2.04.14	Evaluation of Cerebrospinal fluid, Urine, and Plasma Tests for Alzheimer Disease		
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Policy Statement

Tests as an Adjunct to Clinical Diagnosis

I. Cerebrospinal fluid testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins is considered **investigational** for **EITHER** of the following situations:
   A. As an adjunct to clinical diagnosis in individuals with mild cognitive impairment
   B. As an adjunct to clinical diagnosis individuals with mild dementia due to Alzheimer disease

II. Plasma testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins is considered **investigational** for **EITHER** of the following situations:
   A. As an adjunct to clinical diagnosis in individuals with mild cognitive impairment
   B. As an adjunct to clinical diagnosis individuals with mild dementia due to Alzheimer disease

Tests as Part of an Evaluation for the Initiation of Amyloid Beta Targeting Therapy

III. Cerebrospinal fluid testing of amyloid beta peptides and tau protein using tests that confirm amyloid pathology may be considered **medically necessary** for **ALL** of the following situations:
   A. One of these three FDA approved or cleared tests that have proven to confirm amyloid pathology (through establishing clinical equivalency to amyloid PET imaging):
      1. Aβ42:Aβ40 ratio (Lumipulse G Amyloid Ratio 1-42/1-40); or
      2. Aβ42:phosphorylated-tau181 (p-tau181) (Elecsys B-Amyloid 1-42 CSF II, Elecsys Phospho-Tau 181P) CSF); or
      3. Aβ42:total-tau (Elecsys ß-Amyloid 1-42 CSF II, Elecsys Total-Tau CSF).
   B. As part of an evaluation for the initiation of amyloid beta targeting therapy
   C. in individuals with mild cognitive impairment or individuals with mild dementia due to Alzheimer disease

IV. Plasma testing of amyloid beta peptides and tau protein using tests that confirm amyloid pathology as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**.

V. Cerebrospinal fluid testing of neural thread proteins as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**.

VI. Plasma testing of neural thread proteins as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**.

Tests as Part of an Evaluation for the Continuation of Amyloid Beta Targeting Therapy

VII. Cerebrospinal fluid testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as part of an evaluation for the continuation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**.

Evaluation of Urine

VIII. Measurement of urine analytes as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing

The labels for FDA-approved, amyloid beta targeting therapies, LEQEMBI® (lecanemab) and KisunlaTM (donanemab) state that the presence of amyloid beta pathology should be confirmed prior to initiating treatment. In the pivotal randomized controlled trial for lecanemab (Clarity AD), the protocol states that the eligibility criteria related to amyloid beta pathology required "confirmed amyloid pathology indicated by either 1) positive amyloid load confirmed by amyloid PET assessment, or 2) CSF assessment of t-tau / Aβ[1-42].'" In the pivotal randomized controlled trial for donanemab (TRAILBLAZER-ALZ 2), eligibility was based on flortaucipir F18 and florbetapir F18 PET assessment only. Per the protocol, p-tau 181 was removed as a screening and eligibility criterion in February 2021. In May, 2025 the U.S. Food and Drug Administration published the results of a clinical cohort study that evaluated the performance of the Lumipulse G p-tau217/ß-Amyloid 1-42 Plasma Ratio as an aid in the assessment of individuals presenting with cognitive impairment, AD, and other causes of cognitive decline to determine who would test positive or negative for amyloid plaques. The results demonstrated that the test was consistent with both, amyloid PET scans and CSF ratio tests, deeming the test clinically equivalent in its ability to confirm amyloid pathology when used under research conditions using bio-banked samples, which is consistent with the labels of lecanemab and donanemab. Furthermore, donanemab specifically demonstrated a reduction in plasma p-tau217.

No specific non-imaging tests are included in FDA labels for confirmation testing prior to amyloid beta targeting therapies. Clinical input suggests that any test should include, at a minimum, measurement of amyloid beta and/or tau protein and display performance characteristics that are comparable to amyloid PET and/or FDA cleared/approved CSF biomarker tests that are used for confirmation of amyloid pathology (i.e., Lumipulse G Amyloid Ratio 1-42/1-40). There is biological plausibility for the use of plasma-based testing, and clinical utility of such hinges on confirming amyloid pathology and clinical equivalence to the tests used in the trials for the amyloid beta targeting therapies. The FDA 510(k) submission for the Lumipulse G® pTau217/β-Amyloid 1-42 Plasma Ratio (K242706) demonstrated concordance with both amyloid PET scans and CSF ratio tests under research biobank conditions. Whether this performance is attainable under routine clinical laboratory conditions has not been prospectively demonstrated. The product is subject to an active FDA Class 2 recall (Z-1301-2026, initiated December 2025) for falsely elevated ratio results. Clinical equivalence under the usual conditions of medical practice has not been established.'

Coding

See the Codes table for details.

The coding table is limited to proprietary laboratory analyses (PLA) codes of tests included in the evidence review of the reference medical policy. Some studies included exploratory biomarkers outside of primary endpoints, and these are not reviewed in 2.04.14 and associated PLA codes are not included in the coding table.

Evidence reviews do not evaluate test analytical validity, including for laboratory-developed tests. The Clarity AD pivotal trial for lecanemab does not identify which commercially available tests kits were used for the CSF assessment of study eligibility biomarker t-tau / Aβ[1-42]. There is 1 FDA-cleared test kit capturing this analyte with applicable PLA code 0459U: Elecsys ß-Amyloid (1-42) CSF II, Elecsys® Total-Tau CSF (Roche Diagnostics). Additionally, the FDA cleared Elecsys® Phospho-Tau (181P) Plasma (PLA code 0445U) and Lumipulse G® p-tau217/β-Amyloid 1-42 Plasma Ratio in 2025.

Other relevant laboratory-developed tests approved by the New York State Department of Health, which may be subject to additional analytical scrutiny, may be identified through an online search tool at: https://www.wadsworth.org/regulatory/clep/approved-ldt.

See the Regulatory Status section for additional context.

Description

Biochemical changes associated with the pathophysiology of Alzheimer disease (AD) are being evaluated to aid in the diagnosis of the disease. This includes the potential use of biomarkers, such as amyloid beta peptide 1-42 and total or phosphorylated tau protein, in cerebrospinal fluid (CSF), urine, and plasma. Additionally, the potential correlation between CSF and plasma biomarkers as well as positron emission tomography (PET) amyloid scans has been proposed as useful in selecting appropriate individuals for the initiation or discontinuation of amyloid beta plaque targeted therapy.

Summary of Evidence

For individuals who have mild cognitive impairment (MCI) or dementia who receive cerebrospinal fluid (CSF) biomarker testing for Alzheimer disease (AD), the evidence includes systematic reviews. These studies assess using CSF biomarkers for diagnosis of AD or for the prognosis of progression of MCI to AD. Relevant outcomes include test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life (QOL). Most clinical validity studies have been derived from select individual samples and defined optimal test cutoffs without validation; thus, the generalizability of results is uncertain. For predicting conversion from MCI to AD, limited evidence has suggested that testing may define increased risk. Whether an earlier diagnosis leads to improved health outcomes through a delay of AD onset due to medical therapy or other interventions or improved QOL is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or dementia who receive urine biomarker testing for AD, the evidence includes a systematic review. Relevant outcomes include test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and QOL. Clinical validity studies have included normal healthy controls and defined optimal test cutoffs without validation; thus, clinical validity is uncertain. Whether an earlier diagnosis leads to improved health outcomes through a delay of AD onset or improved QOL is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or dementia who receive plasma biomarker testing for AD, the evidence includes 2 systematic reviews and cohort studies. Relevant outcomes include test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and QOL. Clinical validity studies have primarily focused on e plasma p-tau, particularly p-tau217, and beta amyloid, and have shown that these biomarkers may be beneficial in screening for and diagnosing

AD, with p-tau217-based measures demonstrating the highest classification accuracies across commercial platforms. The evidence base is predominantly derived from White cohorts, though limited evidence suggests comparable performance by race for ratio-based biomarkers. Whether an earlier diagnosis leads to improved health outcomes through a delay of AD onset or improved QOL is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or mild dementia due to AD who are being considered for initial treatment with an approved amyloid beta plaque targeting therapy who receive cerebrospinal fluid testing, the evidence includes randomized controlled trials, multisite longitudinal studies, and an analysis of mixed cohort studies, including FDA decision summary documents. These studies assess both the correlation between CSF biomarkers and positron emission tomography (PET) amyloid scans and the clinical utility of amyloid PET and CSF biomarkers in cognitively impaired individuals who are being evaluated for treatment with anti-amyloid therapies. Relevant outcomes include test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. Overall, the diagnostic accuracy of CSF biomarkers versus amyloid PET scans to identify MCI-AD was found to be similar. CSF biomarkers have been used as an alternative to PET amyloid scans to establish eligibility regarding the presence of amyloid beta pathology in randomized controlled trials that showed the efficacy of anti-amyloid therapies, which in turn demonstrates that the CSF biomarkers can identify individuals who may benefit from therapy. The FDA-approved labels for lecanemab and donanemab state that the presence of amyloid beta pathology should be confirmed prior to initiating treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or mild dementia due to AD who are being considered for initial treatment with an approved amyloid beta plaque targeting therapy who receive plasma biomarker testing, the evidence includes multisite longitudinal studies, and an analysis of mixed cohort studies, including FDA decision summary documents. These studies assess the correlation between CSF and plasma biomarkers as well as positron emission tomography (PET) amyloid scans and the clinical utility of amyloid PET, CSF, and plasma biomarkers in cognitively impaired individuals who are being evaluated for treatment with anti-amyloid therapies. Relevant outcomes include test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. Overall, the diagnostic accuracy of plasma biomarkers versus CSF biomarkers and amyloid PET scans to identify MCI-AD was found to be similar. CSF biomarkers have been used as an alternative to PET amyloid scans to establish eligibility regarding the presence of amyloid beta pathology in randomized controlled trials that showed the efficacy of anti-amyloid therapies, which in turn demonstrates that the CSF biomarkers can identify individuals who may benefit from therapy. Plasma biomarkers have established clinical equivalency to amyloid PET and CSF biomarkers in their ability to characterize amyloid beta pathology under research conditions using bio-banked samples. However, limited evidence has been generated regarding the utility of these tests when used in clinical laboratory setting or real-world settings with the findings of these studies suggesting varying test performance metrics. In order for plasma biomarkers to substitute or replace CSF biomarkers or amyloid PET scans for selecting targeted treatment with anti-amyloid therapy, prospective data demonstrating that plasma biomarkers are non-inferior to CSF biomarkers or amyloid PET scans within a clinical or real-word setting are needed, thus a chain of evidence cannot be constructed to demonstrate clinical utility that plasma biomarkers can identify individuals who may benefit from therapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or mild dementia due to AD, who are being treated with an amyloid beta plaque targeting therapy and are being evaluated for therapy continuation, the evidence includes multisite longitudinal studies and an analysis of a mixed cohort. Two of these studies assess the correlation between CSF biomarkers and PET amyloid scans and another assesses the clinical utility of amyloid PET in cognitively impaired individuals who met appropriate use criteria for clinical

amyloid PET. Relevant outcomes include test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. The diagnostic accuracy of CSF biomarkers versus amyloid beta PET scans to identify MCI-AD was found to be similar. Further research is required to determine whether the use of CSF biomarkers alone in conjunction with amyloid beta PET scans is useful for determining whether or not amyloid beta targeting therapy should be continued. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

2024 Input

Clinical input was sought to help determine whether the use of cerebrospinal fluid biomarker testing for individuals who are being considered for an approved amyloid beta plaque targeting therapy would provide a clinically meaningful improvement in net health outcome. In response to requests, clinical input was received from 3 respondents; 1 physician-level response identified through a specialty society; 2 physician-level responses (joint response) identified through an academic medical center.

For individuals who have early AD who receive amyloid-beta targeting therapy, clinical input supports this use provides a clinically meaningful improvement in net health outcome with the criteria described.

Further details from clinical input are included in the Appendix.

Related Policies

- Genetic Testing for Alzheimer Disease

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests (LDTs) must be certified by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests. Several AD biomarker tests are available as LDTs.

Clinical laboratories located in New York State, and laboratories conducting testing on specimens originating in New York State, must hold a New York State Department of Health clinical laboratory permit pursuant to Title V, Section 574 of the New York State Public Health Law. The Clinical Laboratory Evaluation Program (CLEP) regulates clinical laboratories that accept clinical specimens collected in New York State. Laboratories holding a New York State clinical laboratory permit must

participate in regular proficiency testing to demonstrate analytical validity. For additional details, see https://www.wadsworth.org/regulatory/clep.

Laboratory-developed tests approved by the New York State Department of Health may be identified through an online search tool at: https://www.wadsworth.org/regulatory/clep/approved-ldt. Laboratories may administer FDA-cleared (510k), approved (PMA/De Novo), exempted, or Emergency Use Authorization (EUA) applicable assays that have not been modified to change the procedure or the intended use without further action if the laboratory holds a permit in the test appropriate category. A listing of approved clinical laboratories is available at: https://wadsworth.org/regulatory/clep/approved-labs

Several AD biomarker tests are available as LDTs. Not all laboratories choose to seek a New York State clinical laboratory permit. Several plasma based tests have received Breakthrough Device Designation from the FDA, including Roche and Eli Lilly's Elecsys p-Tau217 plasma assay, and Beckman Coulter Diagnostics p-Tau217/β-Amyloid 1-42 plasma ratio.

