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Consensus statement

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Acceptable performance of blood biomarker tests of amyloid pathology — recommendations from the Global CEO Initiative on Alzheimer's Disease

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Abstract

Anti-amyloid treatments for early symptomatic Alzheimer disease have recently become clinically available in some countries, which has greatly increased the need for biomarker confirmation of amyloid pathology. Blood biomarker (BBM) tests for amyloid pathology are more acceptable, accessible and scalable than amyloid PET or cerebrospinal fluid (CSF) tests, but have highly variable levels of performance. The Global CEO Initiative on Alzheimer's Disease convened a BBM Workgroup to consider the minimum acceptable performance of BBM tests for clinical use. Amyloid PET status was identified as the reference standard. For use as a triaging test before subsequent confirmatory tests such as amyloid PET or CSF tests, the BBM Workgroup recommends that a BBM test has a sensitivity of ≥90% with a specificity of ≥85% in primary care and ≥75–85% in secondary care depending on the availability of follow-up testing. For use as a confirmatory test without follow-up tests, a BBM test should have performance equivalent to that of CSF tests — a sensitivity and specificity of ~90%. Importantly, the predictive values of all biomarker tests vary according to the pre-test probability of amyloid pathology and must be interpreted in the complete clinical context. Use of BBM tests that meet these performance standards could enable more people to receive an accurate and timely Alzheimer disease diagnosis and potentially benefit from new treatments.

Sections

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Introduction

Since 2021, the first disease-modifying treatments (DMTs) for Alzheimer disease (AD) have been entering clinical practice: the amyloid-β (Aβ) antibodies aducanumab and lecanemab were approved by the FDA[1–5], and a third — donanemab — is currently under consideration for FDA approval[6,7]. These new therapies are indicated for early symptomatic AD, including mild cognitive impairment (MCI) or mild dementia caused by AD, and biomarker confirmation of amyloid pathology is required before their initiation[8,9]. Therefore, the new availability of these treatments creates a pressing need for accurate, biomarker-based diagnosis of AD in people with MCI and mild dementia[10], to enable initiation of treatment early in the course of symptomatic AD, when it is likely to be most effective[7].

A range of health-care professionals are involved in the diagnosis of symptomatic AD, including primary care providers, advanced practice clinicians (for example, nurse practitioners and physician assistants) and specialists, such as geriatricians, neurologists and geriatric psychiatrists[11]. An assessment typically includes a history from individuals who know the patient well, review of medical records, physical and neurological examinations, cognitive testing, routine laboratory tests and structural neuroimaging[12]. However, 85% of diagnoses are made by clinicians who are not dementia specialists, most commonly primary care providers[13], and clinicians report that diagnosis of symptomatic AD is challenging[14–16]. Although data on the accuracy of symptomatic AD diagnosis in primary care are limited, a review suggests that 31–74% of patients with symptomatic AD are not identified[17]. Even when patients were evaluated by a dementia specialist, the aetiological diagnosis changed in 36% of patients following an amyloid PET scan[18]. Misdiagnosis can lead to delays in care, administration of inappropriate therapies and incorrect prognostic guidance.

Difficulties with the diagnosis and management of dementia are exacerbated by a growing population of older adults and a shortage of dementia specialists. Currently, ~55 million people worldwide live with dementia, of whom an estimated 60–80% have AD[11,19], and the number of people with dementia is expected to increase to >139 million by the year 2050 (ref. 19). According to projections by the National Center for Health Workforce Analysis, the demand for neurologists will exceed supply throughout every region of the USA by 2025 (ref. 20), and access to specialist services is already limited or even absent in some low-income and middle-income countries[21]. As a result of these shortages, many people with cognitive impairment currently do not undergo an appropriate assessment, and access to dementia specialists is likely to become even more limited in future.

As anti-amyloid treatments become more widely available, biomarker testing to determine the presence of amyloid pathology is likely to become an essential component of the routine assessment of people who present for evaluation of cognitive impairment. Clinical tests to determine the presence of amyloid pathology have been available for over a decade and include amyloid PET and cerebrospinal fluid (CSF) tests that incorporate measurements of $A\beta_{42}$, $A\beta_{40}$, total tau (t-tau) and tau phosphorylated at position 181 (p-tau181)[22–24]. These imaging and fluid biomarkers are strongly associated with AD neuropathology, including amyloid plaques and neurofibrillary tangles[1,22,25–27]. However, biomarkers have infrequently been used in clinical practice until recently, partly because DMTs have not been available so biomarker results have been unlikely to change patient management and outcomes[2,3,24], and also because of the high costs, limited access and perceived risks of the biomarker tests[2,4]. Over the past 5 years, multiple blood biomarker (BBM) tests for the detection of AD pathology have been developed and are now widely used in AD research studies and clinical trials[3–5]. In comparison with amyloid PET and CSF tests, BBM tests are more acceptable and accessible and can be rapidly scaled up to meet increased need for biomarker testing[3,5]. Additionally, BBM tests could potentially be used in both primary and secondary care settings.

Although multiple BBM tests are now clinically available, the performance of these tests varies widely, raising the question of the minimum accuracy required for a test to be clinically useful. In this Consensus Statement, we present recommendations from The Global CEO Initiative (CEOi) on Alzheimer's Disease BBM Workgroup on the minimum acceptable performance of BBM tests for clinical use. These recommendations are intended to provide patients, providers and test developers with minimum standards for clinically used BBM tests, as well as describe the rationale for these standards.

Methods

The CEOi is a partnership of individuals in academia, patient advocacy organizations, pharmaceutical companies and other private industry groups that work together to address major challenges in the field of AD. The patient advocacy organization USAgainstAlzheimer's convened the CEOi and initiated the BBM Workgroup in 2022 to prepare stakeholders for the widespread adoption of BBM tests in clinical practice[28]. The BBM Workgroup consists of academics who are involved in the validation of BBM tests, multiple diagnostics companies that are developing BBM tests, multiple pharmaceutical companies that expect BBM tests to be useful in treatment pathways and patient advocacy groups that hope to improve care and treatment for people with AD. Multiple patient advocacy organizations and private industry groups contributed to the funding of the BBM Workgroup. Within the BBM Workgroup, a workstream was established to examine the minimum acceptable performance of BBM tests for clinical use. Rather than considering specific BBM tests, the BBM Workgroup sought to define performance standards that could be applied to any test.

The BBM Workgroup nominated co-leaders of the workstream (S.E.S. and O.H.), who are dementia specialists, routinely use biomarker tests in clinical diagnosis of dementia and have extensive expertise and publications on the validation of fluid biomarker tests. The co-leaders then recruited a core team of dementia specialists who routinely use biomarker tests in the clinical diagnosis of dementia (D.G., A.C.P., G.D.R., S.S. and M.S.-C.) and who also have expertise and publications on fluid and/or imaging biomarkers of AD. The core team of seven dementia specialists represented three countries (Sweden, Spain and the USA) and different regions of the USA (California, Midwest and East Coast). The co-leaders and the core team served voluntarily and without financial compensation. The CEOi provided administrative support, such as coordinating meetings, note taking and help with creating presentations.

