molecules; agents in orange areas are symptomatic agents addressing cognition enhancement; and those in the blue sections of the figure target behavioral and neuropsychiatric symptoms[5]

From currently ongoing clinical trials, around two third enroll individuals at very early stages of the disease and fifty percent use a biomarker for eligibility [5]:

- 5% involve cognitively unimpaired persons with biomarker or genetic evidence of AD;
- 35% include participants with MCI due to AD or prodromal AD (with or without biomarker confirmation of AD patholo-gy);
- 27% involve participants with early AD (MCI or mild AD dementia);
- 53% enroll patients with mild AD dementia;
- 33% include participants with moderate or severe AD dementia (with or without biomarker confirmation of AD)

Biomarkers have therefore transformed clinical trials by enabling investigators to: confirm the diagnosis of AD for trial eligibility; stratify or enroll patients based on likelihood of progression; monitor therapeutic effects longitudinally; and verify the pharmacodynamic effect of candidate therapies as a study outcome.

## Clinical Decisions Across Modern Alzheimer's Care Continuum

In 2021, a practical guide for the early diagnosis of AD in clinical practice was published, with recommendations that divided the diagnosis of AD into the following steps highlighting the most valuable tests for each step (Figure 3):

1: detect
2: assess/differentiate
3: diagnose
4: treat

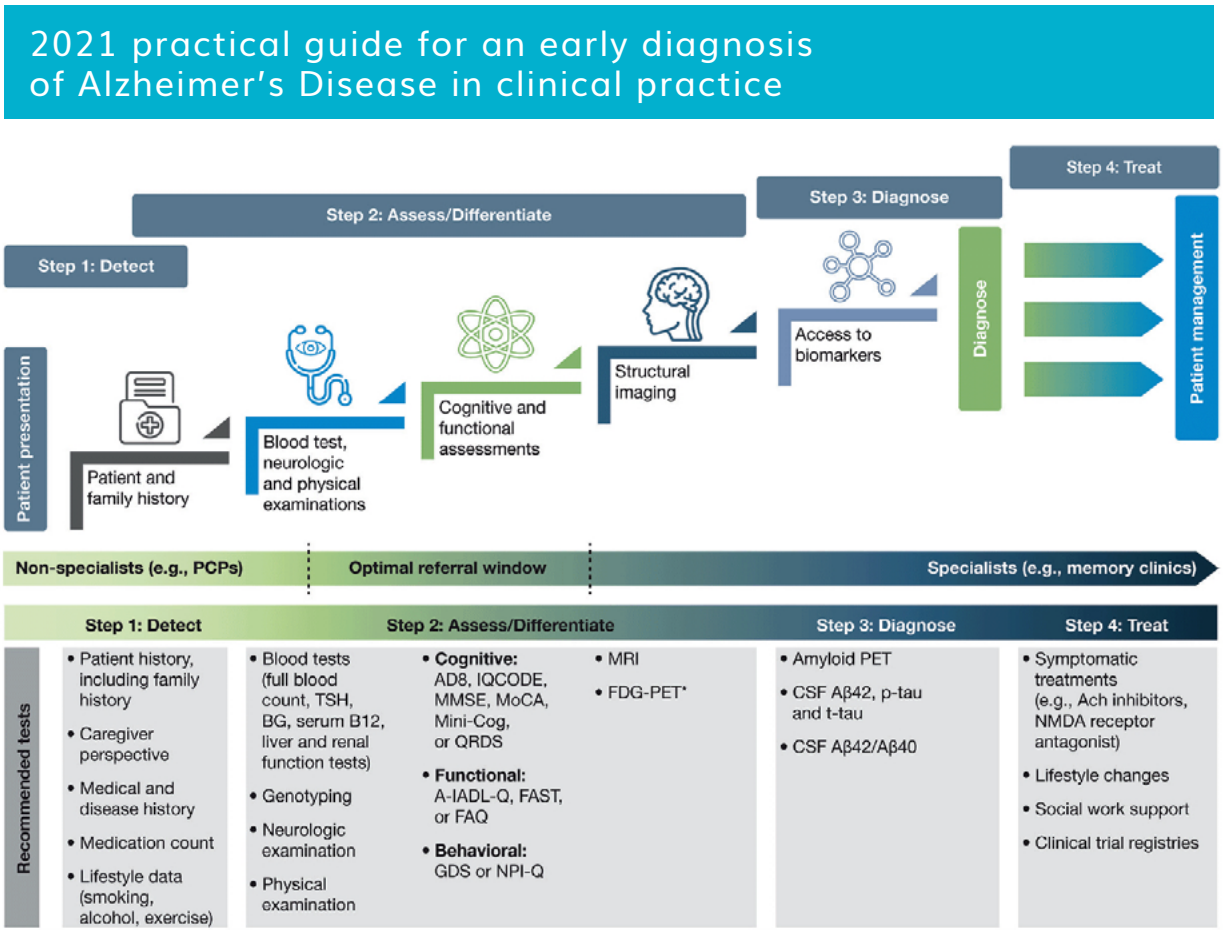


Figure 3: In 2021, a practical guide for an early diagnosis of AD in clinical practice was published with a stepwise infographic to highlight key stages within the diagnostic process, along with the recommended tests to support each step. The diagnostic process for AD was divided into the following steps: detect, assess/differentiate, diagnose, and treat [3]

The approval of DMTs in the more recent years has driven a strong shift toward earlier and more scalable detection of AD pathology, increasing pressure to refine clinical care pathways. The modern AD care continuum consists of a sequence of tightly linked, interdependent decisions spanning **early detection, diagnostic confirmation, treatment initiation, and longitudinal management**. Decisions at early-stage influence treatment eligibility, timing of intervention, and healthcare resource allocation. Inefficiencies in early screening and triage can propagate downstream, affecting diagnostic accuracy, access to therapy, and system capacity.