The FDA has cleared CSF and plasma -based AD biomarker tests for marketing via the De Novo and 510(k) pathways with product code QSE, see Table 2.

Table 2. FDA Cleared Biomarker Tests for Alzheimer Disease

Test	Manufacturer	Location	Date Cleared	De Novo or 510(k) Number	Indication(s)
Lumipulse *G* Amyloid Ratio (1-42/1-40)	Fujirebio Diagnostics, Inc	Malvern, PA	May 2022	DEN200072	• CSF test • Intended to be used in adult individuals, aged 55 years and older, presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. • A test result ≥0.073 is a negative result which is consistent with a negative amyloid PET scan result. A negative result reduces the likelihood that a individual's cognitive impairment is due to AD. • A test result ≤0.058 is a positive result which is consistent with a positive amyloid PET scan result. A positive result does not establish a diagnosis of AD or other cognitive disorder. • A test result between 0.059 and 0.072 is considered as a likely positive result as it is more likely consistent with a positive amyloid PET scan result. A likely positive result does not establish a diagnosis of AD or other cognitive disorders and has increased uncertainty in regard to amyloid PET positivity. • The Lumipulse G P-Amyloid Ratio (1-42/1-40) results must be interpreted in conjunction with other individual clinical information. This test is not intended as a screening or stand-alone diagnostic test.

Test	Manufacturer	Location	Date Cleared	De Novo or 510(k) Number	Indication(s)
Lumipulse G p-tau217/β-Amyloid 1-42 Plasma Ratio[a]	Fujirebio Diagnostics, Inc	Malvern, PA	May 2025	K242706	• Plasma test • Intended to be used in adult individuals, aged 50 years and older, in the initial assessment for AD and other causes of cognitive decline presenting at a specialized care setting with signs, symptoms, or complaints of cognitive decline. • A test result ≤ 0.00370 is a negative result which is consistent with individuals who are unlikely to have amyloid pathology. These individuals should be investigated for other causes of cognitive decline. • A test result ≥0.00738 is a positive result which is consistent with individuals who are likely to have amyloid pathology. This result does not establish a diagnosis of Alzheimer's disease or other cognitive disorder. • A test result between 0.00371 and 0.00737 is an indeterminate result which is consistent with individuals who are uncertain to have amyloid pathology. These individuals should be considered for further testing. • Lumipulse G p-tau217/β-Amyloid 1-42 Plasma Ratio results must be interpreted in conjunction with other individual clinical information. This test is not intended as a screening or stand-alone diagnostic test.
Elecsys B-Amyloid (1-42) CSF II, Elecsys Phospho-Tau (181P) CSF	Roche Diagnostics	Indianapolis, IN	December 2022	K221842	• CSF test • Intended to be used in adult individuals, aged 55 years and older, being evaluated for AD and other causes of cognitive impairment to generate a p-tau181/Abeta42 ratio value. • The adjusted ratio cutoff is 0.023. • A negative result, defined as p-tau181/Abeta42 ratio value below cutoff or an Abeta42 value above the measuring range, is consistent with a negative amyloid PET scan result. A negative result reduces the likelihood that an individual's cognitive impairment is due to AD. • A positive result, defined as p-tau181/Abeta42 ratio value above cutoff, is consistent with a positive amyloid PET scan result. A positive result does not establish a diagnosis of AD or other cognitive disorder.

Test	Manufacturer	Location	Date Cleared	De Novo or 510(k) Number	Indication(s)
					• The p-tau181/Abeta42 ratio result is used as an adjunct to other clinical diagnostic evaluations. • The performance of the p-tau181/Abeta42 ratio has not been established for predicting development of dementia or other neurologic conditions or monitoring responses to therapies
Elecsys Phospho-Tau (181P) Plasma	Roche Diagnostics	Indianapolis, IN	October 2025	K252163	• Plasma test • Intended to be used in adult individuals, aged 55 years and older, in the initial assessment for AD and other causes of cognitive decline presenting with signs, symptoms, or complaints of cognitive decline. • A negative result, defined as p-tau181 levels ≤ 0.722 pg/mL, is consistent with a negative amyloid PET scan result. A negative result reduces the likelihood that a individual's cognitive impairment is due to amyloid pathology. • A positive result, defined as p-tau181 levels > 0.722 pg/mL, is consistent with a positive amyloid PET scan result. A positive result does not establish a diagnosis of AD or other cognitive disorder and should be further investigated to determine whether the amyloid pathology can be a cause of cognitive impairment. • The p-tau181 result is used as an adjunct to other clinical diagnostic evaluations. • The performance of the p-tau181 has not been established for predicting development of dementia or other neurologic conditions or monitoring responses to therapies
Elecsys ß-Amyloid (1-42) CSF II, Elecsys Total-Tau CSF	Roche Diagnostics	Indianapolis, IN	June 2023	K231348	• CSF test • Intended to be used in adult individuals, aged 55 years and older, being evaluated for AD and other causes of cognitive impairment to generate a tTau/Abeta42 ratio value. • The numerical ratio must be compared to the cutoff of 0.28. • A negative result, defined as tTau/Abeta42 ratio value below cutoff or an Abeta42 value above the measuring range, is consistent with a negative amyloid PET scan result. A negative result reduces the likelihood

Test	Manufacturer	Location	Date Cleared	De Novo or 510(k) Number	Indication(s)
					that a individual's cognitive impairment is due to AD. • A positive result, defined as tTau/Abeta42 ratio value above cutoff, is consistent with a positive amyloid PET scan result. A positive result does not establish a diagnosis of AD or other cognitive disorder. • The tTau/Abeta42 ratio result is used as an adjunct to other clinical diagnostic evaluations. • The performance of the tTau/Abeta42 ratio has not been established for predicting development of dementia or other neurologic conditions or monitoring responses to therapies.

AD: Alzheimer disease; CSF: cerebral spinal fluid; FDA: Food and Drug Administration; PET: positron emission tomography; p-tau: phosphorylated tubulin associated unit.
[a]Note: Subject to active FDA Class 2 Device Recall Z-1301-2026 (initiated December 11, 2025; status: Open) for falsely elevated ratio results. FDA-determined cause: Under Investigation by firm.

Rationale

Background

Alzheimer Disease

Alzheimer Disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 12 million by 2050.[1,] Per the 2018 American Academy of Neurology practice guideline update on mild cognitive impairment (MCI), the prevalence of MCI was 6.7% for ages 60 to 64, 8.4% for ages 65 to 69, 10.1% for ages 70 to 74, 14.8% for ages 75 to 79, and 25.2% for ages 80 to 84.[2,] The cumulative dementia incidence was 14.9% in individuals with MCI >65 years of age followed for 2 years.

Data from the National Institute on Aging have shown that Black Americans are approximately 1.5 to 2 times more likely to develop AD and related dementias as compared to Whites.[3,] Additionally, Black participants in AD research studies were 35% less likely to be diagnosed with AD and related dementias and were found to have more risk factors for the disease as well as greater cognitive impairment and symptom severity than White participants. Findings from 2 national surveys conducted by the Alzheimer's Association also found that people of color face discrimination when seeking health care for AD and related dementias with the highest level of discrimination in dementia health care reported by Black Americans (50%) followed by Native (42%), Asian (34%), and Hispanic (33%) Americans.[4,] Non-Hispanic White Americans reported a discrimination rate of 9%.

Pathophysiology

Alzheimer disease (AD) is now conceptualized as a clinical continuum from preclinical phases of disease (asymptomatic, but with evidence of AD pathology), to mild cognitive impairment (MCI; in which cognitive impairment occurs without significant functional decline), to dementia (in which capacity for instrumental and basic activities of daily living is compromised). The pathologic

hallmarks of AD are extracellular deposits of amyloid beta (Aβ), referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. Different plasma phosphorylated tau (p-tau) species reflect different pathological processes of AD, with p-tau231 showing the greatest association with the earliest increases in brain Aβ accumulation, while p-tau217 shows greater association with both brain Aβ and early tau pathology, and other p-tau and tau fragment species show greater association with later stages of brain tau pathology.[5,] Likewise, there are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and their contributions to the pathophysiology of AD is not well understood. Generally referred to as the "amyloid hypothesis", it is believed that aggregation of amyloid beta oligomers in the brain leads to amyloid plaques. Amyloid aggregation in addition to accumulation of tau pathology and neurodegeneration are thought to be the main drivers of the disease process. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.[6,7,]

The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before symptoms arise.[8,] The National Institute on Aging-Alzheimer's Association (NIA-AA) has created a "numeric clinical staging scheme" (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme is primarily used in the research setting and reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia. A detailed clinical assessment provides reasonable diagnostic accuracy for AD in the majority of individuals; however, other neurodegenerative diseases may complicate the diagnosis as their clinical symptoms and syndromes overlap with one another. A definitive diagnosis of AD requires histopathologic examination, but is rarely done in practice, thus, the clinical criteria outlined by the National Institute on Aging and the Alzheimer's Association (NIA-AA) for AD is commonly used to make a diagnosis and includes a history of insidious onset and progressive course of cognitive decline, exclusion of other etiologies, and documentation of cognitive impairments in one or more domains. In recent years the field has moved from diagnosing and characterizing AD based on clinical presentation alone to diagnosing the disease biologically. This change in perspective emerged after the FDA approval of amyloid PET imaging and clinical findings that demonstrated amyloid PET results significantly impacted clinical management and etiologic diagnosis. [9,]

Table 1. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum[a]

Stage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Severity	Pre-clinical	Pre-clinical	MCI due to Alzheimer disease	Mild Dementia	Moderate Dementia	Severe Dementia
Clinical Features	• Performance within an expected range on objective cognitive tests.	• Normal performance within the expected range on objective cognitive tests.	• Performance in the impaired/abnormal range on objective cognitive tests. • Evidence of decline	• Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance.	• Progressive cognitive impairment or neurobehavioral changes. • Extensive	• Progressive cognitive impairment or neurobehavioral changes. • Clinical intervi

Stage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
	• No evidence of recent cognitive decline or new neurobehavioral symptoms.	• Transitional cognitive decline (change from individual baseline within the past 1 to 3 years, and persistent for at least 6 months). • Mild neurobehavioral changes may coexist or maybe the primary complaint rather than cognitive. • No functional impact on daily life activities.	from baseline. • Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life.	• Clearly evident functional impact on daily life, affecting mainly instrumental activities. • No longer fully independent/requires occasional assistance with daily life activities.	functional impact on daily life with impairment in basic activities. • No longer independent and requires frequent assistance with daily life activities.	ew may not be possible. • Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

Adapted from Table 6, Jack et al (2018)[10,]
[a]Applicable only to individuals in the Alzheimer continuum that fall into 1 of the 4 biomarker groups: 1) A+T+N+ 2) A+T-N- 3) A+T+N- 4) A+T-N+ where A: Aggregated Aβ or associated pathologic state (CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio or Amyloid PET), T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau or Tau PET) and N: Neurodegeneration or neuronal injury (anatomic MRI, FDG PET or CSF total tau)
For stages 1 to 6: Cognitive test performance may be compared to normative data of the investigator's choice,

with or without adjustment (choice of the investigators) for age, sex, education, etc.
For stages 2 to 6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.
For stages 3 to 6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.
CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

Biomarkers

Several potential biomarkers of AD are associated with AD pathophysiology (e.g., amyloid beta plaques, neurofibrillary tangles). Altered cerebrospinal fluid (CSF) levels of specific proteins have been found in individuals with AD. These include tau protein, phosphorylated at AD-specific epitopes such as phosphorylated threonine 181 or total tau protein, an amyloid beta peptide such as 1-42 (Aβ42), and the synaptic protein, neurogranin.[11] Other potential CSF[12,13], urine, and blood[14] peptide markers have been explored. One study demonstrated that decreased gamma-aminobutyric acid (GABA) levels within CSF or plasma are implicated in AD pathophysiology. [15] Tau protein is a microtubule-associated molecule found in neurofibrillary tangles that are typical of AD. Tau protein is thought to be related to degenerating and dying neurons and high levels of tau protein in the CSF have been associated with AD. Amyloid beta-42 is a subtype of amyloid beta peptide produced from the metabolism of the amyloid precursor protein. Amyloid beta-42 is the key peptide deposited in amyloid plaques characteristic of AD. Low levels of amyloid beta-42 in the CSF have been associated with AD, perhaps because amyloid beta-42 is deposited in amyloid plaques instead of remaining in the fluid. Investigators have suggested the tau/amyloid beta-42 ratio may be a more accurate diagnostic marker than either alone.[16] Neurogranin is a dendritic protein and CSF measurement may serve as a biomarker for dendritic instability and synaptic degeneration.[11] Elevated CSF neurogranin may predict prodromal AD in MCI and has been confirmed in AD dementia and prodromal AD in several studies.