The BBM Workgroup invited stakeholders from academia, industry, private foundations and patient advocacy groups to a kick-off meeting, in which the co-leaders described the goal of the group — to determine the minimum performance of BBM tests necessary for use in clinical care — and elicited feedback on the essential issues to consider in formulating recommendations. After this kick-off meeting, the core team met approximately weekly for several months and reviewed the current literature and practice regarding the following topics: clinical use of AD biomarker tests, the advantages and disadvantages of different biomarker modalities, analytical validation and reference standards for BBM tests, one and two cut-off approaches for categorizing test results and the predictive value of BBM tests.

Following this thorough review, the core team developed a methodology to consider the performance of BBM tests using FDA-approved CSF tests as a benchmark.

The BBM Workgroup then developed recommendations for the use of BBM tests in target patient populations in primary and secondary care. The predictive values of BBM tests with various levels of performance were analysed in different clinical settings and patient profiles. After discussion of these analyses with the entire core team, the BBM Workgroup co-leaders proposed recommendations for the minimum performance of the BBM tests. The core team discussed and adjusted the recommendations until all core team members unanimously agreed with the recommendations. The core team then drafted target product profiles for BBM tests with a similar format to those developed for other types of diagnostic tests. The co-leaders then presented the findings of the core team to the stakeholders and elicited feedback.

At the request of the co-leaders, a medical writer (D.R.) was engaged to assist with identifying literature on the epidemiology of AD and health-care system preparedness; the identified literature was reviewed with the co-leaders. A manuscript was outlined and drafted by the co-leaders, including the literature that had been reviewed by the core team and the recommendations of the core team. The core team reviewed and revised the manuscript, after which the manuscript was circulated to stakeholders for additional feedback, which was reviewed by the co-leaders and the manuscript revised appropriately. Criteria for authorship included attendance at stakeholder meetings and review and commentary on the manuscript. A final version of the manuscript was approved by all co-authors before submission.

Clinical use of AD biomarker tests

Amyloid PET and CSF tests are the biomarker modalities typically used in the clinical diagnosis of symptomatic AD, and some providers have started to use BBM tests. Other types of AD biomarker tests are not commonly used in clinical practice. Currently, clinical biomarker testing is only recommended for individuals with cognitive impairment who have undergone a comprehensive assessment including a medical evaluation, neurological examination, cognitive testing and laboratory testing for common reversible causes of cognitive impairment[4,23,24]. Many conditions other than AD can cause or exacerbate cognitive impairment, and the comprehensive assessment is designed to identify these alternative aetiologies. Given that cognitive symptoms often have multiple causes, no AD biomarker test is intended as a standalone diagnostic test for symptomatic AD[29–31].

In 2018, the National Institute on Aging and the Alzheimer's Association established the ATN research framework, in which evidence of the two major categories of AD pathology — amyloid (A) and pathological tau (T) — is needed for the diagnosis of AD[32]. Biomarkers of neurodegeneration and/or neuronal injury (N) are nonspecific so are not, in this framework, used for diagnosis but to help with staging of the disease[32]. However, this research framework cannot readily be applied to clinical diagnosis. PET is almost never used to detect pathological tau in the clinic, and, although CSF levels of phosphorylated tau were used as a measure of pathological tau in the original ATN research framework, subsequent work has demonstrated that CSF levels of p-tau181 are more closely associated with amyloid pathology than with tau pathology[33,34]. The ATN framework is now being updated, and novel fluid biomarkers that more specifically reflect tau pathology are being studied[35]. At the current time, amyloid pathology is usually the only type of AD pathology evaluated in clinical practice, typically via amyloid PET or CSF biomarker tests. Consequently, symptomatic AD dementia is usually clinically diagnosed on the basis of positive amyloid biomarkers in the context of a typical AD clinical syndrome after ruling out other potential causes[12].

Amyloid PET is highly informative in AD research studies and clinical trials because it enables the density and distribution of amyloid pathology to be visualized in the brain[3,36]. However, amyloid PET has not been widely used in clinical practice because the imaging equipment and radiotracers are expensive and require highly specialized personnel[29–31]. CSF tests are currently the most widely used AD biomarkers in secondary dementia clinics worldwide and are generally less expensive than amyloid PET[3,12,23,37]. The core CSF biomarkers for the diagnosis of AD include the ratio of $A\beta_{42}$ to either $A\beta_{40}$, p-tau181 or t-tau ($A\beta_{42}/A\beta_{40}$, p-tau181/$A\beta_{42}$ or t-tau/$A\beta_{42}$ ratios)[3,22]. Although collection of CSF via lumbar puncture is safe and typically well tolerated, some people are unwilling to undergo the procedure on the basis of misconceptions that it is associated with substantial risks[3,38]. In addition, some people who take anti-coagulant drugs are ineligible to undergo lumbar punctures owing to the risk of bleeding complications[39]. More common limitations include the fact that relatively few clinicians are comfortable performing lumbar punctures, and reimbursement for the procedure can be inadequate[40].

Following their rapid development, BBM tests for AD are now widely used in AD research studies and clinical trials, and multiple BBM tests are now clinically available[2–5]. In the prescribing information for lecanemab, the modality of biomarker testing required to establish the presence of amyloid pathology was not specified, leaving open the option of using BBM tests[8,9]. Given that confirmation of amyloid pathology is required for initiation of anti-amyloid treatments, BBM measures that are strongly associated with amyloid pathology are highly desirable. The most promising BBM measures for amyloid status include the $A\beta_{42}/A\beta_{40}$ and tau phosphorylated at different sites, including p-tau181, p-tau217 and p-tau231 (refs. 41–50).

BBM tests have unique advantages over amyloid PET and CSF tests, which could enable their use more widely in the clinical diagnosis of symptomatic AD. Blood tests are seen as safe and acceptable by most patients and blood tests are commonly used in clinical practice throughout the world[51]. Use of blood tests can also be scaled up more easily than use of other AD biomarker modalities because blood collection does not require highly specialized personnel or equipment (although blood must be collected and stored under the appropriate conditions)[5,52].

The different BBM tests that have been developed have widely varying performances for classification of amyloid status. Even BBM tests that are designed to measure the same analyte have major differences in performance associated with the assay type (mass spectrometry versus immunoassay), antibodies or other reagents used or the specific assay platform[2]. The accuracy of different tests in classifying amyloid status is typically quantified with the receiver operating characteristic area under the curve (AUC; Fig. 1), in which 1.00 is perfect accuracy and 0.50 is chance performance. Assays of the plasma $A\beta_{42}/A\beta_{40}$ ratio have AUCs of 0.70–0.85 in classification of amyloid PET status, and mass spectrometry-based assays are typically more accurate than immunoassays[53–56]. Assays for various phosphorylated tau species perform even better in predicting amyloid status as determined with amyloid PET or CSF tests[5,57]. In particular, assays of plasma levels of p-tau217 or the ratio of p-tau217 to non-phosphorylated tau have AUCs of 0.92–0.98, which is similar to those of CSF tests for classifying amyloid PET status[48,58–61]. Although BBM tests could enable much broader use of AD biomarker testing, the wide variation in their