This shift requires both new diagnostic tools and restructured clinical workflows across primary care, specialist neurology, and memory clinic settings, supported by scalable and decentralized technologies. It also increases complexity in interpreting multimodal biomarkers across heterogeneous care environments. Effective implementation depends on a coordinated, patient-centred model involving healthcare providers (HCPs), specialists, and payers to ensure early signs of AD are not missed and appropriate testing is used at the right stage. Clear separation between screening in non-specialist settings and diagnostic confirmation is essential, given their distinct performance requirements[3].

## Early detection of Alzheimer's Disease

When a patient presents with symptoms suggestive of early-stage AD, clinicians must first conduct a comprehensive clinical assessment to rule out other potential causes of cognitive impairment. Even in cases of subtle symptoms, HCPs should use validated tools to confirm and characterize early cognitive decline consistent with possible AD[3]. Screening tests for early detection of AD should prioritize accessibility, scalability, and sensitivity with the objective of identifying individuals at increased risk of underlying AD pathology. At this stage, triage tests are used to rule out disease with high confidence when negative, whereas positive results require specialist evaluation and confirmatory diagnostic testing.

### The role of primary care

Primary care is typically the first point of contact for individuals with cognitive complaints, but early recognition of AD remains challenging. The gradual and heterogeneous onset of symptoms, combined with time constraints in consultations, limits reliable detection of early disease. Rapid identification of potential AD-related symptoms is therefore critical in this setting[3].

Over the past decade, significant efforts have focused on developing tools to support early detection of AD pathology in individuals presenting to the primary care with cognitive concerns, and to identify those at risk of developing AD in the future. While cognitive assessments can achieve good diagnostic performance, they may lack sufficient sensitivity in the earliest disease stages.

Blood-based biomarkers (BBMs), particularly phosphorylated tau species such as p-tau181 and p-tau217, have recently received regulatory approval from the FDA and Conformité Européenne (CE), supporting their use in improving diagnostic accessibility, efficiency, and referral quality[8–10]. Because blood testing is already widely integrated into routine clinical practice, BBMs are well suited for use as an initial step in a multistage diagnostic pathway. In primary care, they may help identify individuals who require referral for specialist evaluation and confirmatory testing.

### Plasma p-tau181

The p-tau181 plasma test measures the level of phosphorylated tau 181 in the blood, a protein linked to Aβ plaque and tau pathology characteristic of AD. Elevated levels of p-tau181 can indicate the presence of Alzheimer's-type changes in the brain, helping to identify individuals with a low likelihood of underlying amyloid pathology and guide further clinical investigation.

In 2025, Roche Elecsys® p-tau181 received CE mark and FDA clearance as an aid in the initial assessment to rule out Alzheimer's pathology in the primary care setting. Clinical data from the presented prospective multicentre study showed that the test achieves a high negative predictive value (93.8%) in a diverse patient population, aged 55 and older presenting with signs, symptoms or complaints of cognitive decline (83.6% sensitivity)[8].

Although p-tau181 was one of the first highly successful BBMs of AD and useful as a rule-out assay, it has shown more overlap between healthy adults and Alzheimer's patients, making its predictive power slightly lower than p-tau217[9]. The test can however be highly valuable screening tool as a rule-out assay in primary care.

## Plasma p-tau217

P-tau 217 is a newer BBM that is more specific to Aβ plaques and tau NFTs in the brain. P-tau217 appear to increase early in the AD continuum and correlate strongly with cerebral amyloid pathology. It has shown to outperform p-tau181 in differentiating clinical AD[9].

In May 2025, FDA cleared the Lumipulse G p-tau217/ß-Amyloid 1-42 plasma ratio for the early detection of amyloid plaques associated with AD in adults aged 55 years and older who exhibit signs and symptoms of the disease. In May 2026, Lumipulse G p-tau217 received CE marking.

In the clinical study presented, the manufacturer's reported performance claims were 98% sensitivity and 91% specificity, and at a 51.1% amyloid pathology prevalence, a positive predictive value (PPV) of 91.8% and a negative predictive value (NPV) of 97.3%. Also, approximately 20% of patients received an indeterminate result requiring further confirmatory testing with CSF or PET[10, 12].

In May 2026, Roche Elecsys® p-tau217 (developed in collaboration with Eli Lilly and Company) also received CE marking, as the first blood test for AD pathology with a single-assay design, intended to rule in and rule out amyloid pathology with same high and low cutoff values across primary and secondary care settings in people presenting with symptoms or complaints of cognitive decline[11].

In order to evaluate performance generalizability and real-world utility of plasma biomarkers, a recent study evaluated the performance of Lumipulse p-tau217/Aβ42 ratio cut points in a tertiary care subspecialty clinic – referred to as cohort 1 (Mayo Clinic) - and compared results with those from a risk-enriched AD cohort – referred to as cohort 2 (Wisconsin Alzheimer's Disease Research Center [WADRC] and Wisconsin Registry for Alzheimer's Prevention [WRAP]), which was used as part of the assay's FDA validation study (Figure 4)[12]. P-tau217/Aβ42 ratio cut points achieved lower diagnostic accuracy in cohort 1 (77%) vs cohort 2 (95%), driven by reduced specificity and PPV. In contrast, Mayo Clinic established p-tau217/Aβ42 ratio and p-tau217 concentration cut points achieved diagnostic accuracy and PPV exceeding 90% in both cohorts, although the NPV was lower in cohort 2. In cohort 1, diagnostic performance of the p-tau217/Aβ42 ratio using FDA-cleared cut points considerably differed from manufacturer claims, particularly due to unexpectedly low specificity. After excluding preanalytical sample-handling differences, it was concluded the likely explanation for the observed differences was reagent performance variation between sites and/or compared with reagents used in the FDA validation study[12]. The findings support the need for ongoing evaluation of biomarker assays in diverse populations to ensure accurate diagnosis and risk stratification in routine practice.