A variety of kits are commercially available to measure amyloid beta-42 and tau proteins. Between-laboratory variability in CSF biomarker measurement is large.[17,18] Neural thread protein is associated with neurofibrillary tangles of AD. Both CSF and urine levels of this protein have been investigated as a potential marker of AD. Urine and CSF tests for neural thread protein may be referred to as the AD7C test.

More recently, research has focused on blood, more specifically plasma, as a new matrix for AD biomarkers that have already been validated in the CSF. As blood is more accessible than CSF, blood sampling would be preferable to CSF when taking samples to measure AD biomarkers, both for clinical diagnosis or screening.[11] However, developing blood AD biomarkers has proven complex. While the CSF is continuous with the brain extracellular fluid, with a free exchange of molecules from the brain to the CSF, only a fraction of brain proteins enter the bloodstream. Examples of blood biomarkers that are currently under examination for use in AD include amyloid beta, tau protein, and neurofilament light.[19] Results from initial studies show that these blood biomarkers may potentially assist in early and more precise diagnosis, prognosis, or monitoring of disease progression and treatment in AD. In 2019, the Geneva AD Biomarker Roadmap Initiative expert panel concluded that of the currently assessed blood biomarkers plasma p-tau has shown analytical validity and initial evidence of clinical validity, whereas the maturity level for amyloid beta remains to be partially achieved.[20]

Amyloid PET using an FDA-approved tracer are used as qualitative assessments of beta-amyloid (Aβ) plaque density with positive scans being indicative of amyloid plaque pathology. Furthermore, the FDA has authorized amyloid CSF Ratio tests to be routinely used in clinical practice to confirm amyloid pathology as it has proven to be just as effective as amyloid PET in characterizing the biological underpinnings of amyloid etiology with RCTs demonstrating the utility of these tests in identifying individuals who would benefit from anti-amyloid therapy. [21]Amyloid-targeted therapies refer to recombinant monoclonal antibodies directed against amyloid beta. These agents are highly effective in reducing amyloid plaque burden on positron emission tomography (PET) imaging and are

therefore believed to be disease modifying. However, their use is limited to those individuals proven to be amyloid positive (by amyloid PET scan or the presence of AD biomarkers in the cerebrospinal fluid [CSF]), as was required in the clinical trials that evaluated these drugs, as their efficacy on clinical outcomes is modest, slowing progression by approximately 25 to 30 percent in carefully selected individuals, and are associated with risk for significant adverse effects.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Cerebrospinal Fluid, rine, or Plasma Biomarker Testing for Alzheimer Disease

Clinical Context and Test Purpose

The purpose of cerebrospinal fluid (CSF), urine, or plasma biomarker testing for Alzheimer disease (AD) is to provide an alternative or superior method for diagnosis to inform a decision to proceed with appropriate treatment in individuals with AD or mild cognitive impairment (MCI).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with MCI or dementia who are being evaluated for diagnosis of AD.

Interventions

The tests being considered are CSF, urine, or plasma biomarker testing for AD.

Comparators

Comparators of interest include a clinical diagnosis of AD.

A definitive diagnosis of AD requires histopathologic examination. Both the Diagnostic and Statistical Manual of Mental Disorders (DSM) and National Institute on Aging-Alzheimer's Association (NIA-AA) have proposed criteria for diagnosis of probable AD.[22,23,24,]

NIA-AA criteria for the diagnosis of probable AD requires the presence of dementia and the following:[23,24,]

- Interference with ability to function at work or usual activities;
- Decline from previous level of functioning and performing;
- Not explained by delirium or major psychiatric disorder;
- Cognitive impairment established by history from the individual and informant and objective mental status examination or neuropsychologic testing;
- Cognitive impairment involving at least 2 of the following:
    - Impaired ability to acquire and remember new information;
    - Impaired reasoning and handing of complex tasks, poor judgment;
    - Impaired visuospatial abilities;
    - Impaired language functions;
    - Changes in personality, behavior, or comportment.

- Insidious onset;
- History of worsening;
- Most prominent cognitive deficits are: amnestic, nonamnestic with a language presentation; visuospatial; or dysexecutive;
- No evidence of another concurrent, active neurologic or non-neurologic disease or use of medication that could have a substantial effect on cognition.

The most common disorders considered in the differential diagnosis of AD are vascular dementia and other neurodegenerative dementias such as dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD).

Outcomes

The general outcomes of interest are test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life (QOL) for testing to diagnose AD. For testing to predict progression of MCI, the outcomes of interest are correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and QOL.

Follow-up is at months to years for CSF, urine, or plasma biomarker testing for the outcomes of interest.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- The study population represents the population of interest. Eligibility and selection are described;
- The test is compared with a credible reference standard;
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test;
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative;
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Cerebrospinal Fluid Biomarker Testing

Diagnosis of Alzheimer Disease

Systematic Reviews

Most studies have relied on clinically diagnosed AD as the criterion standard. Results from the majority of systematic reviews are summarized in Table 3. Studies included in these systematic reviews are not individually reviewed.

Table 3. Systematic Reviews Assessing CSF Biomarkers Performance for Distinguishing Alzheimer Disease From Controls With Clinical Diagnosis as the Reference Standard

Biomarker Studies	Controls Without Dementia, %		Controls With Dementia, %[a]	
	Sensitivity	*Specificity*	*Sensitivity*	*Specificity*
Aβ42				
Rosa et al (2014)[25,]	84 (81 to 85)	79 (77 to 81)	NR	NR
Bloudek et al (2011)[26,]	80 (73 to 85)	82 (74 to 88)	73 (67 to 78)	67 (62 to 72)
Formichi et al (2006)[27,]	NR	NR	55 to 100	80 to 100

Biomarker Studies	Controls Without Dementia, %		Controls With Dementia, %[a]	
tTau				
Bloudek et al (2011)[26]	82 (76 to 87)	90 (86 to 93)	78 (72 to 83)	75 (68 to 81)
Formichi et al (2006)[27]	NR	NR	52 to 100	50 to 100
p-tau				
Ferreira et al (2014)[28]	78 to 80	83 to 88	72 to 88	78 to 83
Bloudek et al (2011)[26]	80 (70 to 87)	83 (75 to 88)	79 (72 to 84)	80 (71 to 86)
Formichi et al (2006)[27]	NR	NR	37 to 100	80 to 100

Values in parentheses are 95% confidence intervals.
Aβ42: amyloid-β peptide 1-42; CSF: cerebrospinal fluid; NR: not reported; p-tau: phosphorylated tau protein; tTau: total tau protein.
[a]Or unspecified.

Fink et al (2020) conducted a systematic review of biomarker accuracy for diagnosing neuropathologically defined AD in older individuals with dementia.[29] The analysis included literature published between January 2012 and November 2019, with 9 cohort studies focusing on CSF biomarkers. Overall, CSF biomarkers and ratios had moderate sensitivity (range, 62% to 83%) and specificity (range, 53% to 69%). Biomarker accuracy was higher with amyloid beta-42/p-tau ratio, tTau/amyloid beta-42 ratio, and p-tau compared with tTau alone.

Cure et al (2014) conducted a systematic review with meta-analysis of CSF and imaging studies for the diagnosis of definite AD (autopsy-confirmed).[30] Literature was searched in January 2012, and 3 studies of CSF markers (p-tau, tTau, amyloid beta-42, amyloid beta-40) were identified (N=337 individuals). Pooled sensitivity of all CSF tests was 82% (95% confidence interval [CI], 72% to 92%), and pooled specificity was 75% (95% CI, 60% to 90%). Statistical heterogeneity was not reported, but studies varied by AD definitions, controls (individuals without dementia or individuals with dementia due to other causes), and test thresholds. The summary area under receiver operating characteristic curve, constructed using multiple test thresholds, was 0.84.

Subsection Summary: Clinical Validity of Cerebrospinal Fluid Biomarker Testing for Diagnosis of Alzheimer Disease

Several studies have examined the diagnostic performance of CSF biomarkers for distinguishing individuals with probable AD from individuals without dementia and from individuals with other types of dementia. The range of reported sensitivities and specificities is broad compared with a clinical diagnosis reference standard. In systematic reviews with meta-analyses, sensitivity and specificity rates ranged from 80% to 82% and 82% to 90%, respectively, for differentiating AD from healthy controls, and were 73% and 67%, respectively, for differentiating AD from other dementias. Positive and negative likelihood ratios were 2 to 8 and 0.2 to 0.4, respectively, in either setting. There is limited evidence examining the incremental diagnostic accuracy of CSF biomarkers for AD diagnosis employing autopsy as a criterion standard. Cutoffs for a positive diagnosis are not standardized.

Prognosis for Progression of Mild Cognitive Impairment

Systematic Reviews

There are a variety of systematic reviews that have evaluated the prognostic value of CSF biomarkers for the progression of MCI and conversion to clinically manifest AD. These studies primarily include clinical diagnosis as a reference standard and varying cutoffs for predicting conversion. Tables 4 and 5 present the characteristics and results of key meta-analyses.

Table 4. Characteristics of Key Meta-Analyses That Evaluate the Prognostic Value of CSF Biomarkers for the Progression of MCI and Conversion to Clinically Manifest AD

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Olsson (2016)[31]	1995-2014	231	individuals with AD or MCI due to AD	AD=15,699 Controls=13,018	Not specified	Not specified

Study	Dates	Studies	Participants	N (Range)	Design	Duration
				Total=27,717 (Range=20 to 1087)		
Ritchie (2017)[32,]	2006-2013	15	individuals with MCI at baseline	N=1282	Longitudinal cohort	2 mo to 11.8 y
Ritchie (2014)[33,]	2003-2013	17	Participants with cognitive decline but no dementia condition at baseline	Total=2228 (Range=37 to 588)	Longitudinal cohort	2 mo to 12 y

AD: Alzheimer disease; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; mo: month(s); y: year(s).

Table 5. Results of Key Meta-Analyses

Study	Aß42	tTau	p-tau
Olsson (2016)[31,]			
Average ratio (95% CI)	0.56 (0.55 to 0.58)	2.54 (2.44 to 2.64)	1.88 (1.79 to 1.97)
p value	<.001	<.001	<.001
Ritchie (2017)[32,]			
Sensitivity range, %	-	51 to 90	40 to 100
Specificity range, %	-	48 to 88	22 to 86
Median specificity, %	-	72	47.5
Sensitivity at median specificity, % (95% CI)	-	75 (67 to 85)	81 (64 to 91)
Ritchie (2014)[33,]			
Sensitivity range, %	36 to 100	-	-
Specificity range, %	29 to 91	-	-
Median specificity, %	64	-	-
Sensitivity at median specificity, % (95% CI)	81 (72 to 87)	-	-

Average ratio: Alzheimer disease to control ratio for cerebral spinal fluid biomarker concentration.
Aβ42: amyloid-β peptide 1-42; CI: confidence interval; NR: not reported; p-tau: phosphorylated tau protein; tTau: total tau protein.

Subsection Summary: Clinical Validity of Cerebrospinal Fluid Biomarker Testing for Prognosis for Progression of Mild Cognitive Impairment

The evidence suggests that biomarker testing may identify an increased risk of conversion from MCI to AD. Studies primarily include clinical diagnosis as a reference standard and varying cutoffs for predicting conversion.

Clinically Useful

Possible clinical uses of CSF biomarker testing could include confirming the diagnosis of AD to begin medications at an earlier stage or ruling out AD, which could lead to further diagnostic testing to determine the etiology of dementia and/or avoidance of unnecessary medication.

Testing for treatment of MCI and early AD using anti-amyloid therapies is discussed in another section. Outside of that indication, no other trials were identified that have reported health outcomes after CSF biomarker testing; thus, there is no direct evidence for clinical utility. Decision models can provide indirect evidence of utility if the likelihood of benefits and consequences are estimable. To evaluate the benefits and consequences of CSF biomarker interventions, models would need to describe disease progression, resources used, and QOL. Such estimates are scarce and highly variable.

Although not without controversy because of modest efficacy, cholinesterase inhibitors are used to treat symptoms of mild-to-moderate AD.[34,35,] Memantine, an *N*-methyl-d-aspartate receptor antagonist, appears to provide a small benefit in treating symptoms in those with moderate-to-advanced disease.[34,36,] Neither cholinesterase inhibitors nor memantine is disease-modifying. Clinical trial entry criteria and benefits for cholinesterase inhibitors and memantine have been based on clinical diagnosis. There is less evidence to support the use of cholinesterase inhibitors in other dementias, but they are still frequently used to treat cognitive symptoms. While the possibility that a

more accurate differential diagnosis may lead to improved outcomes is plausible, it is not based on current evidence. Use of cholinesterase inhibitors and memantine for MCI have not demonstrated benefit in reducing progression to AD.[37,38,39,40,] The chain of evidence of clinical utility is incomplete.

Section Summary: Cerebrospinal Fluid Biomarker Testing

Most clinical validity studies of both diagnosis of AD and prognosis for progression of MCI to AD use select individual samples and define optimal test cutoffs without validation. There is no evidence that improved diagnosis or prognosis leads to improved health outcomes or QOL outside of the use to select individuals for anti-amyloid therapy discussed in a separate section.