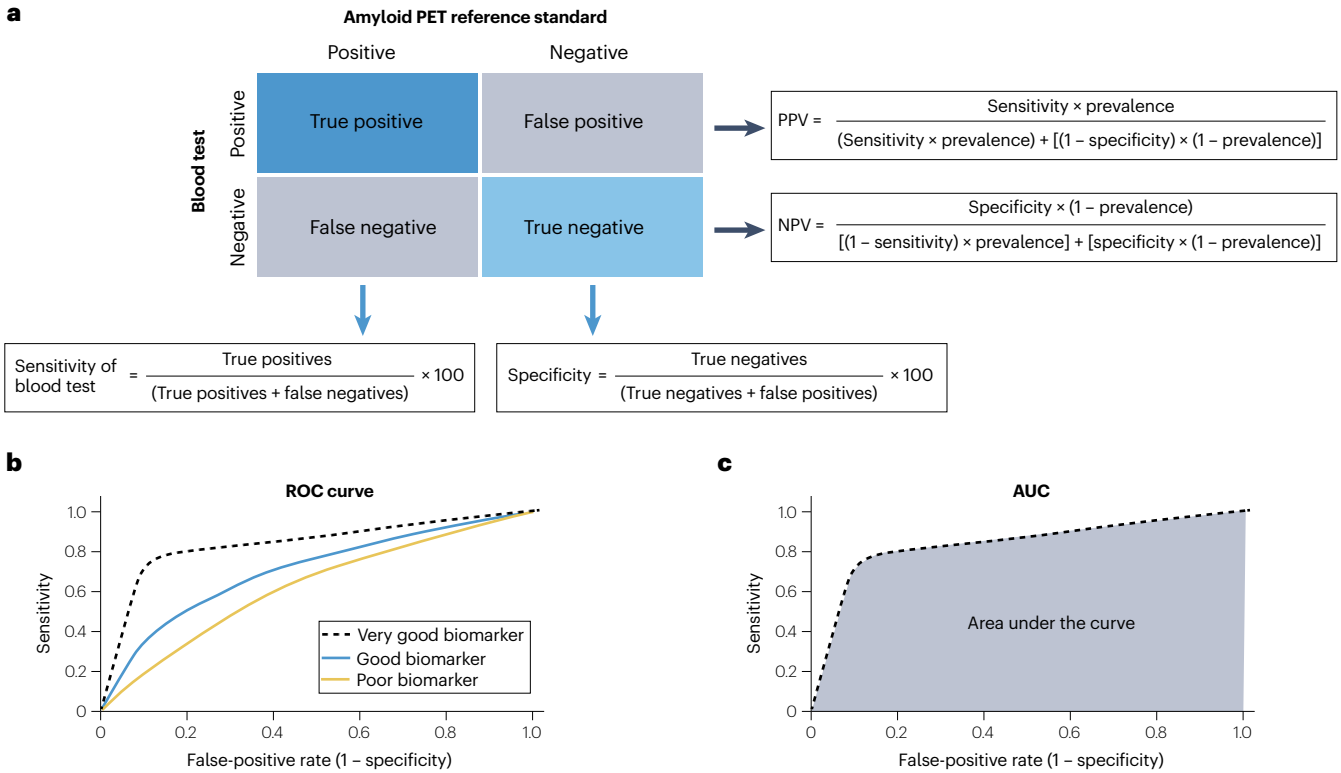

Fig. 1 | Determining performance of blood biomarker tests for amyloid pathology. a, Amyloid PET is used as the reference standard for evaluating the performance of blood biomarker (BBM) tests for amyloid pathology. A positive BBM result is considered a true positive if amyloid PET is also positive and is considered a false positive if amyloid PET is negative. A negative BBM result is considered a true negative if amyloid PET is also negative and considered a false negative if amyloid PET is positive. The sensitivity of a BBM test is defined as the percentage of amyloid PET-positive individuals with a positive BBM test. The specificity is defined as the percentage of amyloid PET-negative individuals with a negative BBM test. Sensitivity, specificity and the prevalence of amyloid pathology in the tested population are used to determine the positive predictive value (PPV; the likelihood that an individual with a positive BBM test is amyloid PET positive) and negative predictive value (NPV; the likelihood that an individual with a negative BBM test is amyloid PET negative) of a test. Calculation of the PPV and NPV of a test is critical when determining its clinical utility. **b**, The receiver operating characteristic (ROC) curve quantifies the ability of a test to distinguish between individuals with and without amyloid pathology. The curve is a plot of the sensitivity as a function of the false-positive rate and across a range of potential cut-offs. **c**, The area under the ROC curve (AUC; indicated by the shaded area) is a measure of test performance that does not depend on a specific cut-off value so can be used to compare the performance of various biomarker tests. The AUC provides a measure of the ability of a test to discriminate between individuals who are amyloid PET-positive and PET-negative; an AUC of 1.0 indicates perfect discrimination, whereas an AUC of 0.5 indicates performance no better than chance.

performance raises the question of how accurate a test must be for use in clinical practice.

Analytical validation and reference standard

The initial step in the evaluation of a BBM test is analytical validation to assess its ability to reliably measure the analyte of interest. Factors such as the variability of measurements, the sensitivity of the test, the range of values measured and the effects of potentially interfering substances are examined. Pre-analytical sample handling and processing can affect biomarker values, so a consistent protocol for blood collection and handling is necessary[52]. The clinical performance of a test depends on the analytical performance of the assay and pre-analytical factors, as well as the association of the analyte with key clinical outcomes.

A key consideration for any diagnostic test is the reference standard against which it is compared. Three PET tracers that bind to amyloid plaques were validated using neuropathology as the reference standard and were subsequently approved by the FDA: ^{18}F-florbetapir in 2012, ^{18}F-flutemetamol in 2013 and ^{18}F-florbetaben in 2014 (refs. 22,29–31,62). The sensitivities and specificities of these three tracers (determined by the accuracy with which positive or negative amyloid PET visual read reflects the presence or absence of AD neuropathology) were 96% and 100% for ^{18}F-florbetapir, 86% and 92% for ^{18}F-flutemetamol and 98% and 89% for ^{18}F-florbetaben, respectively[25,63,64]. One PET tracer that binds to tau-containing neurofibrillary tangles, ^{18}F-flortaucipir, was approved by the FDA in 2020 (refs. 65–68). A visual read of ^{18}F-flortaucipir PET had a sensitivity of 95% and a specificity of 81% for a measure of neurofibrillary tangle and amyloid pathology[67]. Given the high agreement of amyloid PET visual read with AD neuropathology, the FDA accepted amyloid PET visual read as the reference standard in its approval of three CSF tests for amyloid pathology associated with AD (Table 1).

However, amyloid PET visual read is not a perfect reference standard for amyloid status. In a study of 9,958 clinical amyloid PET scans, positive or negative amyloid PET visual reads were discordant with

quantitative measures of the same scans in 14% of cases; discordance was particularly high in cases with borderline values[69]. Even at expert centres, discordance between visual read and quantitative measures of the same amyloid PET scans is ~5%, also usually in cases with borderline values[70]. Therefore, although amyloid PET has been accepted as a reference standard for fluid biomarker tests, even a CSF or BBM test that perfectly classifies individuals according to the presence or absence of amyloid pathology would not be expected to have 100% concordance with amyloid PET status by visual read[70]. Given that some BBM tests might rival or even exceed the performance of amyloid PET for determining amyloid status, studies that look at correlations between BBM tests and neuropathology are particularly important to truly understand the accuracy of fluid biomarker tests. Nevertheless, on the basis that amyloid PET has been used as the reference standard for current FDA-approved CSF tests, the BBM Workgroup also used amyloid PET as the reference standard in the analysis of BBM test performance.