Overall, the available data suggest that p-tau 217 can reliably predict the absence of amyloid pathology associated with AD at the time of the testing in cognitively impaired patients. However, these tests are not intended to serve as stand-alone diagnostic tools, but rather to support the early detection of AD alongside standard clinical and neuropsychologic assessments. It should also be highlighted that BBMs carry a risk of false-positive results, which may lead to inappropriate diagnosis, unnecessary treatment, additional confirmatory testing, or delays in appropriate care.

In 2025, a panel of clinicians, subject-matter experts, and guideline methodologists formulated the first in a series of clinical practice guidelines on the use of BBMs to assess levels of AD pathology as part of a full diagnostic workup of patients with cognitive impairment within specialized care settings[13]. Given the significant variability in the diagnostic accuracy of currently available tests, and the fact that many commercially available BBM tests do not meet the recommended sensitivity and specificity, the panel cautioned against replacing comprehensive clinical evaluation and confirmatory testing with BBMs alone.

## p-tau 217 to β-Amyloid 1-42 (Aβ42) ratio and p-tau217 concentration measures by amyloid status across cohorts

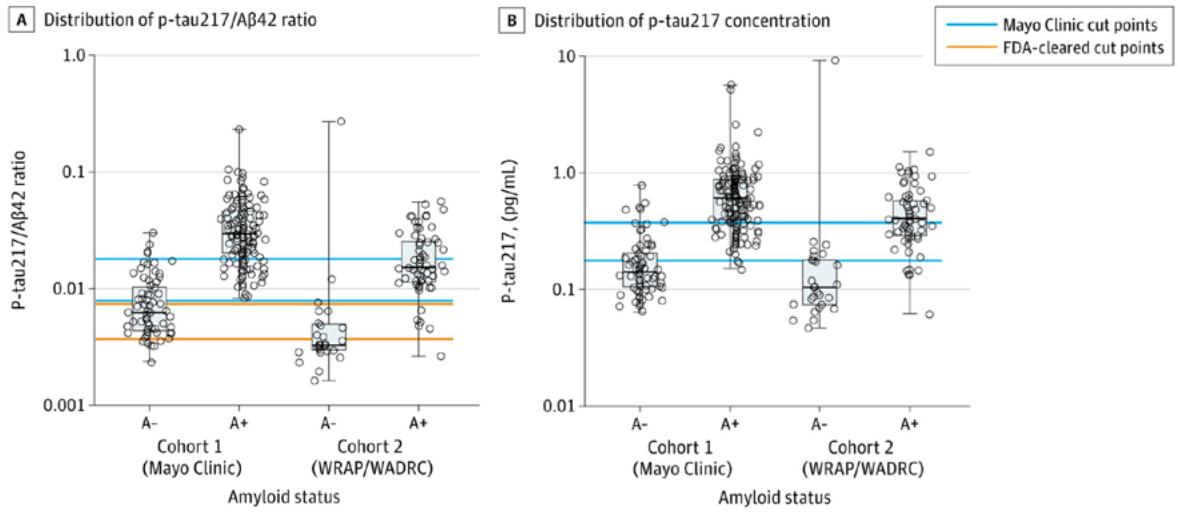


Figure 4: Box-and-Whisker Plots Showing Distribution of the Phosphorylated Tau 217 (P-tau217) to β-Amyloid 1-42 (Aβ42) Ratio and P-tau217 Concentration Measures by Amyloid Status Across Cohorts: cohort 1 (Mayo Clinic) and cohort 2 (Wisconsin Alzheimer's Disease Research Center [WADRC] and Wisconsin Registry for Alzheimer's Prevention [WRAP]). For the p-tau217/Aβ42 ratio, the Mayo Clinic–established cut points are as follows: 0.0074 or lower indicates negative; 0.0075 to 0.0131, intermediate; and 0.0132 or higher, positive. The US Food and Drug Administration (FDA)–cleared cut points are as follows: 0.00370 or less, negative; 0.00371 to 0.00737, indeterminate; and 0.00738 or higher, positive. B, For the p-tau217 concentration, the Mayo Clinic–established cut points are as follows: 0.185 pg/mL or less indicates negative; 0.186 to 0.324 pg/mL, intermediate; and 0.325 pg/mL or higher, positive. The center horizontal line of each box indicates median; lower and upper borders of boxes, 25$^{th}$ and 75$^{th}$ percentiles, respectively; error bars, range; and circles, data points [12]

## Diagnostic Confirmation

Confirmatory testing requires high specificity and direct pathophysiological evidence, particularly in the context of treatment eligibility. Patients with abnormal results at initial assessment/triaging, or persistent clinical concern despite negative tests, are typically referred to neurology or memory clinics for specialist evaluation. The goal of confirmatory evaluation is differential diagnosis and distinguishing AD from other neurodegenerative or reversible causes of cognitive impairment. Established biomarker modalities such as amyloid PET, tau PET, Fluorodeoxyglucose (FDG)-PET, and CSF remain reference biomarker standards for detecting core pathological processes with high diagnostic accuracy.

## Positron Emission Tomography (PET)

PET plays a central role in the in vivo biological confirmation and differential diagnosis of AD. FDG-PET reflects regional glucose metabolism and serves as a marker of neurodegeneration detecting patterns of hypometabolism that support diagnosis and may help predicting conversion from MCI to AD [3].