Urine Biomarker Testing

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Zhang et al (2014) conducted a systematic review and meta-analysis of urine AD-associated neural thread protein (NTP) for diagnosing AD in individuals with suspected AD.[41,] Nine studies were included (n=841 individuals with probable or possible AD; 37 individuals with MCI, 992 with non-AD dementia or controls without dementia). The reference standard was a clinical diagnosis in 8 studies and not described in another. Varying cutoffs for positive diagnosis were used across included studies. Controls were both healthy volunteers and individuals with other dementias. For probable AD, pooled sensitivity and specificity were 89% (95% CI, 86% to 92%) and 90% (95% CI, 88% to 92%), respectively. Pooled positive and negative likelihood ratios were 8.9 (95% CI, 7.1 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively.

Clinically Useful

There is no direct evidence to support the clinical utility of urine markers for diagnosing AD and the chain of evidence is incomplete.

Section Summary: rine Marker Testing

A systematic review and meta-analysis that evaluated urine AD-associated NTP with regard to diagnosing AD in individuals with suspected AD concluded that, for probable AD, pooled sensitivity and specificity were 89% (95% CI, 86% to 92%) and 90% (95% CI, 88% to 92%), respectively. Pooled positive and negative likelihood ratios were 8.9 (95% CI, 7.1 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively.

Plasma Biomarker Testing

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Screening and Diagnosis of Alzheimer Disease

Systematic Reviews

Kim K., Shin K., and Chang K.A. (2025) conducted a systematic review and meta-analysis (16 studies) to assess phosphorylated tau proteins (p-tau) as blood-based biomarkers for dementia and how it performs in comparison to tau PET, the gold standard for in vivo tau assessment. [42,] When comparing individuals with AD to controls the pooled standardized mean difference (SMD) for p-tau181 (SMD: 1.55, 95% confidence interval [CI]: 1.20 to 1.90; p<.00001), p-tau217 (SMD: 1.95, 95% CI:1.55 to 2.34; p <.00001), and p-tau231 (SMD:1.12, 95% CI: 0.63 to 1.61; p <.00001) indicated that individuals with AD have a statistically significant increase in levels of p-tau proteins. The comparison between mild cognitive impairment (MCI) and controls also demonstrated elevated levels of tau protein that were statistically significant for p-tau181 (SMD: 0.59, 95% CI: 0.30 to 0.89; p<.0001), p-tau217 (SMD: 0.97, 95% CI: 0.70 to 1.24; p<00001), and p-tau231 (SMD:0.33, 95% CI: 0.10 to 0.55; p=.004) for individuals with MCI. Furthermore, when evaluating p-tau proteins in plasma between individuals with AD or

MCI, individuals with AD had increased serum levels of p-tau181 (SMD: 0.75, 95% CI: 0.49 to 1.02; p<.00001) and p-tau217 (SMD: 0.93, 95% CI: 0.51 to 1.36; p<.0001). Plasma p-tau isoforms (p-tau181, p-tau217, and p-tau231) were significantly elevated in individuals with AD and MCI compared with controls, and these changes broadly paralleled the tau-PET findings. However, these studies had substantial heterogeneity, had possible cohort overlap, variability in analytic approaches, and limited longitudinal evidence, thus plasma p-tau levels remain a preliminary biomarker. Standardized methods and further prospective validation and longitudinal studies are needed to establish the clinical validity and utility of p-tau proteins as a meaningful biomarker to aid in the clinical diagnosis of AD and MCI.

Three additional systematic reviews examined the performance characteristics of plasma biomarkers compared to amyloid-PET, tau-PET, CSF, and neuropathological reference standards for Alzheimer's disease. [43,44,45,] Therriault et al (2025) conducted a meta-analysis on 113 studies comprising of 29,625 individuals to evaluate plasma phosphorylated tau (p-tau) proteins to identify biologically defined Alzheimer's disease. Pooled sensitivity, specificity, area under the receiver operating characteristic curve (AUROC), and diagnostic odds ratios for plasma p-tau proteins are presented in Table 6. Of note, 90% of the studies included in this meta-analysis were rated to have a high risk of bias for not having used predefined or externally derived thresholds. Pahlke et al (2025) performed a meta-analysis on 49 observational studies to assess the diagnostic test accuracy of plasma p-tau and amyloid beta (Aβ) tests (p-tau217, %p-tau217, p-tau181, p-tau231, and Aβ42/Aβ40) compared to reference standard tests (cerebrospinal fluid [CSF] AD biomarkers, amyloid positron emission tomography [PET], or neuropathology) in individuals with cognitive impairment (mild cognitive impairment or dementia). The pooled sensitivity ranged from 49.3% (95% confidence interval [CI]: 41.2 to 57.4) to 91.4% (95% CI: 86.6 to 94.6), and the pooled specificity ranged from 61.5% (95% CI: 45.6 to 75.3) to 96.7% (95% CI: 87.8 to 99.2). Most of the included studies were judged to be at high risk of bias, particularly in domains related to individual selection, index test conduct, and reference standard. A diagnostic test accuracy meta-analysis of 30 studies (n=9787) evaluated plasma and CSF p-tau217 against amyloid and tau PET as the reference standard (Khalafi et al., 2025). For detecting amyloid PET positivity, plasma p-tau217 demonstrated pooled sensitivity of 82% (95% CI: 79% to 84%) and pooled specificity of 86% (95% CI: 84% to 88%), with a summary receiver operating characteristic (SROC) AUC of 0.91. Performance was higher among cognitively impaired individuals (sensitivity 85%, specificity 86%) than cognitively unimpaired individuals (sensitivity 76%, specificity 83%). Plasma p-tau217 showed comparable accuracy to CSF p-tau217 in detecting amyloid deposition (SROC AUC 0.91 vs. 0.88), though CSF p-tau217 demonstrated higher sensitivity for tau PET positivity (91% vs. 83%). Substantial heterogeneity was observed across studies (I^2 >50%), which the authors attributed to differences in assay platforms, study populations, and PET radiotracers. The included studies predominantly used clinic-based cohorts with bio-banked specimens. The World Health Organization and the Global CEO initiative have proposed that plasma biomarkers require 90% sensitivity and specificity to have clinical utility as a diagnostic test for AD.[46,] Furthermore, the Alzheimer's Association Workgroup corroborated this requirement with the recommendation that a minimum accuracy of 90% is needed for the intended use population since FDA-approved CSF biomarker tests have achieved this feat with amyloid-PET.

Table 6. Performance Characteristics for Plasma Based Biomarkers

Biomarker	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	AUROC (95% CI)	Diagnostic OR (95% CI)
Therriault et al (2025) [43,]				
p-tau217	88.1% (86.7 to 89.5)	88.7% (87.4 to 89.8)	91.1% (88.9 to 92.4)	50.7 (40.6 to 63.4)
p-tau181	80.5% (78.4 to 82.4)	76.4% (74.1 to 78.6)	81.5% (80.2 to 82.9)	13.4 (11.4 to 16.7)
p-tau205	76.6% (70.7 to 81.6)	86.0% (78.6 to 91.2)	85.1% (80.7 to 89.6)	20.2 (10.5 to 38.7)
p-tau212	84.5% (75.5 to 90.6)	87.3% (79.5 to 92.5)	90.3% (86.6 to 94.1)	41.2 (22.0 to 77.3)
p-tau231	75.2% (71.3 to 78.8)	75.3% (71.2 to 78.9)	80.2% (77.6 to 82.7)	9.3 (7.0 to 12.2)

Cohort Studies

Benina et al (2026) evaluated the diagnostic performance of the Lumipulse G pTau217/Aβ 1-42 plasma ratio and pTau217 alone for detecting amyloid pathology in 208 participants from 3 research cohorts (BioFINDER2, BIOCARD, MissionAD) comprising individuals with subjective cognitive decline, mild cognitive impairment, Alzheimer's disease dementia, and other cognitive conditions (average age 72.3 years; 54.8% amyloid positive by PET and/or CSF). [47,] Using the Fujirebio Lumipulse G1200 automated platform with FDA-cleared PET (standardized uptake value ratio [SUVR] ≥1.13) and/or CSF biomarker ratios as reference standards, the pTau217/Aβ 1-42 ratio achieved an area under the curve (AUC) of 0.932 (95% CI: 0.896 to 0.967) compared to 0.918 (95% CI: 0.880 to 0.956) for pTau217 alone. At the optimal Youden threshold, the ratio achieved 84% sensitivity and 95% specificity compared to 81% sensitivity and 93% specificity for pTau217 alone. Under a 2-threshold approach using positive and negative likelihood ratio (PLR/NLR) targets of 14/20, the ratio achieved a positive predictive value (PPV) of 94.62% (95% CI: 88.0 to 97.7), a positive likelihood ratio of 14.51 (95% CI: 6.93 to 39.80), and reduced indeterminate results to 20.2%, compared to 35.1% for pTau 217 alone after nonparametric reclassification. When evaluated against CSF alone, the ratio's PPV reached 97.8%; against PET alone, PPV was 88.9%. Age, sex, and APOE ε4 status did not significantly affect classification accuracy. These results meet the Global CEO Initiative consensus recommendations for confirmatory-level blood biomarker performance (PPV ≥90%, NPV ≥90%, indeterminate ≤20%) for the ratio but not for pTau217 alone. [46,] Limitations include, but not limited to, moderate sample size, racially unbalanced cohort (94.7% White), use of bio-banked research specimens rather than prospective clinical samples, absence of an independent external validation cohort, manufacturer-led study design, and no assessment of health outcomes or clinical utility.

Martínez-Dubarbie et al (2025) evaluated the diagnostic performance of plasma p-tau217, the p-tau217/Aβ42 ratio, and NfL in a memory clinic cohort of 493 individuals (340 patients and 153 cognitively unimpaired volunteers; mean age 67.6 years; 50.1% female; 100% Caucasian) using the Fujirebio Lumipulse G600II platform with CSF biomarkers as the reference standard (amyloid positivity defined as CSF Aβ42/Aβ40 <0.067). [48,] Clinical diagnoses included AD (n=203), frontotemporal dementia (FTD; n=46), non-degenerative pathology (n=68), and other degenerative dementias (n=11). Plasma p-tau217 achieved an AUC of 0.95 (95% CI: 0.93 to 0.97) to discriminate between amyloid-positive and amyloid-negative individuals, with an optimal Youden cutoff of 0.18 pg/mL (sensitivity 92%, specificity 91%). The plasma p-tau217/Aβ42 ratio achieved a significantly higher AUC of 0.97 (95% CI: 0.95 to 0.98; p<.001) vs. p-tau217 alone with an optimal cutoff of 0.008 (sensitivity 91%, specificity 94%). Using a 2-cutoff approach at 95% sensitivity and specificity, plasma p-tau217 achieved 95% overall accuracy with 15.2% of individuals falling within the indeterminate zone (3.4% false positive, 1.4% false negative) and the p-tau217/Aβ42 ratio achieved 91% accuracy with only 4.7% falling within the indeterminate zone. At 97.5% sensitivity and specificity thresholds, both biomarkers achieved 97% accuracy, though the indeterminate zone expanded to 42.6% for p-tau217 and 27.1% for the ratio. Plasma p-tau217 was significantly higher in AD patients than in healthy controls, FTD, and non-degenerative dementias (all p<.001), and increased progressively along the disease continuum. The p-tau217/Aβ42 ratio was less influenced by glomerular filtration rate than p-tau217 alone. Limitations include a cross-sectional, single-center design; an entirely Caucasian population; use of CSF as the sole reference standard (no amyloid PET); small subgroups for non-AD dementias; and thresholds derived within the study cohort without independent external validation.

Dyer et al (2025) assessed the clinical performance of the fully automated Lumipulse G plasma p-tau217 assay of bio-banked samples from 148 consecutive participants (mean age 69.4 years; 54.1% female; 101 MCI, 47 mild dementia) undergoing diagnostic lumbar puncture at a regional specialist memory clinic in Ireland. [49,] CSF-defined amyloid positivity (Aβ42/Aβ40 ≤0.067) was present in 60.8% of participants. Median plasma p-tau217 was more than 4-fold higher in amyloid-positive versus amyloid-negative individuals (0.64 vs. 0.15 pg/mL; p<.001), with an AUC of 0.92 (95% CI: 0.87 to 0.97) for detection of amyloid status. Using a 2-threshold approach at 90% sensitivity and specificity, 16.9% of participants fell in the indeterminate zone (PPV 91.3%, NPV 83.3%), which is below the 20% threshold recommended by the Global CEO Initiative. [46,] At 95% thresholds, the indeterminate zone

was 30.4% (PPV 94.5%, NPV 87.5%), and at 97.5% thresholds, 42.6% (PPV 94.3%, NPV 93.8%). The authors estimated that 57.4% to 83.1% of diagnostic lumbar punctures could hypothetically have been avoided if plasma p-tau217 had been used as an initial triage test. Limitations include, but are not limited to, the small sample size (n=148), single-center design, bio-banked samples, use of CSF as the sole reference standard without amyloid PET, lack of demographic diversity data, and thresholds derived within the study cohort without external validation.