Determining sensitivity and specificity

In research studies, continuous measures are often used for biomarker analyses, whereas clinical tests, including those for AD biomarkers, typically involve cut-offs that categorize results as positive (abnormal) or negative (normal)[32]. The terms sensitivity and specificity are typically used to describe the performance of a test in classifying a gold standard clinical outcome, such as neuropathologically confirmed AD. In some studies evaluating the agreement between fluid biomarkers of AD and amyloid PET, the term positive percent agreement is used in place of sensitivity and the term negative percent agreement is used in place of specificity because amyloid PET is not a perfect measure of amyloid pathology. However, given that amyloid PET has a high correspondence with neuropathology, we use the terms sensitivity and specificity because they are more familiar. If amyloid PET is used as the reference standard, the sensitivity of a BBM test is defined as the percentage of amyloid PET-positive individuals with a positive BBM test. The specificity is defined as the percentage of amyloid PET-negative individuals with a negative BBM test (Fig. 1).

For a test to rule out amyloid pathology, a cut-off that results in high sensitivity is needed to minimize false-negative results and ensure that most individuals with amyloid pathology are identified. Minimizing false-negative results is important because they can lead to delays in care or even misdiagnosis, resulting in inappropriate or inadequate care[71]. For a test to confirm amyloid pathology, a cut-off that results in high specificity is needed to minimize false-positive results and ensure that individuals without amyloid pathology are identified[2]. False-positive results can lead to unnecessary anxiety, referrals and associated expenses[71], as well as the possibility of unnecessary treatment with amyloid-lowering DMTs, the risks of which are unclear in individuals without amyloid pathology[72,73].

Various methods can be used to determine single cut-offs for fluid biomarker tests that classify individuals as positive or negative[74,75]. However, 5–20% of individuals (depending on the cohort) have a borderline level of amyloid pathology, meaning the values are near the cut-off and repeat testing could result in discordant results (for example, a positive result followed by a negative result when repeated)[76–78]. For this reason, the BBM Workgroup considered the use of two cut-offs to define three categories of results: positive, intermediate and negative (Fig. 2). This approach is currently used by the FDA-approved Lumipulse CSF test, in which the intermediate category is defined as 'likely positive', and a similar approach has been applied to a test for plasma p-tau217 (refs. 78,79). The use of two cut-offs increases the overall accuracy of a test for classifying individuals with or without amyloid pathology. Although the BBM Workgroup recommends consideration of a two cut-offs approach, this approach is not required if a single cut-off yields acceptable accuracy.

Tests with poorer performance typically have higher variability in measurements, thereby increasing the proportion of tests that result in intermediate values. The use of two cut-offs can enable tests with performance slightly below acceptable levels of accuracy to reach the threshold for acceptable performance. However, because intermediate BBM test results do not provide a clear answer regarding amyloid status, the BBM Workgroup recommended that a BBM test should result in intermediate values for no more than 15–20% of individuals in a typical clinical population. The core team of dementia specialists reported obtaining borderline CSF test results in ~15–20% of patients, which were often uninformative and frustrating for patients and providers. The BBM Workgroup members agreed that if an even higher percentage of patients received borderline BBM tests results, this would not be acceptable.

The most appropriate approach if BBM tests results are intermediate varies by patient and care setting[5,76,78]. For patients whose BBM test results are intermediate but greater certainty regarding amyloid status is needed in the short term, for example, if an individual is a potential candidate for anti-amyloid treatments, an amyloid PET or CSF test would be appropriate if these modalities are available. However, if determining amyloid status is not likely to affect short-term patient management, such as if the individual simply desired greater diagnostic certainty, or if amyloid PET or CSF tests are not available, repeating the BBM test at a later time (for example, in 1 year) might be reasonable.

Table 1 | Performance of FDA-approved CSF assays for the classification of amyloid PET status by visual read

Test	Biomarker	Cohort	Cohort size	Sensitivity (%)	Specificity (%)	Prevalence of amyloid pathology (%)	PPV (%)	NPV (%)
Fujirebio Lumipulse[79]	$A\beta_{42}/A\beta_{40}$	ADNI	292	92[a]	84[a]	68	92[a,b]	84[a,b]
Roche Elecsys[91]	p-tau181/$A\beta_{42}$	BioFINDER	277	91	89	NA	NA	NA
		ADNI	646	88	93	54	93	87
Roche Elecsys[92]	t-tau/$A\beta_{42}$	BioFINDER	277	91	89	NA	NA	NA
		ADNI	646	85	94	54	94	84

Aβ, amyloid-β; $A\beta_{42}$, Aβ peptide 42; $A\beta_{40}$, Aβ peptide 40; ADNI, Alzheimer's Disease Neuroimaging Initiative study; BioFINDER, Swedish BioFINDER study; NA, not available (not included in FDA summary); NPV, negative predictive value; PPV, positive predictive value; p-tau181, tau phosphorylated at position 181; t-tau, total tau. [a]When the categories of 'positive' and 'likely positive' were both considered as positive; when likely positive results were excluded, sensitivity was 92% and specificity was 93%. [b]If the prevalence of amyloid pathology in the Lumipulse cohort was the same as that in the Elecsys cohort (54%), the PPV would be 87% and the NPV would be 90% when positive and likely positive results are both considered positive.

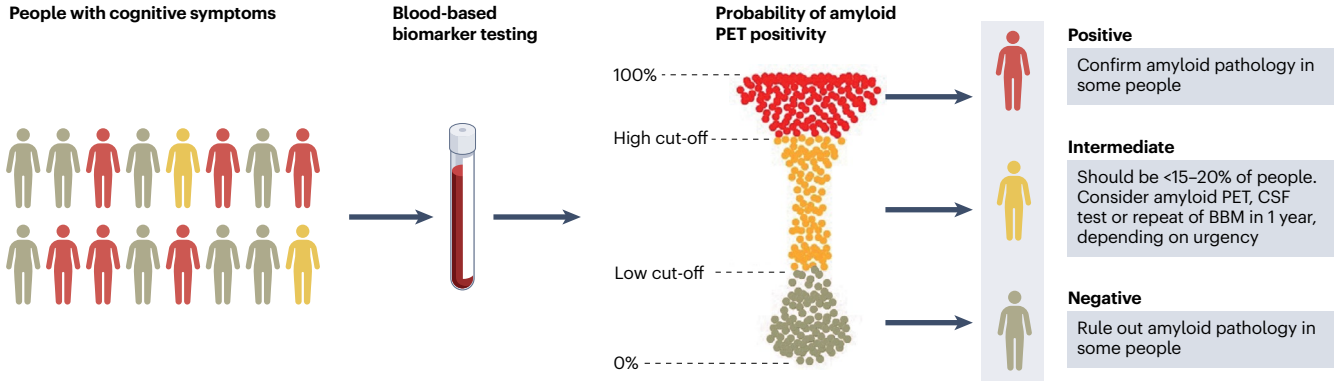

Fig. 2 | The two cut-off approach for blood biomarker tests of amyloid pathology. Use of two cut-off values for blood biomarker (BBM) testing in a group of people with cognitive symptoms leads to three categories of results: positive, intermediate and negative, increasing the accuracy with which people can be classified as having or not having amyloid pathology. Ideally, no more than 15–20% of individuals would be classified as having intermediate results. Interpretation of positive and negative results depends on the clinical suspicion of Alzheimer disease (Tables 3 and 4). CSF, cerebrospinal fluid. Adapted from ref. 78, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Determining the predictive value of BBM tests