Amyloid and tau PET have been instrumental in confirming AD, defining disease staging, validating therapeutic targets, and structuring clinical trial populations, all of which have direct implications for clinical management (Figure 5) [14]. They provide direct in vivo spatial visualization of aggregated pathology in the brain, with amyloid tracers binding to fibrillar Aβ plaques and tau tracers reflecting NFT distribution consistent with Braak staging.

Amyloid PET is valuable in distinguishing between etiologically distinct forms of neurodegeneration, particularly in cases of mixed pathologies, and is widely used in diagnostic workflows, trial stratification, and treatment monitoring [14, 15]. Three Fluorine-18 (F18) amyloid-PET tracers are currently approved for routine clinical use: F18-florbetapir (Amyvid™, Eli Lilly), F18-flutemetamol (Vizamyl™, GE HealthCare), and F18-florbetaben (Neuraceq®, Life Molecular Imaging). These agents show high correlation with the historical gold-standard tracer Pittsburgh compound B (PiB, $^{11}$C) in cortical binding and diagnostic classification. Quantification of amyloid PET has been standardized through the Centiloid scale which facilitates harmonization across tracers and sites, and is recognized as a validated measure of global amyloid load in the brain [15].

## Examples of positive and negative Aβ and tau PET scans

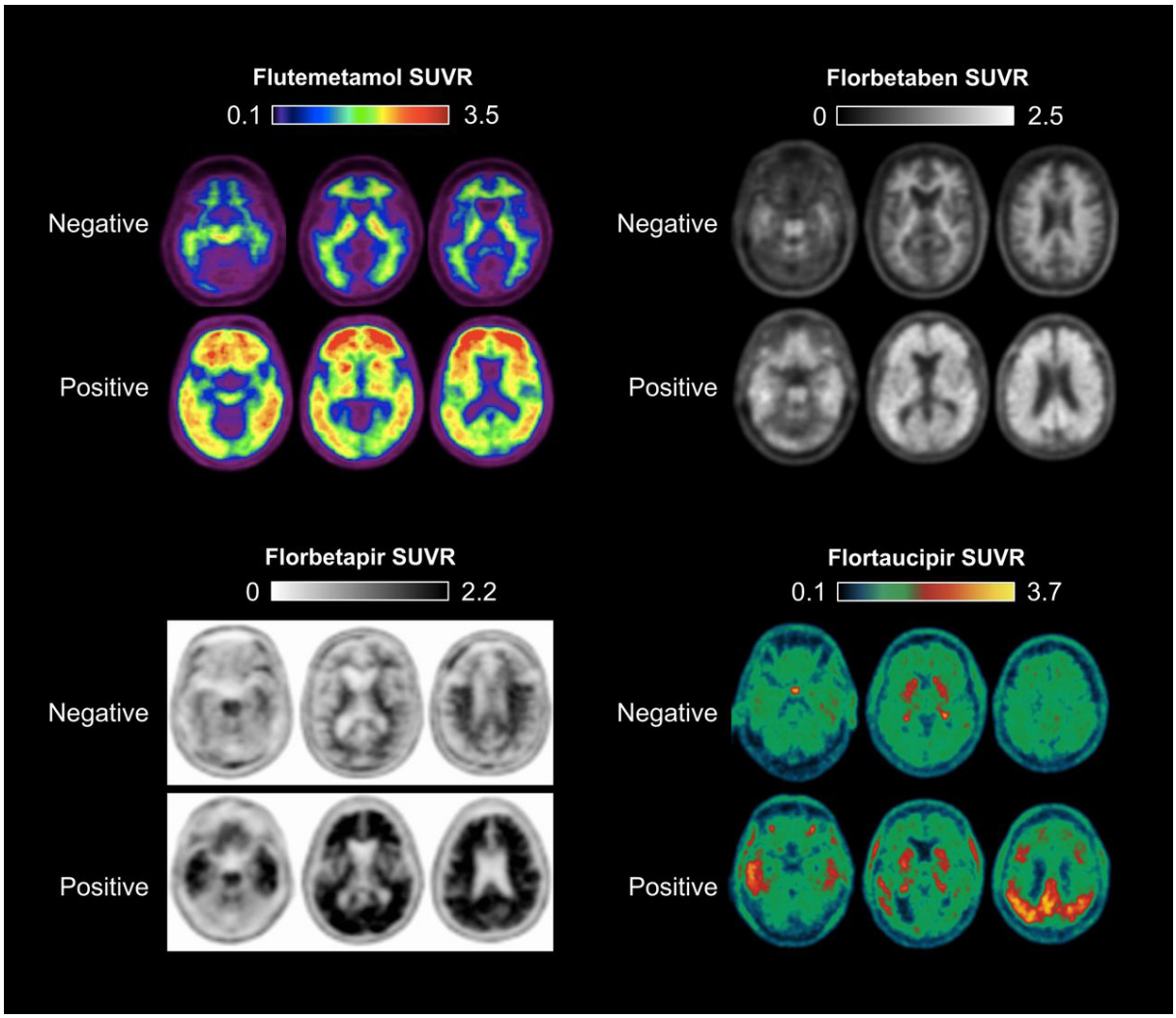


Figure 5: Examples of positive and negative Aβ and tau PET scans with FDA-approved radiotracers. SUVR images were created using pons (18F-flutemetamol), whole cerebellum (18F-florbetaben, 18F-florbetapir), and inferior cerebellar gray matter (18F-flortaucipir) as reference regions. Each image is displayed in approved gray and white or color scale for clinical interpretation [14]