Cousins et al (2025) evaluated the performance of plasma p-tau217/Aβ42 ratio, p-tau217 alone, and Aβ42/Aβ40 ratio across self-reported racial groups using the Fujirebio Lumipulse G1200 platform with amyloid PET as the reference standard. [50,] Cut points were derived in a racially diverse training set from the University of Pennsylvania (n=289; 28% Black/African American; 62% cognitively normal, 28% MCI, 11% dementia) using a 2-threshold approach at 95% sensitivity and specificity, then validated in an independent test set from the Alzheimer's Disease Neuroimaging Initiative (ADNI; n=846; 12% Black/African American; 55% cognitively normal, 45% MCI). In the training set, plasma p-tau217/Aβ42 had the highest AUC (0.95; 95% CI: 0.91 to 0.97), with consistent performance in Black participants (AUC 0.96) and White participants (AUC 0.94). In the independent ADNI test set, p-tau217/Aβ42 achieved accuracy of 0.88 in Black participants and 0.91 in White participants, with the lowest proportion of intermediate classifications among the 3 biomarkers (≤16%). Classification accuracy did not differ significantly by race (odds ratio [OR]=1.45; 95% CI: 0.66 to 2.95; p=.33). Race-by-amyloid PET severity interactions were not significant for any biomarker in either propensity-matched or unmatched analyses, indicating that the relationship between plasma biomarker levels and amyloid burden was consistent across racial groups. Plasma Aβ42/Aβ40 was significantly higher in Black versus White participants in the UPenn matched sample, though this finding was not replicated in ADNI. False-negative results by p-tau217/Aβ42 were associated with cognitively normal status (OR=7.79; p<.001), female sex, and higher BMI. Higher creatinine was associated with elevated p-tau217, Aβ42, and Aβ40 levels but not with the p-tau217/Aβ42 ratio, suggesting that ratio-based biomarkers may mitigate the influence of renal function on individual analyte levels. Limitations include the relatively small proportion of Black participants in the ADNI test set (12%), preponderance of cognitively normal participants in the Black subgroups, collection from specialized academic centers rather than community settings, and the absence of Hispanic/Latino participants in the analysis.

Wang et al (2025) evaluated the diagnostic performance of the Lumipulse G plasma p-tau217/Aβ42 ratio test using Aβ and tau positron emission tomography (PET) as reference standards in a clinic cohort (n = 391) and a community cohort (n = 121). [51,] For the classification of Aβ PET status the p-tau217/Aβ42 ratio test achieved high diagnostic performance with an area under the curve (AUC) of 0.966 (95% CI: 0.945 to 0.983; p <.05) in the clinical cohort and an AUC of 0.963 (95% CI: 0.924 to 0.992; p <.05) on the community cohort, which was deemed statistically significant with comparable results seen for the classification of tau PET status (clinical cohort: 0.974, 95% CI: 0.952 to 0.992, p>.05; community cohort: 0.947, 95% CI: 0.900 to 0.979, p>.05). The researchers also performed a head-to-head comparison of plasma (p-tau217/Aβ42: AUC of 0.978, 95% CI: 0.952 to 0.996; p>.05) and CSF (CSF Aβ42/40: AUC of 0.964, 95% CI: 0.931 to 0.989) biomarkers based on the Lumipulse platform, which demonstrated that the biomarkers were clinically equivalent. Furthermore, using a 2 cutoff approach the p-tau217/Aβ42 ratio biomarker was assessed on its performance in the differential diagnosis of AD and the p-tau217/Aβ42 ratio had a 92.3% accuracy for distinguishing AD from non-AD individuals, with a positive predictive value (PPV) of 88.8% and negative predictive value (NPV) of 95.5%. Additionally, when applying a 2-cutoff approach the p-tau217/Aβ42 ratio biomarker had improved specificity without impeding sensitivity and reduced the number of intermediate results. Limitations include, but are not limited to, an entirely Chinese population across both cohorts limiting generalizability to diverse populations, reliance on bio-banked samples rather than prospective clinical testing, a relatively young cohort (mean age ~66 years) with underrepresentation of individuals over 80, selection bias in the community cohort toward higher AD risk, differing biomarker levels between cohorts precluding a common cutoff, and absence of independent prospective validation or health outcome assessment.

In October of 2025, the Food and Drug Administration of the U.S. published results from a clinical cohort study that enrolled 312 individuals who presented with cognitive complaints or impairment, subjective or objective, of unknown cause, at 8 geographically diverse intended use enrollment sites across U.S. (n=6) and Europe (n=2) with the goal of assessing the Elecsys Phospho-Tau (181P) Plasma test when compared to amyloid PET scans. [52,] Cognitive Assessments (Quick Dementia Rating System, Mini-Mental State Examination, Clinical Dementia Rating (CDR) Global, CDR–Sum of Boxes), Imaging (amyloid PET, Magnetic Resonance Imaging) and Questionnaires (Medical History, Medication, Quality of Life, Physical Activity, Socio-demographics) were collected from the enrolled individuals. These individuals were categorized into 3 diagnostic groups based on cognitive test results and clinical assessments: 41.0% (128/312) subjective cognitive decline (SCD), 56.1% (175/312) mild cognitive impairment (MCI), and 0.96% (3/312) mild dementia. Forty-one individuals had amyloid PET scan positive results with 38 of those individuals also eliciting a positive result via the Elecsys Phospho-Tau (181P) Plasma test. Additionally, 271 individuals had negative results when using amyloid PET, but only 139 had negative results via the Elecsys Phospho-Tau (181P) Plasma test. The positive percent agreement (PPA), negative percent agreement (NPA), positive predictive value (PPV), and negative predictive value (NPV) were 92.7% (95% CI: 80.6% to 97.5%), 51.3% (95% CI: 45.4% to 57.2%), 22.4% (95% CI: 19.5% to 25.0%), and 97.9% (95% CI: 94.0% to 99.3%), respectively. The results demonstrate that the Elecsys Phospho-Tau (181P) Plasma assay is characterized by high PPA and high NPV and is clinically validated for aiding to rule out amyloid pathology.

In May, 2025 the US FDA published the results of a clinical cohort study that evaluated the performance of the Lumipulse G p-tau217/ß-Amyloid 1-42 Plasma Ratio as an aid in the assessment of individuals presenting with cognitive impairment, AD, and other causes of cognitive decline would test positive or negative for amyloid plaques. [53,] The study comprised of 499 plasma samples from individuals that participated in different cohort studies (Polaris-AD, AR1001-ADP3-US01; BioFINDER 2; Wisconsin Registry for Alzheimer's Prevention; and BioHermes-001). To estimate clinical performance the results were compared to 2 adjudicated reference standards, amyloid PET using an FDA-approved tracer or with an FDA authorized amyloid CSF Ratio test, and were described by PET-positive predictive value (indicated as Predictive Value, PV) and frequency of positive test results of the tested samples (indicated as Frequency of Results, FR) for positive, indeterminate, and negative test results. The results for the Lumipulse G tests were as follows, 91.8 % had a positive result, 50.0% had an indeterminate result, and 2.7% had a negative result, which were consistent with both amyloid PET scans and CSF ratio tests, deeming the test as clinically equivalent to the reference standards.

Schindler et al (2024) reported results from a head-to-head comparison of 6 leading commercial plasma biomarker assay panels conducted by the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium using samples from 392 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants (median age 78.1 years; 49.2% female; 93.4% White; 48.7% amyloid PET positive; 49.0% cognitively impaired). [54,] The assays evaluated included 4 p-tau217 assays (C2N PrecivityAD2, Fujirebio Lumipulse, ALZpath Quanterix, Janssen LucentAD Quanterix), 2 p-tau181 assays (Roche NeuroToolKit, Quanterix Neurology 4-Plex), 4 Aβ42/Aβ40 assays, and assays for GFAP and NfL (see Table 7). Using amyloid PET (>20 Centiloids) as the reference standard, plasma p-tau217 measures had the highest classification accuracies for amyloid status across all platforms. In the full cohort, the unadjusted AUCs ranged from 0.882 to 0.929 for individual p-tau217 assays, compared to 0.734 to 0.815 for p-tau181 assays and 0.734 to 0.787 for Aβ42/Aβ40 assays. In the cognitively impaired sub-cohort (n=192), classification accuracies were higher: C2N %p-tau217 combined with Aβ42/Aβ40 achieved an AUC of 0.958 (95% CI: 0.932 to 0.985) and Fujirebio Lumipulse p-tau217 with Aβ42/Aβ40 had an AUC of 0.952 (95% CI:0.925 to 0.980). Plasma p-tau217 also had the highest classification accuracies and correlations with tau PET status, cortical thickness, and dementia severity. Plasma Aβ42/Aβ40 had much lower classification accuracy due to the small magnitude of change (~10 to 13%) associated with amyloid pathology. In a sub-cohort with CSF data (n=122), plasma biomarker classification accuracies were not significantly different from CSF Elecsys p-tau181/Aβ42 (AUC 0.915, 95% CI: 0.864 to 0.967), though the comparison was underpowered. Limitations include, but are not

limited to, very low racial diversity (3.6% Black), use of a single research cohort (ADNI), absence of health outcome data, thresholds derived via Youden Index within the study cohort rather than pre-specified externally, and limited power for sub-cohort analyses.

Table 7. Test Performance Characteristics for Plasma Biomarkers for Amyloid PET Status

Assay	Analyte	Final N	AUC (95% CI)	Cutoff	PPA	NPA	Accuracy	PPV	NPV
C2N PrecivityAD2	%p-tau217	392	0.927 (0.900 to 0.955)	4.06 (%)	0.885	0.871	0.878	0.867	0.888
	p-tau217	392	0.916 (0.887 to 0.946)	2.34 (pg/mL)	0.864	0.871	0.867	0.864	0.871
	Aβ42/Aβ40	392	0.751 (0.703 to 0.799)	0.0924	0.717	0.672	0.694	0.675	0.714
Fujirebio Lumipulse	p-tau217	392	0.896 (0.864 to 0.928)	0.158 (pg/mL)	0.843	0.821	0.832	0.817	0.846
	Aβ42/Aβ40	392	0.787 (0.741 to 0.833)	0.0869	0.723	0.751	0.737	0.734	0.740
ALZpath Quanterix	p-tau217	392	0.885 (0.851 to 0.920)	0.444 (pg/mL)	0.843	0.831	0.837	0.826	0.848
Janssen LucentAD Quanterix	p-tau217	392	0.882 (0.848 to 0.916)	0.0615 (pg/mL)	0.806	0.831	0.819	0.819	0.819
Roche NeuroToolKit	p-tau181	392	0.815 (0.772 to 0.858)	1.14 (pg/mL)	0.775	0.746	0.760	0.744	0.777
	Aβ42/Aβ40	392	0.775 (0.728 to 0.823)	0.126	0.864	0.627	0.742	0.688	0.829
	GFAP	392	0.758 (0.710 to 0.806)	0.113 (ng/mL)	0.728	0.682	0.704	0.685	0.725
	NfL	392	0.677 (0.624 to 0.729)	4.29 (pg/mL)	0.592	0.682	0.638	0.638	0.637
Quanterix Neurology 4-Plex	GFAP	342	0.756 (0.704 to 0.807)	205 (pg/mL)	0.597	0.814	0.713	0.736	0.700
	p-tau181	342	0.747 (0.694 to 0.799)	20.5 (pg/mL)	0.717	0.694	0.705	0.671	0.738
	Aβ42/Aβ40	342	0.734 (0.681 to 0.787)	0.0582	0.730	0.689	0.708	0.671	0.746
	NfL	342	0.670 (0.613 to 0.727)	21.7 (pg/mL)	0.686	0.574	0.626	0.583	0.677

Adapted from Schindler et al. (2024) [54,]
AUC: area under the receiver operating characteristic curve; CI: confidence interval; GFAP: glial fibrillary acidic protein; NfL: neurofilament light; NPA: negative percent agreement; NPV: negative predictive value; PET: positron emission tomography; PPA: positive percent agreement; PPV: positive predictive value.
[a]The single cutoff for each plasma biomarker that best distinguishes amyloid PET status based on the Youden Index is shown. The full cohort has a 48.7% rate of amyloid PET positivity based on a cutoff of >20 Centiloids. All individuals (n=392) had measures for C2N PrecivityAD2, Fujirebio Lumipulse, ALZpath Quanterix, Janssen LucentAD Quanterix, and Roche NeuroToolKit assays. A sub-cohort (n=342) additionally had measures for Quanterix Neurology 4-Plex assays.