Sensitivity and specificity are helpful for describing the performance of a test in research studies, but the clinical utility of a BBM test is better reflected by the likelihood that an individual with a positive BBM test is amyloid PET-positive — the positive predictive value (PPV) — and the likelihood that an individual with a negative BBM test is amyloid PET-negative — the negative predictive value (NPV) (Fig. 1). The PPV and NPV are strongly influenced by the prevalence of amyloid pathology in the population being tested. The relationships among PPV, NPV, test performance (sensitivity and specificity) and the prevalence of amyloid pathology can be visualized with an online calculator of the predictive value of blood tests for brain amyloidosis developed by S.E.S. and co-workers.

The prevalence of amyloid pathology varies by age, severity of clinical symptoms, race and/or ethnicity, sex and *APOE* genotype[80–85]. In a large study of people with cognitive impairment of uncertain aetiology (the Imaging Dementia — Evidence for Amyloid Scanning (IDEAS) study), the prevalence of amyloid pathology was 55.3% among people with MCI and 70.1% among people who met the criteria for dementia[18]. The prevalence of amyloid pathology — or the pre-test probability of amyloid positivity — varies according to patient and provider characteristics, but an estimate of this parameter is necessary to calculate the PPV and NPV of a BBM test. Therefore, when considering use of BBM tests in secondary care settings, the BBM Workgroup considered three different levels of prevalence of amyloid pathology on the basis of key studies and clinical experience in the BBM Workgroup: 80%, 50% and 20%, corresponding to individuals with high, intermediate or low clinical suspicion of AD, respectively, based on the assessment of a dementia specialist[18,80,86,87]. When considering use of BBM tests in primary care, two different levels of amyloid prevalence were considered: 50% for older individuals with more concerning symptoms (for example, people aged ≥70 years with forgetfulness of personal events that occurs daily and has progressively worsened over the past year) and 20% for younger patients with less concerning symptoms (for example, an individual aged ≤65 years with occasional memory lapses)[80,86].

Estimating the likelihood of amyloid pathology is critical for appropriate interpretation of BBM test results. Calculators that incorporate easily ascertainable parameters that are strongly associated with the prevalence of amyloid pathology, such as age and performance on cognitive tests, would enable a preliminary estimate of the likelihood of amyloid pathology, thereby enabling calculations of the PPV and NPV of the test for a given individual[88,89]. This type of preliminary estimate could be especially helpful for providers who have limited experience with biomarker testing. An example of such a calculator for estimating the prevalence of amyloidosis based on age and Mini Mental State Examination, based on a research cohort, has been developed by S.E.S. and co-workers. Similar calculators or estimates could be provided by diagnostics companies in conjunction with BBM test results to help providers to interpret the results. However, clinicians should refine the estimated likelihood of amyloid pathology on the basis of their complete diagnostic work-up and adjust their estimate as additional clinical data about the patient become available to them. For example, if a young patient with subtle symptoms and a lower initial estimated likelihood of amyloid pathology exhibits progressive worsening of memory symptoms at their follow-up appointment, the estimate should be adjusted upwards.

CSF tests as a benchmark

FDA-approved CSF tests for amyloid pathology are an important benchmark for BBM test performance. The FDA approved the Fujirebio Lumipulse G CSF β-Amyloid Ratio test (which measures the $A\beta_{42}/A\beta_{40}$ ratio) on the basis of its relatively high agreement with amyloid PET status by visual read in a study of 292 participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI)[79,90]. In this study, two cut-offs were used and the CSF test had a sensitivity of 92% and a specificity of 84% for amyloid PET status by visual read when individuals with 'positive' and 'likely positive' results were both considered positive, and 92% sensitivity and 93% specificity when the category of likely positive was excluded[79].

The Roche Elecsys tests, which measure the p-tau181/$A\beta_{42}$ or t-tau/$A\beta_{42}$ ratio and use a single cut-off, received FDA approval on the basis of substantial equivalence to amyloid PET in two research cohorts[91]. In a training cohort of 277 individuals from the Swedish BioFINDER study, the p-tau181/$A\beta_{42}$ test had a sensitivity of 91% and a specificity of 89% for amyloid PET status by visual read. In a second validation cohort of 646 participants enrolled in the ADNI, the same test had a sensitivity

of 88% and a specificity of 93% for amyloid PET status by visual read[91]. The t-tau/$A\beta_{42}$ test performed similarly[92].

These FDA-approved CSF tests provide benchmarks for the performance of AD biomarker tests and suggest that ~90% sensitivity and specificity for amyloid PET status by visual read is substantially equivalent to amyloid PET.

Context of use

Two major uses for BBM tests are expected: triaging and confirmation of amyloid pathology. For triaging tests, a negative result would identify individuals who are unlikely to have amyloid pathology and who might therefore benefit from further assessment for causes of cognitive impairment other than AD. A positive result would identify individuals with an increased likelihood of having amyloid pathology and who need further testing with a more accurate test. Therefore, triaging tests primarily serve to identify individuals who are unlikely to have amyloid pathology. These tests are most appropriate for use in patients with a pre-test probability of amyloid positivity ≤50%, as a negative BBM result in this scenario is associated with a high NPV, providing high confidence that the individual does not have amyloid pathology. When the pre-test probability of amyloid positivity is >50%, a negative BBM result does not rule out amyloid pathology so is less helpful. For example, even a BBM test with a sensitivity and specificity of 90% has an NPV of only 69% if the pre-test probability of amyloid positivity is 80%, as might be estimated for a patient aged ≥75 years with a typical AD dementia syndrome (Table 2). Therefore, a BBM test cannot be used to rule out amyloid pathology for all patients, and clinicians must continue to consider AD as a possible (albeit unlikely) aetiology in patients with a negative BBM test result but clinical features that are highly consistent with symptomatic AD.

For confirmatory BBM tests, a positive result would identify the presence of amyloid pathology without the need for a second test[2,4,5]. Such confirmation can only be achieved with high confidence for people whose pre-test probability of amyloid positivity is >50%, as a positive BBM result is associated with a high PPV in this scenario. For people with a pre-test probability of amyloid positivity ≤50%, a positive BBM result does not necessarily rule in amyloid pathology. For example, if the pre-test probability of amyloid positivity is 20%, as in a patient aged ≤60 years with subtle symptoms of cognitive decline, a BBM test with a sensitivity and specificity of 90% has a PPV of only 69% (Table 2). An unexpected positive BBM result should prompt further evaluation, such as more extensive clinical and cognitive testing, to ensure an accurate estimation of the pre-test probability of amyloid pathology.