Tau PET has emerged as a critical tool for in vivo visualization of tau deposits, which correlates closely with clinical severity while its topological distribution defines disease subtypes of AD. Moreover, since tau aggregates into distinct forms, tau accumulation follows a predictable spatial progression, as outlined by Braak staging. Tau PET positivity is associated with a greater risk of future cognitive decline and clinical progression, and it is increasingly being incorporated into routine clinical workflows. Recent joint EANM/SNMMI recommendations on the use of tau PET imaging in AD (June, 2026) provide guidance on appropriate clinical indications, patient preparation, image acquisition, visual interpretation, quantitative analysis, and standardized reporting procedures, primarily focused on the use of F18-flortaucipir (Tauvid, Eli Lilly), which is currently the only approved tau radiotracer, as well as several promising next generation tau PET radiotracers which are already commonly used by the community and are undergoing clinical evaluation to be considered a candidate for future regulatory approval [16].

## Representative images of tau PET radiotracers for Alzheimer's Disease

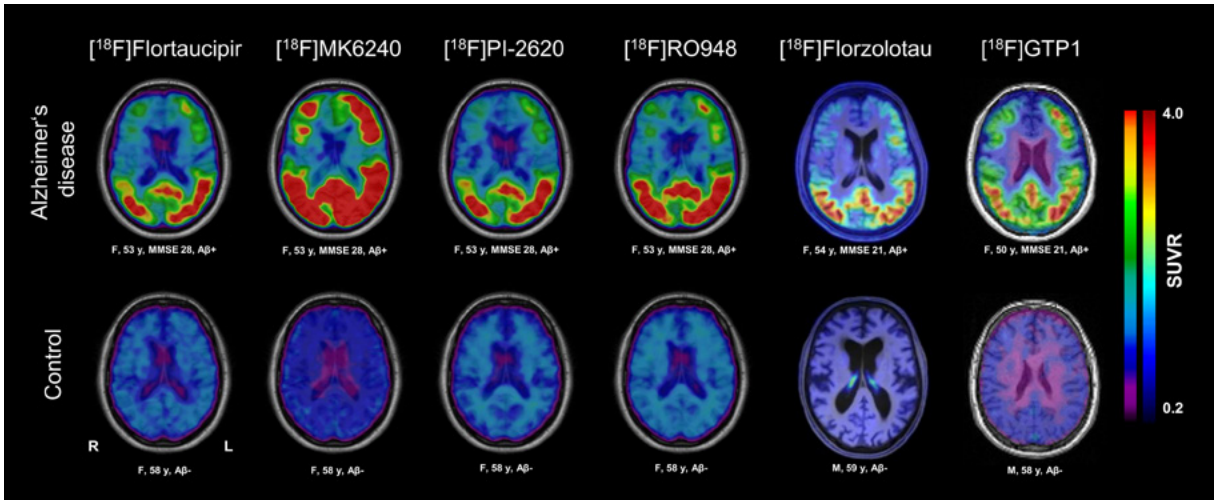


Figure 6: Representative images of tau PET radiotracers for Alzheimer's disease (AD) and controls. Please note that F18-flortaucipir, F18-MK-6240, F18-PI-2620, and F18-RO948 images are derived from the same individuals of the HEAD study, adjusted to the left color bar. The right color bar applies to F18-florzolotau and F18-GTP1 [16]

## Appropriate Use Criteria for amyloid PET and tau PET:

The 2025 updated use criteria for amyloid and tau PET provide expert recommendations for clinical use of these technologies in the evolving landscape of diagnostics and therapeutics for AD [14].

Clinical scenarios generally considered appropriate for use of amyloid PET:

- MCI due to AD/mild AD to confirm biomarker
- Eligibility or monitoring of anti-amyloid therapies
- Atypical presentations
- Early onset (<65 years age)
- Inconclusive CSF or BBMs results

Tau PET is generally considered appropriate in the following scenarios:

- MCI or dementia syndrome, younger than 65 years and in whom AD pathology is suspected
- Prognostic assessment in MCI due to suspected AD
- Determining eligibility for DMTs
- Atypical presentations or mixed pathology

## Conventional PET Limitations

While PET scans are highly effective for visualizing amyloid plaques and tau tangles, they face notable limitations such as:

- Radiation exposure: PET scans utilize small amounts of radioactive tracers and repeated scans over time expose patients to cumulative ionizing radiation.
- Access disparities due to complex infrastructure requirements such as radiation protection and shielding
- High costs of scanner procurement and operation, and radiotracers.
- Reimbursement barriers: while some national health systems and insurers such as Medicare in the U.S. have expanded coverage for amyloid PET scans, out-of-pocket costs remain prohibitively high for many when scans aren't covered.
- Tracer availability: dependence on regional radiotracer manufacturing and distribution infrastructure.
- Workflow complexity involving radiotracer scheduling, uptake periods, patient preparation.