Palmqvist et al (2024) reported results from a primary (n=515) and secondary (n=698) care cohort in Sweden evaluating the performance characteristics of biomarker plasma tests compared to standard clinical diagnosis without biomarker testing.[55,] The blood tests assessed included the ratio of p-tau217 to non-p-tau217 (%p-tau217) and the amyloid probability score 2 (APS2), based on the %p-tau217 and Aβ42/40 ratio. Thresholds were prespecified based on independent cohorts, including the PARIS and MissionAD cohorts, used to validate the PrecivityAD2™ blood test algorithm. Reference pathological diagnosis was based on CSF analysis of Aβ42 and Aβ40 via the Lumipulse assay. In individuals who could not undergo lumbar puncture, pathological diagnosis was based on flutemetamol 18F PET imaging. In the primary care cohort, the accuracy (%), PPV (%), and NPV (%) was 58.0, 56.8, and 58.8 for clinical diagnosis, 91.8, 92.8 and 91.1 for %p-tau217, and 93.5, 94.4, and

92.8 for APS2, respectively. In the secondary care cohort, outcomes were 71.4, 65.6, and 80.7 for clinical diagnosis by a dementia specialist, 94.3, 95.4, and 93.3 for %p-tau217, and 94.6, 97.8, and 92.2 for APS2, respectively. The investigator concluded that future studies should evaluate how these biomarker blood tests influence clinical care.

In a subsequent report, Palmqvist and coworkers (2025) evaluated the performance of the Lumipulse plasma p-tau217 immunoassay in 1219 individuals in secondary care and 548 in primary care across several sites in Sweden, Spain, and Italy.[56,] The overall accuracy (%, 95% CI), PPV (%, 95% CI), and NPV (%, 95% CI) of the assay as applied to the primary care cohort was 92 (89-94), 90 (86-94), and 92 (89-96), respectively. Accuracies did not significantly differ across groups with subjective cognitive decline (SCD), mild cognitive impairment (MCI), and dementia. As expected, the NPV was higher in the SCD group whereas the PPV was higher in the dementia group. Notably, the performance of the assay was significantly decreased with age, as higher p-tau217 concentration have been observed in older participants without AD pathology.

Clinically Useful

There is currently no direct evidence to support the clinical utility of plasma markers for diagnosing AD and the chain of evidence is incomplete.

Section Summary: Plasma Biomarker Testing

Results from 2 systematic reviews and various cohort studies have shown that plasma p-tau, particularly p-tau217, may be beneficial for the early screening and differential diagnosis of AD In a head-to-head comparison of 6 commercial platforms, p-tau217 measures had the highest classification accuracies for amyloid status across all platforms. Limited evidence from one study suggests comparable ratio biomarker performance in Black/African American and White participants, though the evidence base overall is predominantly derived from White cohorts and further validation in diverse populations is needed. Currently, there is no evidence that improved diagnosis with plasma biomarker testing leads to improved health outcomes or QOL.

Cerebrospinal Fluid and Plasma Biomarkers for Selecting Targeted Therapy for Mild Cognitive Impairment or Mild Dementia due to Alzheimer Disease

Clinical Context and Test Purpose

The purpose of CSF and plasma biomarkers or PET amyloid scans for individuals with MCI or mild dementia due to AD is to select appropriate individuals for initiation or discontinuation of treatment with an amyloid beta plaque targeting therapy (eg, lecanemab and donanemab).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with a clinical diagnosis of MCI or mild dementia due to AD, who are being evaluated for an FDA approved amyloid beta plaque targeting therapy or are being evaluated for continuing or discontinuing such therapy.

The NIA-AA has provided guidance on the clinical diagnosis of MCI and dementia due to AD (Table 1).[57,58,24,] This includes utilizing a battery of cognitive tests versus a single test to identify individuals with MCI due to AD (stage 3) or mild dementia due to AD (stage 4). The tests should evaluate multiple domains such as cognition and function and specific tests may vary.

In the pivotal trials for the amyloid beta plaque targeting therapy aducanumab, enrolled individuals had an early stage of AD; MCI due to AD; or mild AD dementia based on an entry criteria of baseline Mini-Mental State Examination (MMSE) score of 24 to 30, baseline Clinical Dementia Rating (CDR) global score of 0.5 and Repeatable Battery for the Assessment of Neurological Status (RBANS)

delayed memory index score ≤85.[59,60,] individuals were also clinically staged based on the National Institute on Aging-Alzheimer's criteria.

In the pivotal trial for lecanemab approval, participants met criteria for either MCI due to AD or mild AD dementia by NIA-AA criteria and were required to have evidence of brain Aβ pathology by either visual read of a PET scan or CSF assessment of t-tau/Aβ1-42.[61,] Participants had a baseline MMSE score of 22 to 30, CDR global score of 0.5 or 1.0 with a Memory Box score of 0.5 or greater, and objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII).

Interventions
The test being considered is CSF biomarkers, from CSF samples collected via lumbar puncture, such as amyloid beta-42/40 ratio or the ratio of total tau (t-tau) to amyloid beta-42.

The amyloid beta-42/40 ratio test quantifies the amount of amyloid beta-42 and 40 proteins in a CSF sample and computes the ratio of those proteins. Lower ratios indicate a higher likelihood of a individual having a clinical diagnosis of AD..[62,].[63,]The t-tau/amyloid beta-42 ratio quantifies the ratio of total tau to amyloid beta-42. Higher values indicate a higher likelihood of AD. See Table 2 for cutoff values for FDA cleared tests.

The test being considered is plasma biomarkers, from blood samples, such as the ratio of phosphorylated tau (p-tau), specifically p-tau217 to amyloid beta-42. The p-tau217/amyloid beta-42 ratio quantifies the ratio of total p-tau217 to amyloid beta-42. Higher values indicate a higher likelihood of AD. See Table 2 for cutoff values for FDA cleared tests.

Comparators
Comparators of interest include the amyloid beta PET scan. Amyloid beta PET imaging is a neuroimaging technique with standardized tracer-specific visual reading procedures and documented high reproducibility across PET centers.[64,] It allows non-invasive, in-vivo detection of amyloid plaques with very high sensitivity (96%; 95% CI, 80 to 100) and specificity (100%, 95% CI, 78 to 100) as determined by correlation in individuals with confirmed AD who had an autopsy within 1 year of PET imaging. Trials of amyloid beta targeting therapy have traditionally used clinical criteria along with amyloid beta PET imaging to select appropriate individuals for participation. While amyloid PET has very high sensitivity (96%) and specificity (100%) against autopsy-confirmed pathology, it is not a perfect reference standard; the definitive reference standard for AD is neuropathological examination. [65,] Studies have documented 10–17% discordance between amyloid PET visual read interpretation and quantitative Centiloid assessment [66,], and CSF biomarkers have been shown to detect cerebral amyloid-β accumulation before PET reaches pathological thresholds.[67,] Concordance metrics between plasma or CSF biomarkers and amyloid PET should therefore be understood as measures of agreement with a highly accurate but imperfect reference, rather than as true sensitivity and specificity against the underlying condition. Some apparent false positive plasma results when compared to PET may represent genuine early-stage amyloid pathology below the detection threshold of PET imaging but further studies are needed to confirm early-stage pathology detection using these biomarker.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. Specific measures of cognitive and functional health outcomes that may be relevant to early AD include the Clinical Dementia Rating-Sum of Boxes (CDR-SOB), MMSE, Alzheimer's Disease Assessment Scale - Cognitive 13-Item Scale (ADAS-Cog 13), Alzheimer's Disease Cooperative Study - Activities of Daily Living - Mild Cognitive Impairment (ADCS-ADL-MCI), and the Neuropsychiatric Inventory-10 (NPI-10).

Follow-up is at months to years for CSF biomarkers or PET amyloid scans for the outcomes of interest.

For individuals, with mild cognitive impairment or mild dementia due to Alzheimer disease, who are being considered for an approved amyloid beta plaque targeting therapy, the consequences of misclassification are clinically significant. A false positive result (incorrectly confirming amyloid pathology) would lead to initiation of therapy in an individual who would not benefit and who would be exposed to the risks of treatment, including amyloid-related imaging abnormalities (ARIA), which occurred in approximately 21% of lecanemab-treated patients during Clarity AD clinical trial [61,] and 24% of donanemab-treated patients in TRAILBLAZER-ALZ 2 clinical trial. A false negative result (incorrectly excluding amyloid pathology) would result in withholding disease-modifying therapy from an individual who could benefit from the approximately 25–30% slowing of cognitive decline demonstrated in the pivotal trials. The magnitude of these consequences underscores the importance of establishing test performance under the conditions of intended clinical use prior to adoption for therapy selection.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- The study population represents the population of interest. Eligibility and selection are described;
- The test is compared with a credible reference standard;
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test;
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative;
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Cerebrospinal Fluid Biomarker Testing

Overall, both PET imaging and CSF biomarkers provide overlapping, and in part complementary, diagnostic information with agreement between CSF and PET amyloid results usually good.[64,] There are various studies that evaluate concordance between CSF biomarkers and PET imaging.

The diagnostic accuracy of CSF biomarkers and amyloid beta PET for diagnosing early-stage AD were compared using data from the prospective, longitudinal Swedish BioFINDER study that consecutively enrolled individuals without dementia with mild cognitive symptoms.[68,] This was the first study to compare the accuracy of regional amyloid beta PET (using the [^{18}F]-flutemetamol) and different CSF assays or ratios of CSF biomarkers, including amyloid beta-42/40, for this diagnostic purpose. The study included 34 individuals with MCI who developed AD dementia within 3 years and 122 healthy elderly controls. Overall, the best CSF measures for the identification of MCI-AD were amyloid-beta 42/total tau (t-tau) and amyloid beta-42/hyperphosphorylated tau (p-tau), with an area under the curve (AUC) of 0.93 to 0.94. The best PET measures (i.e., anterior cingulate, posterior cingulate/percuneus, and global neocortical uptake) performed similarly (AUC 0.92 to 0.93). The AUC for CSF amyloid beta-42/40 was numerically poorer as compared to the majority of PET variables; however, the differences were nonsiginficant (p=.09 to.40). The combination of CSF and PET was not better than using either biomarker separately. The results were replicated in 146 controls and 64 individuals with MCI-AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study that utilized another CSF assay (amyloid beta-42, t-tau and p-tau) and PET (^{18}F-florbetapir) tracer. In the

ADNI cohort, amyloid-beta 42/t-tau and amyloid beta-42/p-tau ratios similarly had higher AUCs than amyloid beta-42 alone.

Lewczuk et al (2017) evaluated whether amyloid beta-42 alone or the amyloid beta-42/40 ratio corresponded better with amyloid beta PET status.[69,] The investigators collected CSF from a mixed cohort (N=200) of cognitively normal and abnormal subjects who had undergone amyloid beta PET within 12 months. Of these, 150 were PET-negative and 50 were PET-positive according to a previously published cutoff. The collected CSF was assayed for amyloid beta-42 alone and the amyloid beta-42/40 ratio. Results revealed that the amyloid beta-42/40 ratio corresponded better than amyloid beta-42 alone with PET results, with a higher proportion of concordant cases (89.4% vs. 74.9%; p<.0001) and a larger AUC (0.936 vs. 0.814; p<.0001) associated with the ratio.

Nisenbaum et al (2022) compared CSF biomarkers to amyloid PET in the EMERGE and ENGAGE phase 3 randomized controlled trials (RCTs) of anti-amyloid therapy, aducanumab.[21,] EMERGE and ENGAGE participants had MCI due to AD or mild AD with confirmed amyloid-beta pathology by amyloid PET scan. A population of 350 participants who were screened for the RCTs (EMERGE; n=208; ENGAGE; n=142) were included in a CSF substudy. Amyloid PET imaging was performed using any of the FDA-approved amyloid PET tracers. Expert central readers classified the amyloid PET scans as positive or negative. CSF samples were tested for p-tau, t-tau, amyloid beta-42 and amyloid beta-40 via the Lumipulse system. The mean age for participants in the substudy was 70 years (SD=7). 46% of the participants were female, 93% of participants were White, 1% were Black and 1% were Asian, 37% of participants were ApoE ε4 noncarriers, 47% were heterozygous and 17% were homozygous. The AUC (95% CI) for the amyloid beta-42/40 ratio was 0.90 (0.83 to 0.97; p<.001) with Positive Percent Agreement of 94% (91 to 97) and Negative Percent Agreement of 88% (74 to 96). The AUC of t-tau/amyloid beta-42 ratio was 0.92 (0.86 to 0.97; p<.001) with Positive Percent Agreement of 92% (89 to 95) and Negative Percent Agreement of 82% (66 to 92).

Plasma Biomarker Testing

Doecke et al (2025) assessed the ability of p-tau217 and Aβ42/40 from the Lumipulse G p-tau217 and β-amyloid ratio (1-42/1-40) tests, individually and combined, to predict Aβ positron emission tomography status in 2 sub-cohorts from the Australian Imaging, Biomarkers, and Lifestyle Study of Ageing (AIBL). [70,] The AD continuum cohort (ADCC) was selected specifically to assess plasma biomarker levels across the AD continuum, including AIBL participants who were cognitively unimpaired and Aβ−, cognitively unimpaired and Aβ+, mild cognitive impairment and Aβ+, and AD Aβ+. The second cohort was designed to fit an "intention-to-treat cohort" (ITTC), thus matching the pre-requisites for disease modifying therapy with either donanemab or lecanemab. The AUC, sensitivity, specificity, and accuracy for the p-tau217/Aβ42 ratio reached 0.961, 93%, 92%, and 93%, respectively when used in the ADCC. Validation in the ITTC demonstrated a similar AUC (0.959), with increased sensitivity (99%), decreased specificity (87%), and increased accuracy (95%).