Table 2 | Minimum acceptable performance of blood biomarker tests for triaging or confirmation of amyloid pathology

Test	Minimum acceptable performance	Predictive value according to prevalence of amyloid pathology	
		Prevalence of amyloid pathology[a]	Predictive values
Confirmatory test	90% sensitivity 90% specificity	80%	PPV 97% NPV 69%
		50%	PPV 90% NPV 90%
		20%	PPV 69% NPV 97%
High-specificity triaging test	90% sensitivity 85% specificity	80%	PPV 96% NPV 68%
		50%	PPV 86% NPV 89%
		20%	PPV 60% NPV 97%
Low-specificity triaging test	90% sensitivity 75% specificity	80%	PPV 94% NPV 65%
		50%	PPV 78% NPV 88%
		20%	PPV 47% NPV 97%

NPV, negative predictive value; PPV, positive predictive value. All calculations assume dichotomous categories or the grouping of intermediate and positive outcomes in a test with two cut-offs. [a]Estimates of the prevalence of amyloid pathology will vary by clinical setting and patient profile. See Table 5 for the complete BBM target product profiles for triage and confirmatory tests in primary and secondary care.

Use of blood biomarker tests in secondary care

The BBM Workgroup considered the use of BBM tests in secondary care by providers with expertise and experience in dementia, such as neurologists, geriatricians, geriatric psychiatrists and generalist medical doctors who have older patient populations and have received additional training. For both triaging and confirmation in this setting, the intended use of BBM tests is to help establish whether amyloid pathology is the likely cause of cognitive impairment after completion of a comprehensive work-up, including a clinical assessment, cognitive testing, structural neuroimaging and routine blood work.

The BBM Workgroup recommends the following criteria are fulfilled to conduct a BBM test for an individual in secondary care:

- Objective tests provide evidence of cognitive impairment and/or a history of progressive cognitive decline is clear.
- After a comprehensive assessment of existing medical conditions and for other causes of cognitive decline, AD is suspected as a possible aetiology of cognitive impairment.
- Biomarker testing is expected to increase the certainty of the aetiological diagnosis of cognitive impairment, improve the diagnostic and prognostic information provided to patients and their caregivers and/or improve management.

Use of blood biomarker tests in primary care

The BBM Workgroup additionally considered the use of BBM tests in primary care by clinicians without highly specialized training in dementia, including physicians, nurse practitioners and physician assistants. An important consideration is that most AD biomarkers have been studied and used only in secondary and tertiary care settings, and the characteristics of patients seen in primary care settings might be different. For example, specialist memory clinics might serve patients with greater resources, in part because these clinics might have requirements such as the patient bringing a friend or family member to the visit[93]. Currently available data are insufficient to understand how use of AD biomarkers varies between primary and secondary care settings, and further studies are needed. Therefore, the BBM Workgroup recommendations for the intended use and target population for BBM tests largely match those for secondary care, with a few differences.

Table 3 | Interpretation of blood biomarker tests in primary care

Clinical suspicion for AD	Accuracy of BBM test	Predictive values	Difference from CSF test	Clinical interpretation of predictive values
High (50% prevalence of amyloid pathology)	Sensitivity 90% Specificity 90%	PPV 90%	0%	Positive test: marker of risk for AD — referral to dementia specialist recommended Negative test: rules out amyloid pathology in most patients
		NPV 90%	0%	
	Sensitivity 90% Specificity 85%	PPV 86%	–4%	
		NPV 89%	–1%	
Low (20% prevalence of amyloid pathology)	Sensitivity 90% Specificity 90%	PPV 69%	0%	Positive test: does not confirm amyloid pathology — referral to dementia specialist recommended Negative test: rules out amyloid pathology in most patients
		NPV 97%	0%	
	Sensitivity 90% Specificity 85%	PPV 60%	–9%	
		NPV 97%	0%	

Clinical suspicion for AD is determined by the expected prevalence of amyloid pathology given the age and clinical presentation of the individual[80]. BBM tests with different levels of sensitivity and specificity (second column) lead to different PPVs and NPVs (third column), which differ from the performance of CSF tests by different amounts (fourth column). On the basis of the PPVs and NPVs, the recommended interpretation of a positive or negative result is given (fifth column). AD, Alzheimer disease; BBM, blood biomarker; CSF, cerebrospinal fluid; NPV, negative predictive value; PPV, positive predictive value.

Owing to the very low pre-test probability of amyloid pathology in the younger population typically seen in primary care settings, the BBM Workgroup recommends use of BBM tests for triaging in primary care only for patients aged 55 years or older. Most AD biomarkers have not been well studied in patients younger than 55 years of age, and CSF tests are approved only for patients aged ≥55 years, so the validity of these biomarkers in people below this age has not been established. However, patients aged <55 years could be tested if suspicion for amyloid pathology is high, for reasons such as a clinical syndrome that is highly consistent with symptomatic AD, a family history of early-onset AD dementia in first-degree relatives, or a diagnosis of Down syndrome.

Given that a higher pre-test probability of amyloid positivity is needed to achieve the high PPV required for a confirmatory test, the BBM Workgroup recommends use of BBM tests for confirmation of amyloid pathology in primary care only for people aged ≥65 years, as the rate of amyloid positivity in this age group is highest. However, this is a general guideline; younger individuals for whom clinical suspicion of AD is high could be tested.

Minimum acceptable performance

With the understanding that the prevalence of amyloid pathology varies across clinical settings and patient profiles, the BBM Workgroup used estimates for the prevalence of amyloid pathology in three theoretical patient categories (80%, 50% and 20%) to calculate the PPVs and NPVs for BBM tests with different performance characteristics. The core team of dementia specialists considered whether the PPVs and NPVs for BBM tests with different levels of performance differed from those of CSF tests with a sensitivity and specificity of 90% substantially enough that: BBM tests should not be used; or BBM tests could be used with subsequent amyloid PET or CSF testing; or BBM tests could be used without subsequent amyloid PET or CSF testing. After analysing various scenarios, the BBM Workgroup reached consensus on the recommended diagnostic accuracy of BBM tests for use in triaging or confirmation of amyloid pathology (Tables 2–4) and developed complete BBM target product profiles for triaging and confirmatory tests in secondary and primary care (Table 5).

Use as a triaging test

For use as a triaging test, after which individuals with a positive result are expected to undergo a second confirmatory test with amyloid PET or CSF testing, the BBM Workgroup concluded that a BBM test should have a sensitivity ≥90% for amyloid PET status and a specificity ≥75–85%, depending on the availability of follow-up testing. High sensitivity is needed to minimize the number of false-negative results, so that most individuals with amyloid pathology are identified. This high sensitivity is especially important because individuals with a negative result are not expected to have a follow-up amyloid PET or CSF test. The minimum acceptable specificity depends on the availability of follow-up testing because most people who receive a positive result on a triaging test are expected to undergo a follow-up test. Given that blood tests are highly acceptable and accessible, a large number of positive results could substantially increase the need for follow-up amyloid PET and CSF tests. If capacity for amyloid PET and/or CSF tests is limited in a given setting, use of a triaging test with high specificity (≥85%) is necessary; otherwise, the number of people who receive positive BBM results (both true positive and false positive) could exceed the number of follow-up tests that can be performed. If the capacity to perform amyloid PET and/or CSF tests is not limited, for example, in secondary care centres, then a triaging test with lower specificity (≥75%) might be acceptable.