## Cerebrospinal Fluid (CSF)

CSF biomarkers of AD, specifically Aß42/ Aß40 ratios, total tau (t-tau), and p-tau, are tested through lumbar pucture, and reflect brain pathophysiology through protein concentrations in CSF. CSF biomarkers are used in clinical practice as diagnostic tools, and remain highly validated and guideline-supported alternatives to PET imaging for confirmation of AD pathology[17]. While PET provides spatial visualization, CSF testing offers distinct clinical and practical advantages that could make it the preferred diagnostic modality in several scenarios:

- Direct cost savings: CSF testing costs a fraction of a PET scan, significantly reducing the financial burden on healthcare systems and out-of-pocket patient expenses
- Broader reimbursement: insurance providers and national health programs e.g. certain European healthcare systems cover lumbar punctures more consistently than expensive amyloid/tau PET scans
- Standard lab infrastructure: in the absence of PET infrastructure, existing lab infrastructure can analyze CSF tests, bypassing the need for specialized nuclear medicine processing
- Scalable diagnostics: community hospitals can easily ship collected CSF samples to centralized reference laboratories, bypassing geographic barriers.
- Longitudinal testing and repeated monitoring for tracking disease progression with no radiation exposure

## CSF Limitations

Despite its advantages, CSF biomarker testing has several limitations:

- Invasiveness and patient burden: CSF collection requires lumbar puncture, which may cause temporary adverse side effects. The procedure can also contribute to patient reluctance due to its invasive nature.
- Spatial limitation: CSF biomarkers reflect global pathological burden but do not provide information on regional distribution of brain pathology.
- Standardization: variability across assay platforms, pre-analytical handling, and biomarker cutoffs can lead to inter-laboratory differences in results.
- Diagnostic overlap: overlapping biomarker profiles across neurodegenerative diseases, as well as co-pathologies, can reduce specificity. Borderline results requiring further testing may occur.

## Therapeutic Decision-Making

AD therapeutic decision-making includes assessment of treatment eligibility and risk, taking into account disease stage, comorbidities, and individual patient characteristics.

As precision medicine approaches become integrated into AD care, patient selection for DMTs increasingly relies on a combination of biological, clinical, and genetic characteristics. These include:

- Biomarker evidence of AD pathology, particularly confirmation of amyloid positivity through PET imaging or fluid biomarkers;
- Clinical disease stage, with current therapies primarily indicated for patients in the early symptomatic stages of AD;
- Genetic factors, including APOE genotype, which may influence both therapeutic benefit-risk assessment and treatment monitoring requirements.

Amyloid PET remains the established imaging modality for confirming amyloid pathology before anti-amyloid therapy initiation. Initial studies suggest that amyloid PET Centiloid quantification could also support identification of high tau burden, as the prevalence of tau PET positivity significantly rises within the 40–70 Centiloid range, reflecting early to established tau pathology[15].

Higher Aβ-PET burden has also been identified as one of the key risk factors for developing Aβ-related imaging abnormalities (ARIA) after treatment with donanemab while lower baseline Centiloid levels were associated with a greater clinical benefit [15]. As a result, it has been suggested that amyloid PET could support the stratification of patients likely to benefit more from therapy versus those having an increased risk of side-effects.

BBMs are increasingly being incorporated into clinical trials for participant pre-screening and cost reduction. Recent studies suggest that combinations of plasma eMTBR-tau243 and %p-tau217 may approximate an amyloid and tau PET-based AD biological staging scheme [18]. However, currently approved BBMs are suboptimal for supporting this important step and future studies should investigate similar combinations of plasma approaches to support effectively determine a patient's risk-benefit profile using fluid biomarkers alone.

Therefore, PET and CSF remain central components of trial designs as the established modalities for confirming amyloid or tau pathology at enrollment, assessing target engagement, monitoring biological treatment effects, and establishing biomarker-based study endpoints. As DMTs, including a growing pipeline of therapies directed against tau, neuroinflammation, synaptic dysfunction, and other disease mechanisms, move into earlier stages of the disease continuum, PET is expected to remain essential for validating therapeutic efficacy and supporting regulatory approval.

## Monitoring Treatment Effects and Longitudinal Surveillance

Regular follow-up is an important responsibility of the clinician managing a patient with DMT to:

- monitor for potential ARIA and other treatment-related abnormalities detected on MRI;
- evaluate treatment efficacy through amyloid PET imaging and potentially determine whether and when a patient has reached Aβ clearance;
- track disease progression and guide ongoing treatment decisions.

However, a challenging potential use of BBMs is as surrogate endpoints in clinical trials of DMT candidates. Current evidence suggests that BBMs cannot yet reliably replace amyloid PET for quantitative assessment of amyloid removal and treatment response at the individual-patient level, as they do not accurately reflect the actual Aβ load or changes after immunotherapy [15].

All plasma p-tau species are associated, to varying degrees, with both amyloid plaques and tau tangles, and it is not yet fully understood how plasma biomarkers' performance translates to treatment-monitoring scenarios. Additional longitudinal studies will be required to determine whether changes in plasma biomarkers reliably reflect therapeutic response, disease modification, or future clinical outcomes.

As a conclusion, although optimal biomarker strategies for longitudinal monitoring remain unresolved, PET will play a crucial role in disease monitoring efforts, particularly in scenarios where accurate quantification of biological treatment effects is important.

Figure 7 summerizes the potential benefits and challenges associated with the use of BBMs in different contexts of use.