As described in the plasma biomarker testing section, the Lumipulse plasma pTau217/Aβ42 ratio achieved an AUC of 0.978 compared with 0.964 for the Lumipulse CSF Aβ42/40 ratio in a general diagnostic cohort, with no statistically significant difference between modalities (Wang et al 2025). [51,]. This comparison was conducted under research biobank specimen handling conditions; whether this concordance is maintained under routine clinical laboratory conditions has not been evaluated.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The clinical use of CSF and plasma biomarkers reviewed in this section is to select individuals who can begin anti-amyloid targeted medications at an early stage of AD.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Treatment Initiation

CSF biomarkers have demonstrated usefulness for identifying individuals who will benefit from anti-amyloid therapy. CSF biomarkers have been used as an alternative to amyloid PET for the purposes of establishing eligibility in terms of amyloid beta pathology in trials that have established the efficacy of anti-amyloid therapies. In brief, lecanemab has been evaluated in 2 double-blind RCTs (Study 201 and Study 301/Clarity AD) with samples sizes of 390 and 1795, respectively. The trials included individuals with MCI due to AD or mild AD dementia with confirmed amyloid beta pathology. In Clarity AD, the protocol states that amyloid beta pathology was confirmed by either 1) positive amyloid load confirmed by amyloid PET assessment, or 2) CSF assessment of t-tau / Aβ[1-42]. Both trials reported an approximately 27% statistically significantly slower rate of decline for the primary cognitive and functional outcome (ADCOMS for Study 201; CDR-SB for Study 301) for lecanemab versus placebo.[71,61,] Lecanemab received traditional FDA approval based on results of these RCTs and the label for lecanemab states that the presence of amyloid beta pathology should be confirmed prior to initiating treatment.[72,]

Treatment Continuation

There are no data on the serial use of these tests to determine if there are changes in biomarker results that correlate with clinical cognitive and functional status and/or amyloid beta imaging to inform continuation of amyloid beta plaque targeting therapy.

Section Summary: Cerebrospinal Fluid and Plasma Biomarkers and Targeted Therapy for Mild Cognitive Impairment or Mild Dementia due to Alzheimer Disease

The evidence supporting a correlation between CSF biomarkers, including amyloid beta-42/40 and t-tau/amyloid beta-42, and PET amyloid scans indicates that the diagnostic accuracy of CSF and amyloid PET biomarkers to identify MCI-AD was similar and that the amyloid beta-42/40 ratio and total tau to amyloid beta-42 ratio corresponded better with PET results compared to single CSF biomarker, alone such as amyloid beta-42. CSF biomarkers have been used as an alternative to PET amyloid scans to establish eligibility regarding the presence of amyloid beta pathology in RCTs that showed the efficacy of anti-amyloid therapies, which in turn demonstrates that the CSF biomarkers can identify individuals who would benefit from therapy. Plasma biomarkers have established clinical equivalency to amyloid PET and CSF biomarkers in their ability to characterize amyloid beta pathology, however this equivalency was only established under research conditions using bio-banked samples. The plasma-based assay, Lumipulse p-tau217/Aβ42 ratio, is a top-performing assay with FDA clearance for classifying amyloid PET status, with an average AUC of ≥90%. However, the FDA-cleared Lumipulse plasma ratio test is subject to an active Class 2 recall for falsely elevated ratio results and is currently being investigated. Limited evidence has been generated to corroborate that plasma-based test can maintain sufficient performance characteristics for selecting treatment with anti-amyloid therapy. As plasma tests would be used in lieu of CSF biomarker tests and/or amyloid PET scans, a chain of evidence cannot be constructed to demonstrate clinical utility, and prospective studies are needed to establish non-inferiority within a clinical or real-world setting to determine if individuals would benefit from therapy. The FDA-approved labels for lecanemab and donanemab state that the presence of amyloid beta pathology should be confirmed prior to initiating treatment.

Supplemental Information

Clinical Input From Physician Specialty Societies And Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers,

input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2024 Input

Clinical input was sought to help determine whether the use of cerebrospinal fluid biomarker testing for individuals who are being considered for an approved amyloid beta plaque targeting therapy would provide a clinically meaningful improvement in net health outcome. In response to requests, clinical input was received from 3 respondents; 1 physician-level response identified through a specialty society; 2 physician-level responses (joint response) identified through an academic medical center.

For individuals who have early AD who receive lecanemab, clinical input supports this use provides a clinically meaningful improvement in net health outcome with the criteria described.

Further details from clinical input are included in the Appendix.

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Alzheimer's Association

In 2009, the Alzheimer's Association initiated a quality control program for CSF markers, noting that "Measurements of CSF AD biomarkers show large between laboratory variability, likely caused by factors related to analytical procedures and the analytical kits. Standardization of laboratory procedures and efforts by kit vendors to increase kit performance might lower variability, and will likely increase the usefulness of CSF AD biomarkers."[26,] In 2012, the Alzheimer's Biomarkers Standardization Initiative published consensus recommendations for standardization of preanalytical aspects (eg, fasting, tube types, centrifugation, storage time, temperature) of CSF biomarker testing.[73,]

In 2013, the Alzheimer's Association published recommendations for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in primary care settings.[74,] The recommended algorithm for cognitive assessment was based on "current validated tools and commonly used rule-out assessments." Guidelines noted that the use of biomarkers (eg, CSF tau and β-amyloid proteins) "was not considered as these measures are not currently approved or widely available for clinical use."

In 2018, the Alzheimer's Association published appropriate use criteria for lumbar puncture and CSF testing for AD.[75,] Table 8 summarizes the indications for these practices. In 2021, the Alzheimer's Association also published international guidelines for the appropriate handling of CSF for routine clinical measurements of amyloid beta and tau.[76,]

Table 8. Indications for Appropriate Use of Lumbar Puncture and CSF Testing in Diagnosing AD

Appropriate Indications
individuals with SCD who are considered at increased risk for AD
MCI that is persistent, progressing, and unexplained
individuals with symptoms that suggest possible AD
MCI or dementia with an onset at an early age (<65 y)

Appropriate Indications
Meeting core clinical criteria for probable AD with typical age of onset
individuals whose dominant symptom is a change in behavior and where AD diagnosis is being considered
Inappropriate Indications
Cognitively unimpaired and within normal range functioning for age as established by objective testing; no conditions suggesting high risk and no SCD or expressed concern about developing AD
Cognitively unimpaired individual based on objective testing, but considered by individual, family informant, and/or clinician to be at risk for AD based on family history
individuals with SCD who are not considered to be at increased risk for AD
Use to determine disease severity in individuals having already received a diagnosis of AD
Individuals who are apolipoprotein E (APOE) ε4 carriers with no cognitive impairment
Use of lumbar puncture in lieu of genotyping for suspected ADAD mutation carriers
ADAD mutation carriers, with or without symptoms

AD: Alzheimer disease; ADAD: autosomal-dominant Alzheimer disease; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; SCD: subjective cognitive decline.

In 2022, the Alzheimer's Association Global Workgroup released appropriate use recommendations for blood biomarkers in AD.[77,] The Workgroup recommended "use of blood-based markers as (pre-)screeners to identify individuals likely to have AD pathological changes for inclusion in trials evaluating disease-modifying therapies, provided the AD status is confirmed with PET or CSF testing." The Workgroup also encouraged "studying longitudinal blood-based marker changes in ongoing as well as future interventional trials" but cautioned that these markers "should not yet be used as primary endpoints in pivotal trials." Further, the Workgroup also recommended cautiously starting to use blood-based biomarkers "in specialized memory clinics as part of the diagnostic work-up of individuals with cognitive symptoms" with the results confirmed with CSF or PET whenever possible. Additional data are needed before the use of blood-based biomarkers as stand-alone diagnostic AD markers, or before considering use in primary care.

In 2025, the Alzheimer's Association published an evidence-based clinical practice guideline for the diagnostic evaluation, testing, counseling, and disclosure of suspected AD and related dementias (DETeCD-ADRD), with executive summaries for primary care and specialty care settings. [78,79,] The guideline recommends a multi-tiered approach to diagnostic testing, with 19 recommendations developed through a modified-Delphi process and systematic review of 7374 publications (133 met inclusion criteria). The guideline recommends that "laboratory tests in the evaluation of cognitive or behavioral symptoms should be multi-tiered and individualized to the patient's medical risks and profile" and that "clinicians should obtain routine Tier 1 laboratory studies in all patients" (Recommendation 8, Strength A). The guideline recommends that "the clinician should obtain structural brain imaging to aid in establishing the cause(s)" (Recommendation 9, Strength A). For molecular biomarkers, the guideline recommends that "a dementia specialist can obtain CSF according to appropriate use criteria (see Shaw et al. 2018 [75,]) for analysis of amyloid beta (Aβ)42 and tau/phosphorylated tau (p-tau) profiles to evaluate for AD neuropathologic changes" (Recommendation 17, Strength B). The guideline recommends that "if diagnostic uncertainty still exists after obtaining structural imaging with or without FDG PET and/or CSF Aβ42 and tau/p-tau, the dementia specialist can obtain an amyloid PET scan according to the appropriate use criteria (see Rabinovici et al 2025 [9,]) to evaluate for cerebral amyloid pathology" (Recommendation 18, Strength B). Plasma biomarkers including phosphorylated tau, neurofilament light chain, and glial fibrillary acidic protein are categorized as Tier X (clinically emerging), with the guideline noting that these tests are "emerging as commercial tests but at the time of this writing have not been validated in most clinical practice settings and diverse populations; reimbursement is not yet available." The guideline also notes that "molecular biomarker confirmation is necessary for consideration of new disease-modifying therapies that target amyloid plaques."

In 2024, the Alzheimer's Association Workgroup published revised criteria for diagnosis and staging of Alzheimer's disease [80,]. Table 9 summarizes relevant biomarkers and their intended use for diagnosing, staging, and identifying co-pathology in AD. The biomarkers are grouped into three

broad categories: biomarkers of AD neuropathologic change (ADNPC), non-specific biomarkers that are important in AD pathogenesis but are also involved in other brain diseases, and biomarkers of common non-AD co-pathologies. Within each of these three broad categories, each biomarker was subcategorized by the specific proteinopathy pathway or pathogenic process that each measures: "A" biomarkers denote the amyloid beta (Aβ) proteinopathy pathway, "T_1" are early changing phosphorylated mid-region tau fragments (p-tau 217, 181, and 231), "T_2" are later-changing biofluid tau fragments (e.g., microtubule-binding region [MTBR]-tau243) along with tau PET, "N" neurodegeneration/neuronal injury, "I" inflammatory/immune mechanisms, "V" vascular brain injury, and "S" alpha-synucleinopathy. Furthermore, they propose "that the following [biomarkers] can be diagnostic of AD: amyloid PET; CSF Aβ 42/40, CSF p-tau 181/Aβ 42, CSF t-tau/Aβ 42; or "accurate" plasma assays where "accurate" can be defined as accuracy that is equivalent to approved CSF assays in detecting abnormal amyloid PET in the intended-use population".

Table 9. Intended Uses for Imaging and Biomarkers for Diagnosing, Staging, and Identifying Co-pathology in Alzheimer's Disease

Intended Use	CSF	Plasma	Imaging
Diagnosis			
A: (Aβ proteinopathy)	—	—	Amyloid PET
T1: (phosphorylated and secreted AD tau)	—	p-tau217	—
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	%p-tau217	—
Staging, prognosis, as an indicator of biological treatment effect			
A: (Aβ proteinopathy)	—	—	Amyloid PET
T1: (phosphorylated and secreted AD tau)	—	p-tau217	—
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	%p-tau217	—
T2: (AD tau proteinopathy)	MTBR-tau243, other p-tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments	MTBR-tau243, other p-tau forms (e.g., p-tau205)	Tau PET
N (injury, dysfunction, or degeneration of neuropil)	NfL	NfL	Anatomic MRI & FDG PET
I (inflammation) astrocytic activation	GFAP	GFAP	—
Identification of co-pathology			
N (injury, dysfunction, or degeneration of neuropil)	NfL	NfL	Anatomic MRI or FDG PET
V vascular brain injury	—	—	Infarction on MRI or CT or WMH
S α-synuclein	αSyn-SAA	—	—

Adapted from Jack et al (2024): [80,]
The focus in this table is on plasma p-tau217 and not p-tau231, p-tau181, or Aβ42/40 because p-tau217 typically outperforms these other plasma assays in head-to-head comparisons. %p-tau is the ratio p-tau217/non-phosphorylated-tau217. Combinations of biomarkers may also be used for diagnosis. P-tau205, MTBR-tau243, and non-phosphorylated tau fragments have not undergone the same level of validation testing as has tau PET.