To illustrate how concerns about confirmatory test capacity influence the minimum acceptable specificity of triaging tests, consider a clinic that can perform 200 confirmatory tests per year and serves a patient population of 1,000 individuals, among whom the prevalence of amyloid positivity is 50%. If a triaging BBM test with a sensitivity of 90% and a specificity of 75% was used, 575 people would have a positive result, exceeding the number that could undergo a confirmatory test. Of these 575 people, 78% would have amyloid pathology. Of the 375 patients with a positive triaging BBM result who would not have access to confirmatory testing, 82 would have a false-positive BBM test result. However, if a triaging BBM test with a sensitivity of 90% and a specificity of 85% was used, 525 patients would receive a positive result and of the 200 individuals with access to confirmatory testing, 86% would have amyloid pathology. Slightly fewer people (325) with a positive triaging BBM result would not have access to confirmatory testing but, more importantly, only 46 would have a false-positive BBM test result. The most clinically concerning issue with triaging tests is the number of individuals with a false-positive result and no ability to obtain a follow-up test; these individuals might accept the false-positive triaging result as final, which could have adverse consequences.

Overall, current resource constraints underlie concerns that substantial numbers of individuals with positive triaging BBM tests will not have access to confirmatory testing and that the BBM test

result will, therefore, be the only AD biomarker test result they obtain. For this reason, the BBM Workgroup recommends higher specificity (≥85%) for triaging BBM tests if there is limited capacity to perform confirmatory tests. However, if a clinic has adequate capacity to perform confirmatory tests (that is, amyloid PET or CSF tests) in all patients with a positive triaging BBM test result, then a specificity of ≥75% is acceptable.

Use as a confirmatory test

For use as a confirmatory test without a follow-up amyloid PET or CSF test, the BBM Workgroup concluded that the performance of BBM tests should be equivalent to that of CSF tests; a sensitivity and specificity of ~90% for amyloid PET status. The core team of dementia specialists agreed that if a BBM test was even slightly less accurate than a CSF test, the CSF test would be strongly preferred for confirmation of amyloid pathology, especially if treatment with a DMT was a consideration.

Additional desirable performance characteristics and validation studies

The BBM Workgroup agreed that BBM tests would ideally have <5% discordance with respect to positive and negative status when blood is collected and analysed on different occasions within a short interval (for example, within 1–2 months). This performance standard has not been applied to CSF tests and the discordance of FDA-approved CSF tests over time has not been rigorously studied, largely because lumbar punctures are not typically repeated within a short interval. One study showed that individuals with discordant CSF test results on repeated testing are likely to have CSF biomarker levels near the cut-off and intermediate levels of amyloid pathology[76]. This finding suggests that a two cut-off approach could reduce the proportion of discordant results[5,78].

For validation studies of BBM tests, the demographic characteristics of the study cohort should ideally match the intended use population. The FDA approved both the Lumipulse and Elecsys CSF tests on the basis of assay performance in <1,000 research participants with minimal racial or ethnic diversity[79,91]. These studies did not determine whether the tests performed consistently across racial and ethnic groups, despite findings from several studies that have demonstrated differences in the concentrations of some CSF biomarkers, including t-tau and p-tau181, between self-identified black individuals and white individuals[94–97]. In addition, three studies have demonstrated differences in the rate of amyloid PET positivity in black and Hispanic individuals compared with white individuals[98–100]. Several studies have assessed the performance of BBM tests in different racial and ethnic groups[97,101,102]. In one such study, the likelihood of amyloid pathology associated with plasma levels of p-tau181, p-tau231 and neurofilament light chain differed between racial groups, but the $A\beta_{42}/A\beta_{40}$ ratio was consistently associated with amyloid pathology across racial groups[102]. In another study, plasma biomarkers did not vary by racial group after adjusting for comorbidities[102].

Multiple medical conditions, including chronic kidney disease, a history of myocardial infarction and stroke, have been associated with plasma levels of biomarkers including $A\beta_{42}$, $A\beta_{40}$, p-tau181 and p-tau217 (refs. 103–105). However, some biomarkers of AD are not as strongly associated with these conditions as others. Examples include the $A\beta_{42}/A\beta_{40}$ ratio[103,105] and the ratio of p-tau217 to non-phosphorylated tau, which was less strongly associated with kidney function than concentrations of p-tau217 alone[106]. In general, BBM tests based on biomarker ratios seem to perform more consistently, although larger studies are needed in cohorts that reflect the characteristics of the broader population[107]. Studies are currently underway to understand the relationships of AD biomarkers with race, ethnicity, medical conditions and

Table 4 | Interpretation of blood biomarker tests in secondary care

Clinical suspicion for AD	Accuracy of BBM test	Predictive values	Difference from CSF test	DMT candidate?	Clinical interpretation of predictive values
High (80% prevalence of amyloid pathology)	Sensitivity 90% Specificity 90%	PPV 97%	0%	Possible	Positive test: acceptable for confirmation of amyloid pathology in most patients Negative test: does not definitively rule out amyloid pathology owing to the low NPV — should be followed by a CSF test, amyloid PET or a second BBM test if possible
		NPV 69%	0%	Unlikely	
	Sensitivity 90% Specificity 85%	PPV 96%	–1%	Possible	
		NPV 68%	–1%	Unlikely	
Intermediate (50% prevalence of amyloid pathology)	Sensitivity 90% Specificity 90%	PPV 90%	0%	Possible	Positive test: acceptable for confirmation of amyloid pathology in most patients Negative test: rules out amyloid pathology in most patients
		NPV 90%	0%	Unlikely	
	Sensitivity 90% Specificity 85%	PPV 86%	–4%	Possible	Positive test: only acceptable for confirmation of amyloid pathology if patient cannot undergo CSF or amyloid PET testing — CSF or amyloid PET preferable if DMTs are being considered Negative test: does not definitively rule out amyloid pathology owing to the low NPV — should be followed by a CSF test, amyloid PET or a second BBM test if possible
		NPV 80%	–10%	Unlikely	
Low (20% prevalence of amyloid pathology)	Sensitivity 90% Specificity 90%	PPV 69%	0%	Unlikely	Positive test: does not confirm amyloid pathology — should be followed by a CSF test of amyloid PET if possible Negative test: rules out amyloid pathology in most patients
		NPV 97%	0%	Unlikely	
	Sensitivity 90% Specificity 90%	PPV 60%	–9%	Unlikely	
		NPV 97%	0%	Unlikely	

Clinical suspicion for AD is determined by the expected prevalence of amyloid pathology given the age and clinical presentation of the individual[80]. BBM tests with different levels of specificity (second column) lead to different PPVs and NPVs (third column), which differ from the performance of CSF tests by different amounts (fourth column) and influence whether an individual is likely to be a candidate for DMTs (fifth column). On the basis of the PPVs and NPVs, the recommended interpretation of a positive or negative result are given (sixth column). AD, Alzheimer disease; BBM, blood biomarker; CSF, cerebrospinal fluid; DMT, disease-modifying treatment; NPV, negative predictive value; PPV, positive predictive value.