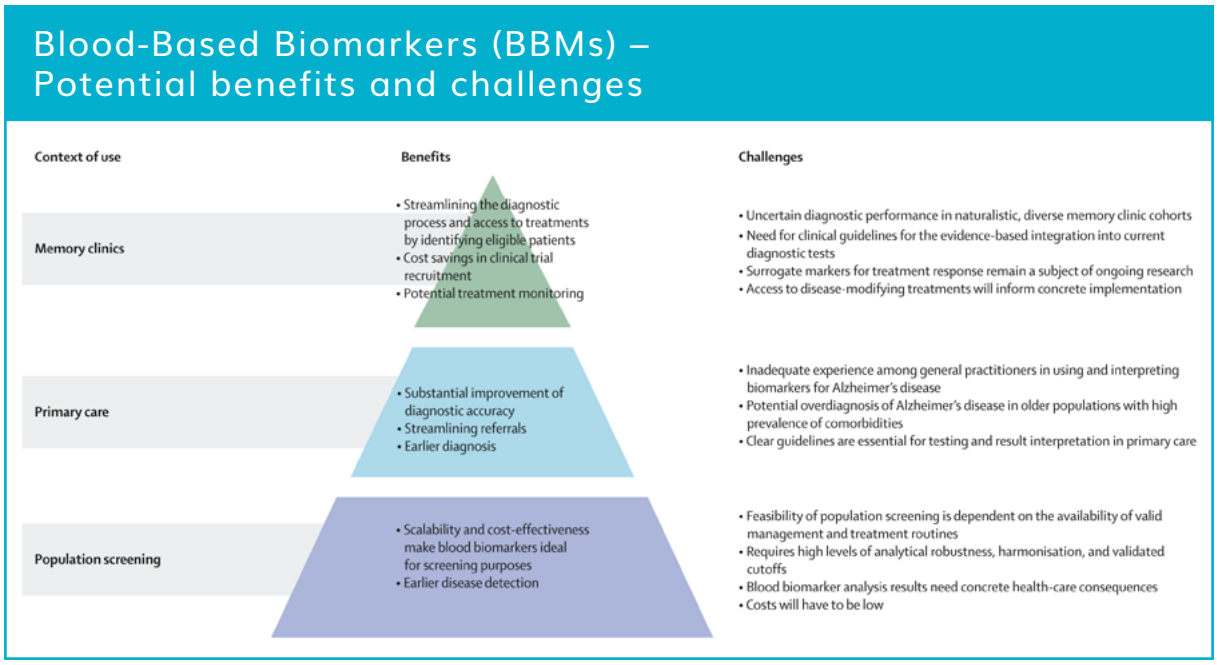


Figure 7: Potential benefits and challenges associated with the use of Blood-based Biomarkers (BBMs) in different contexts of use: population screening; primary care triaging and risk stratification for referral enrichment; and in memory clinic to streamline identification of patients eligible for treatment [19]

## Conclusion: In an Era Where Mild Matters

Available DMTs and drugs in clinical trials increasingly target the preclinical and early symptomatic stages of AD. The emergence of BBMs has raised an important question: "can they replace established biomarker modalities such as PET imaging?" While both BBMs and PET assess the core pathological processes of AD – Aβ deposition and tau aggregation – they provide different biological information and serve distinct clinical purposes.

BBMs, particularly plasma p-tau assays, have demonstrated strong performance for identifying individuals likely to harbor AD pathology and offer a promising solution for large-scale screening, triage, and referral enrichment due to their accessibility, low costs, minimal invasiveness, and compatibility with existing laboratory infrastructure. However, diagnostic performance may vary across clinical settings due to differences in disease prevalence, patient demographics, comorbidities, analytical platforms, and biomarker cut-offs [12]. Two-threshold approaches commonly used to optimize diagnostic accuracy still leave a clinically relevant proportion of patients requiring confirmatory testing. Furthermore, current BBMs remain limited in their ability to accurately provide regional and biologically staged quantification of amyloid and tau pathology or monitor treatment response longitudinally [15]. Consequently, BBMs are best viewed as probabilistic tools that estimate the likelihood of underlying AD pathology rather than provide definitive pathological confirmation. Their broader implementation in the clinical context will require continued analytical harmonization, standardized interpretation, and clear clinical guidance regarding appropriate use (Figure 7) [19].

PET imaging fulfills a fundamentally different role. Unlike BBMs, PET directly visualizes pathological burden in vivo, enabling confirmation of amyloid and tau pathology, regional assessment of disease distribution, biological staging, and quantitative monitoring of pathological change over time. PET therefore remains a highly specific biomarker modality for diagnostic confirmation, treatment selection, and longitudinal assessment in both clinical practice and research. Table 1 highlights some of the main strengths and limitations of PET versus BBMs in AD Care.

Table 1: Strengths and Limitations of Positron Emission Tomography (PET) versus Blood-Based Biomarkers (BBMs) in Alzheimer's Disease Care

| PET IMAGING STRENGTHS | BBMS STRENGTHS |
|---|---|
| • In vivo visualization of amyloid and tau pathology<br>• High specificity for diagnostic confirmation and treatment decision-making<br>• Spatial mapping and biological staging of pathology<br>• Quantification of regional Aβ and tau burden<br>• Established biomarker standard in clinical trials and clinical practice<br>• Monitoring treatment response and longitudinal pathological change | • Lower cost and broad accessibility<br>• Scalable for large-scale screening and triage<br>• Minimally invasive and suitable for repeated testing<br>• Sensitive to early pathological changes<br>• Efficient risk stratification and referral enrichment<br>• Potential to reduce demand on specialist diagnostic services |
| **PET IMAGING LIMITATIONS** | **BBMS LIMITATIONS** |
| • Limited availability in many healthcare systems<br>• High infrastructure and operational costs<br>• Radiotracer dependence: production, cost, availability<br>• Limited scalability for screening<br>• Requires specialized imaging expertise | • Lack of spatial information<br>• Indirect measure of brain pathology<br>• Variability across assays, platforms, settings, and cut-offs<br>• Increased risk of false-positive results in low-prevalence screening populations<br>• Limited ability to provide regional or anatomical disease staging*<br>• Limited utility for treatment monitoring * |

* Current evidence is evolving, and future studies may further define the role of blood-based biomarkers (BBMs) in disease staging [18], treatment monitoring, and longitudinal assessment of AD pathology.

## Future Directions

AD diagnostic accuracy has both clinical and economic implications. Poorly performing pathways risk inappropriate treatment decisions, delayed diagnosis, and missed opportunities for early intervention, while increasing pressure on specialist services and healthcare budgets through inefficient resource utilization.

To combine the scalability and cost-effectiveness of BBMs with the diagnostic precision of PET, current evidence supports a sequential, complementary biomarker strategy [15]. This approach improves pathway efficiency while maintaining the level of diagnostic confidence required for modern AD management. In this model, BBMs serve as triage tools to identify individuals with an increased likelihood of AD pathology, whereas PET imaging is reserved for confirmatory testing, indeterminate cases, atypical presentations, and treatment-related decision-making (Figure 8).

Ultimately, the success of these pathways will depend not only on technological innovation, but also on their integration into clinical guidelines, reimbursement models, and healthcare system capacity planning.

Several innovations are likely to reshape modern AD care pathways in the coming years. Multimodal AI-assisted diagnostic platforms that integrate plasma biomarkers, imaging data, clinical assessments, and demographic information may improve diagnostic accuracy, risk stratification, and clinical decision-making across the care continuum. Digital biomarkers derived from smartphones, wearable devices, computerized cognitive assessments, home-based testing and remote monitoring have the potential to detect subtle functional changes earlier and enable more continuous disease tracking and longitudinal follow-up outside traditional clinical settings, reducing barriers to care and alleviating pressure on specialist services.

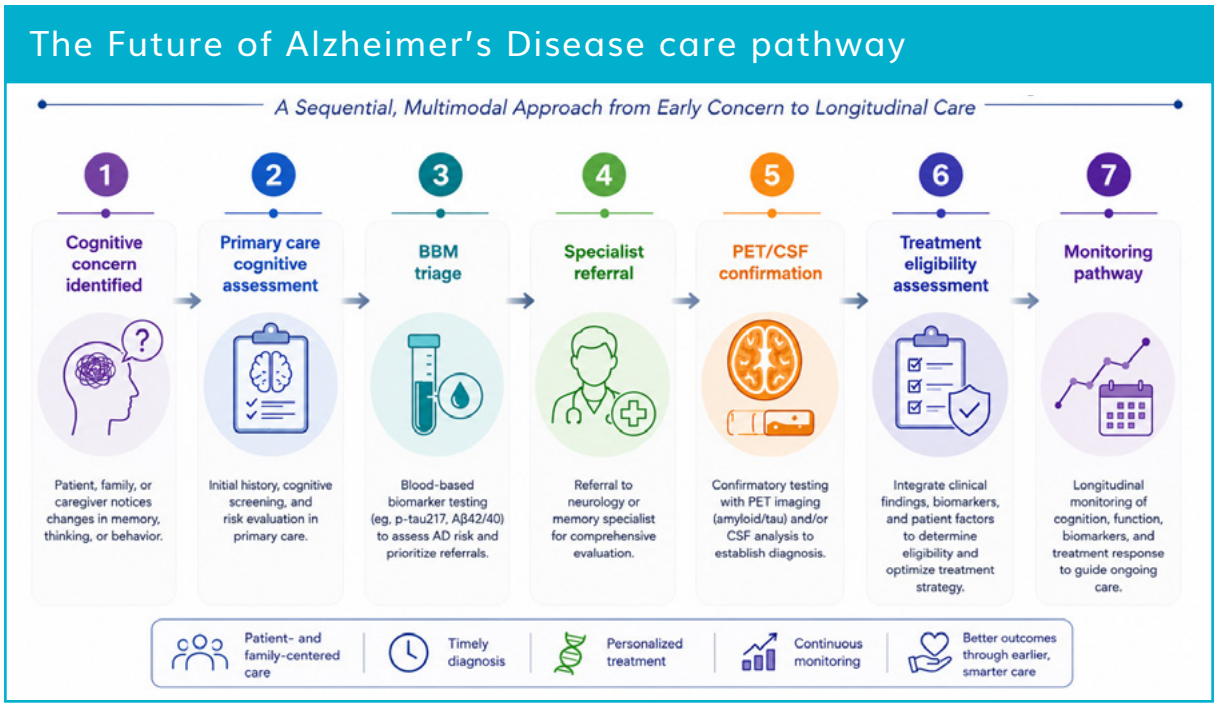


Figure 8: Proposed future AD care pathway incorporating a structured, sequential, and multimodal diagnostic framework. **1** – Identification of a patient with cognitive concerns; **2** – cognitive assessment in primary care; **3** – BBM-based triage to rule out AD pathology or identify individuals requiring specialist referral; **4** – comprehensive specialist evaluation in neurology or memory clinic settings; **5** – confirmation of AD pathology using PET imaging or CSF biomarkers; **6** – treatment eligibility and therapeutic strategy determined through integration of biomarker and clinical findings; and **7** – longitudinal monitoring based on treatment selection, safety requirements, and disease progression. Image created with the assistance of ChatGPT.

Beyond diagnostics, the therapeutic landscape continues to evolve. While current DMTs primarily target amyloid pathology, a growing pipeline of therapies directed against tau, neuroinflammation, synaptic dysfunction, and other disease mechanisms may broaden treatment options and support a more personalized approach to AD management.

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## Disclaimer

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Camilia Hoorvash, PhD, began her doctoral research in MRI neuroimaging of dementia at the University of Aix-Marseille, France, before earning a PhD in Electrical Engineering from the University of Sherbrooke, Canada, in 2011, where her research focused on small-animal PET system design and performance improvement. Since then, she has held a range of scientific, clinical, and leadership roles within the medical technology and pharmaceutical industries, including Senior Scientist and AI Lead at Siemens Healthineers, and Medical Affairs and Innovation Lead for Alzheimer's disease at Roche. She currently leads Clinical Applications and Medical Affairs for NeuroLF, Positrigo's dedicated brain PET imaging device, where she focuses on advancing the clinical adoption of this novel molecular neuroimaging technology.

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