Table 5 | Target product profiles for triaging and confirmatory blood biomarker tests in primary and secondary care

Profile feature	BBM test for use in primary care		BBM test for use in secondary care	
	Triaging test	Confirmation test	Triaging test	Confirmation test
Target users	Primary care providers		Dementia specialists	
Target patient population	Evidence of cognitive impairment from objective tests and/or a clear history of progressive cognitive decline, preferably supported by an individual who knows the patient well. Biomarker testing would be expected to help establish the aetiology of cognitive impairment and alter medical management			
	AD is the suspected aetiology of cognitive impairment after assessment for other medical conditions		AD is suspected as the aetiology of cognitive impairment after a comprehensive assessment for other medical conditions	
	Age>55 years	Age>65 years	No age cut-off	
Biomarker target	Analytes should reflect the key AD pathologies			
Comparative reference	Amyloid: correspondence with amyloid PET or AD amyloid plaque neuropathology Tau: correspondence with tau PET or AD neurofibrillary tangle neuropathology			
Intended use	Positive test would identify individuals with a high likelihood of amyloid pathology but for whom a second test is needed to confirm pathology. Negative test would identify individuals who are unlikely to have amyloid pathology	Positive test would confirm amyloid pathology when interpreted in the context of all clinical findings. Negative test would identify individuals who are unlikely to have amyloid pathology	Positive test would identify individuals with a high likelihood of amyloid pathology but for whom a second test is needed to confirm pathology. Negative test would identify individuals who are unlikely to have amyloid pathology	Positive test would confirm amyloid pathology when interpreted in the context of all clinical findings. Negative test would identify individuals who are unlikely to have amyloid pathology
Accuracy required	Sensitivity ≥90% Specificity ≥85% For a test with two cut-offs, <20% of individuals should have an intermediate result	Sensitivity ≥90% Specificity ≥90% For a test with two cut-offs, <20% of individuals should have an intermediate result	Sensitivity ≥90% Specificity ≥85% (75–85% might be acceptable with high capacity for follow-up amyloid PET or CSF testing) For a test with two cut-offs, <20% of individuals should have an intermediate result	Sensitivity ≥90% Specificity ≥90% For a test with two cut-offs, <20% of individuals should have an intermediate result
Reproducibility	<5% discordance in positive or negative status when blood is collected and analysed on different occasions			

AD, Alzheimer disease; BBM, blood biomarker; CSF, cerebrospinal fluid.

social determinants of health, including the Study of Race to Understand Alzheimer Biomarkers (SORTOUT-AB)[108], the Health & Aging Brain Study-Health Disparities (HABS-HD)[109] and the recently initiated Alzheimer's Diagnosis in Older Adults with Chronic Conditions (ADACC)[110]. In the meantime, confidence in biomarker results based on BBM tests (as well as for amyloid PET and CSF tests) is highest for individuals with demographics that resemble those of the research cohorts in which the tests have been studied.

Barriers to use

If implemented effectively, BBM tests could improve access to AD biomarker testing, but several barriers and complexities need to be addressed. First, cognitive impairment is often considered by the general public to be a normal sequela of ageing, which could reduce the likelihood that people will present for care before symptoms are advanced. Second, people might not know how to access appropriate care or might have limited access to care, especially given the shortage of dementia specialists. Barriers to equitable care, such as language barriers, lack of health-care insurance and limited finances, can also be considerable[16]. Third, primary care practitioners need more education on how to assess people with cognitive impairment and estimate the likelihood of amyloid pathology on the basis of factors such as age and severity of symptoms, keeping in mind that AD biomarkers become abnormal many years before the onset of cognitive impairment. Finally, providers need to know the level of accuracy of the specific BBM tests they are ordering. Before undergoing AD biomarker testing, patients and their caregivers should be counselled about potential risks and benefits of testing, the results of which could affect their work, driver licensing and insurance, and could also cause stigmatization[111]. Measures must be taken to mitigate these issues and thereby maximize the potential of BBM tests for improving the diagnosis of early symptomatic AD.

Conclusions

The emergence of DMTs for AD is expected to transform the diagnosis and management of people with cognitive impairment. These treatments specifically target amyloid pathology, so biomarker confirmation of this pathology is required before their initiation. Amyloid PET and CSF tests that accurately detect amyloid pathology have been available for many years but their use in clinical practice has been infrequent owing to the lack of specific AD treatments and the drawbacks of these tests. However, now that biomarker confirmation of amyloid pathology could have a major impact on patient care, the need for AD biomarkers is likely to increase by orders of magnitude. Given the limitations and capacity constraints of amyloid PET and CSF tests, BBM tests are likely to be the only modality that can reach the scale required for testing of all people who might benefit from an accurate diagnosis and, potentially, DMTs.

The CEOi BBM Workgroup collaborated to develop target product profiles to describe the minimum acceptable performance of BBM tests for triaging or confirmation of amyloid pathology in primary and secondary care settings. Given the major implications of BBM test results for individuals, the BBM Workgroup recommends high standards of performance. For triaging in primary care, BBM tests can only be slightly less accurate than CSF tests (≥90% sensitivity and ≥85% specificity

for amyloid PET status); otherwise, many people with false-negative BBM test results would not be identified or the number of people with positive BBM test results could exceed the capacity for confirmatory amyloid PET or CSF testing. For triaging in secondary care, a BBM test with lower specificity (≥75–85%) might be acceptable in clinics with a high capacity to perform follow-up amyloid PET or CSF testing. For confirmation of amyloid pathology, the performance of BBM tests should be equivalent to that of FDA-approved CSF tests, with a sensitivity and specificity of ~90%. If BBM tests are less accurate than CSF tests, amyloid PET or CSF tests are preferable for confirmation of amyloid pathology, especially if the individual could be a candidate for DMT.

A large number of BBM tests are currently in development for clinical use[2], and the quality and quantity of information available regarding their performance are highly variable. Therefore, rather than judging specific BBM tests, the CEOi BBM Workgroup recommends performance standards that could be applied to any test; the BBM Workgroup does not endorse any specific BBM test. Several BBM tests that are currently available have high accuracy in classification of amyloid status and might meet the standards recommended by the BBM Workgroup, especially when the two cut-off approach is used. Given the major capacity constraints and drawbacks of amyloid PET and CSF testing, integration of such high-performance BBM tests in clinical care could enable many more people with cognitive impairment to receive an accurate and timely diagnosis and to benefit from new DMTs for early symptomatic AD.

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Author contributions
S.E.S., O.H., D.G., A.C.P., G.D.R., S.S. and M.S.-C. were members of the core team that reviewed the literature and developed the consensus recommendations. S.E.S. and O.H. were the primary writers of the manuscript; they provided the initial outline, drafted much of the text and identified the majority of references. S.E.S. and her co-workers developed the online applications. G.V. convened the CEOi, which supported the formation of the Workgroup. D.R. reviewed the epidemiology of AD and health-care system preparedness and assisted S.E.S. and O.H. with preparation of the manuscript. D.H., K.A.P., E. Scholler and D.Y. provided support to the BBM Workgroup, including coordinating meetings, note taking during meetings, facilitating communications with stakeholders and verification of specific numbers cited in the manuscript (for example, for CSF biomarker assays). All other authors are stakeholders who represent academia, industry, private foundations and patient advocacy groups and who reviewed the manuscript and provided suggested revisions to the core team. All authors reviewed the manuscript and approved the final submitted version.

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