Aβ: amyloid beta; AD: Alzheimer's disease; αSyn-SAA: alpha-synuclein seed amplification assay; CSF: cerebrospinal fluid; CT: computed tomography; FDG: fluorodeoxyglucose; GFAP: glial fibrillary acidic protein; MRI: magnetic resonance imaging; MTBR: microtubule-binding region; NfL: neurofilament light chain; PET: positron emission tomography; p-tau: phosphorylated tau; WMH: white matter hyperintensity.

In 2025, the Alzheimer's Association published a clinical practice guideline on the use of blood-based biomarkers (BBMs) in the diagnostic workup of suspected Alzheimer's disease within specialized care settings, developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and informed by a systematic review of 49 observational studies evaluating 31 BBM tests. [81,] The panel issued two conditional recommendations (low certainty evidence): (1) BBM tests with at least 90% sensitivity and 75% specificity may be used as a triaging test in which a negative result rules out AD pathology with high probability and a positive result is followed by confirmatory CSF or amyloid PET testing; and (2) BBM tests with at least 90% sensitivity and 90% specificity may serve as a substitute for amyloid PET or CSF AD biomarker testing. The guideline further states that BBM tests should not be obtained before a comprehensive clinical evaluation and that results should always be interpreted within the clinical context, with careful consideration of pretest probability.

National Institute of Aging
2011 Revised Diagnostic Criteria
In 2011, probable Alzheimer disease (AD) was defined by the National Institute on Aging and the Alzheimer's Association workgroup using the following diagnostic criteria:[24,]

"Meets criteria for dementia…and in addition has the following characteristics:

2. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
3. Clear-cut history of worsening of cognition by report or observation; and
4. The initial and most prominent cognitive deficits are evident on history and examination in 1 of the following categories.
    1. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least 1 other cognitive domain, as defined earlier in the text.
    2. Nonamnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem-solving. Deficits in other cognitive domains should be present.
5. The diagnosis of probable AD dementia should not be applied when there is evidence of:
    1. Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
    2. Core features of dementia with Lewy bodies other than dementia itself; or
    3. Prominent features of behavioral variant frontotemporal dementia; or
    4. Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or
    5. Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition."

The diagnosis for possible AD dementia should meet the following criteria:

1. Core criteria for the nature of cognitive deficits for AD dementia but is marked by sudden onset of cognitive impairment or insufficient history or documentation describing progressive decline; or
2. All core clinical criteria for AD dementia but presents with concomitant cerebrovascular disease, features of dementia with Lewy bodies, or evidence of another neurological disease or any condition that could affect cognition.

Additionally, a category "Probable AD dementia with evidence of the AD pathophysiological process" has been added. Evidence of the AD pathophysiologic process is supported by detection of low cerebrospinal fluid (CSF) amyloid beta peptide 1-42 (Aβ42), positive positron emission tomography amyloid imaging, or elevated CSF tau, and decreased fluorine 18 fluorodeoxyglucose uptake on positron emission tomography in the temporoparietal cortex with accompanying atrophy by magnetic resonance imaging in relevant structures. Detection of the "pathophysiological process" is further divided by when in the disease natural history markers are expected to be detectable. Biomarker evidence in cases of probable AD may increase the certainty that the dementia is due to AD pathophysiological process.

Note on the 2011 Revised Criteria and Biomarkers
Some of the biomarkers considered in this evidence review are in a category among the 2011 revisions to AD diagnostic criteria, "probable AD dementia with evidence of the AD pathophysiological process."[24,] However, the diagnostic criteria workgroup noted the following:

"[We] do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. There are several reasons for this limitation: 1) the core clinical criteria provide very good diagnostic accuracy and utility in most individuals; 2) more research needs to be done to ensure that criteria that include the use of biomarkers have been appropriately designed, 3) there is limited standardization of biomarkers from 1 locale to another, and 4) access to biomarkers is limited to varying degrees in community settings. Presently, the use of biomarkers to enhance certainty of AD pathophysiological process may be useful in 3 circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician."[24,]

National Institute for Health and Care Excellence
In 2018, the National Institute for Health and Care Excellence (NICE) released a guideline on assessment, management, and support for people living with dementia and their caregivers.[82,] The guideline states that in cases of uncertain diagnosis, but highly suspicious for AD, providers can consider examining CSF for total tau or total tau and phosphorylated-tau 181 and either beta amyloid 42 or beta amyloid 42 and beta amyloid 40. People who are older are more likely to receive a false positive with a CSF analysis.

U.S. Preventive Services Task Force Recommendations
In 2020, the U.S. Preventive Services Task Force released recommendations for screening cognitive impairment in older adults, concluding that the current evidence is insufficient to determine benefits versus harms of screening for cognitive impairment in older adults.[83,] The statement discusses that screening tests are not intended to diagnose MCI or dementia, but a positive screening test result should prompt additional testing consisting of blood tests, radiology examinations, and/or medical and neuropsychologic evaluation.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT05379348	Davos Alzheimer's Collaborative Study: Sequential Administration of Digital Testing To Screen For Cognitive Impairment Followed By Blood Based Biomarkers To Assist With Timely Detection And Accurate Diagnosis Of Alzheimer's Disease (DAC)	1423	Dec 2025
NCT05020106	Study on the Diagnostic Cut-off Value for Core Biomarkers in Cerebrospinal Fluid and Blood of Alzheimer's Disease	3200	Sep 2025 (recruiting)
NCT04575337	Study on Body Fluid, Gene and Neuroimaging Biomarkers for Early Diagnosis of Alzheimer's Disease	6000	Jun 2025 (recruiting)
NCT06304129	Threshold Values and Diagnostic Performance of Plasma Biomarkers of Alzheimer's Disease Compared With CSF Markers (PLASM-ALZ)	189	Sep 2026 (not yet recruiting)
NCT06661564	Identification of Diagnosis Biomarkers in the Tears of Alzheimer's Disease Patients: the COG-EYE Pilot Study (COG-EYE)	90	Jan 2027 (recruiting)
NCT05531526[a]	A Phase 3 Double-blind, Randomized, Placebo-controlled, Multi-center Trial to Evaluate the Efficacy and Safety of AR1001 Over 52 Weeks in Participants With Early Alzheimer's Disease (Polaris-AD)	1150	Dec 2027 (active)
NCT06561906	Establish Diagnostic and Prognostic Models for Preclinical AD Patients Based on Multimodal MRI, Behavioral, Genetic, and Plasma Biomarkers	1000	Dec 2027 (recruiting)
NCT06856681[a]	A Study of the Clinical Effect of the Implementation of a Blood Biomarker Into Memory Clinics in the Department of Veterans Affairs and Other Closed System Healthcare Memory and Dementia Sites in the United States (ADELAIDE)	800	Mar 2028 (not yet recruiting)
NCT06547099	Study to Understand Novel Biomarkers in Researching Dementia (SUNBIRD)	1800	Dec 2028 (recruiting)
NCT06120361	The Swedish BioFINDER - Primary Care Study (ADetect)	1200	Dec 2028 (recruiting)
NCT07071649	Evaluation of a Plasma Marker (p-Tau217) for the Biological Diagnosis of Alzheimer's Disease, and Comparison With CSF Markers	40	Feb 2027
NCT07099001[a]	Establishing Clinical Utility Evidence for a Novel Alzheimer's Disease Blood-Based Biomarker Assay: A QURE Virtual Patient Randomized Controlled Trial	150	Dec 2025 (recruiting)
NCT06661564	Identification of Diagnosis Biomarkers in the Tears of Alzheimer's Disease Patients: The COG-EYE Pilot Study (COG-EYE)	90	Jul 2027 (recruiting)
NCT07142954[a]	A Longitudinal, Prospective Epidemiology Study in Alzheimer's Disease: Assessing Neurocognitive and Biomarker Changes and Health Outcomes in Individuals at Risk for Symptoms of Alzheimer's Disease (ANCHOR-AD)	3400	Jul 2033

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Appendix 1

2024 Clinical Input

Objective

Clinical input was sought to help determine whether the use of cerebrospinal fluid biomarker testing for individuals who are being considered for an approved amyloid beta plaque targeting therapy would provide a clinically meaningful improvement in net health outcome.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Cliatt Brown, Christine J, MD; Behavioral Neurology, identified by University of Utah
- Sorweid, Michelle K., DO, MPH, Geriatrics, identified by University of Utah

- Anonymous**, MD, PhD, Behavioral Neurology and Neurology, identified by American Academy of Neurology (AAN)

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the clinical input process provide review, input, and feedback on topics being evaluated. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the opinion published by BCBSA or any Blue Plan.

Ratings

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Respondent Profile

	Specialty Society				
#	Name of Organization			Clinical Specialty	
1	American Academy of Neurology			Neurology	
	Physician				
#	Name	Degree	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training
1	Anonymous	MD, PHD	Anonymous	Behavioral Neurology	Neurology
Identified by University of Utah					
2	Cliatt Brown, Christine J.;	MD	University of Utah	Behavioral Neurology	Neurology
3	Sorweid, Michelle K.	DO, MPH	University of Utah	Geriatrics	Behavioral Neurology & Neuropsychiatry

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	No		Yes	I am a member of a work group at the American Academy of Neurology regarding anti	Yes	I have received compensation for my participation on an advisory board and the	No	

		amyloid therapies. I also have served on an advisory board for Eisai and am a member of the Eisai Speaker's bureau	Speaker's bureau for Eisai.	
2	No	No	No	No
3	No	No	No	No

#	Conflict of Interest Policy Statement
1	N/A
2	N/A
3	N/A

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response. NR = not reported

Responses

Note that the request for clinical input included questions related to several policies. Questions 1 through 3 were related to policy 5.01.38, questions 4 was related to 2.04.13, question 5a was related to 6.01.55. More details on responses for questions 1-5a can be found in the Appendix of those policies. Question 5b. Is the use of CSF biomarkers to select individuals with mild cognitive impairment or mild dementia due to Alzheimer disease who have amyloid beta pathology for treatment with lecanemab clinically appropriate? If yes, then please answer 5c below.

#	Indications	YES / NO	Comment
1	Indication 1, testing to select for treatment with lecanemab	Yes	NA
2, 3 (joint response)	Indication 1, testing to select for treatment with lecanemab	Yes	NA

Question 5c. Which CSF biomarkers are appropriate to select individuals for treatment with lecanemab (select all that apply):

Aβ[1-42]
Aβ[1-42] / Aβ[1-40]
t-tau / Aβ[1-42]
p-tau / Aβ[1-42]
FDA-cleared CSF biomarker tests for Alzheimer disease
Other (specify)

#	Indications	Biomarkers selected	Comment
1	Indication 1, testing to select for treatment with lecanemab	Aβ[1-42] / Aβ[1-40]t-tau / Aβ[1-42]p-tau / Aβ[1-42]FDA-cleared CSF biomarker tests for	I don't think all the commercially available biomarker tests are FDA-cleared (but all are CLIA certified). I would lean towards selecting all of the ratios as well as the FDA-cleared option. I don't think AB42 is enough on its own as there will be numerous false positives

#	Indications	Biomarkers selected	Comment
		Alzheimer disease	
2, 3 (joint response)	Indication 1, testing to select for treatment with lecanemab	t-tau / Aβ[1-42]p-tau / Aβ[1-42]FDA-cleared CSF biomarker tests for Alzheimer disease	Aβ 42 alone is not considered sufficient as other conditions can lower Aβ 42 including CSF dynamics disorders. Additionally, Aβ 42 alone may be indicative of asymptomatic or incidental amyloid positivity while tau/neurodegeneration must be considered.

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Documentation for Clinical Review

Please provide the following documentation:

- Documentation confirming diagnosis and clinical stage of:
  - Mild cognitive impairment (MCI)
  - Mild dementia due to Alzheimer disease
- Clear statement of indication for the test, specifying ONE of the following:
  - Adjunct to clinical diagnosis
  - Evaluation for initiation of amyloid beta targeting therapy
  - Evaluation for continuation of therapy
- Test type, including identification of the following:
  - Specimen type (CSF, plasma, or urine)
  - Biomarker(s) requested (amyloid beta, tau, neural thread proteins, etc.)
  - Specific FDA-cleared/approved test being requested

Post Service (in addition to the above, please include the following):

- Test result report, including interpretation
- Confirmation that results were used to support initiation decision for amyloid beta therapy, if applicable

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	82233	Beta-amyloid; 1-40 (Abeta 40)
	82234	Beta-amyloid; 1-42 (Abeta 42)
	84393	Tau, phosphorylated (eg, pTau 181, pTau 217), each
	84394	Tau, total (tTau)
	0358U	Neurology (mild cognitive impairment), analysis of B-amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative Includes Lumipulse® G ß-Amyloid Ratio (1-42/1-40) Test, Fujirebio Diagnostics, Inc, Fujirebio Diagnostics, Inc
	0412U	Beta amyloid, AB42/40 ratio, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and qualitative ApoE isoform-specific proteotyping, plasma combined with age, algorithm reported as presence or absence of brain amyloid pathology Includes PrecivityAD® blood test, C2N Diagnostics LLC, C2N Diagnostics LLC

Type	Code	Description
	0443U	Neurofilament light chain (NfL), ultra-sensitive immunoassay, serum or cerebrospinal fluid Includes Neurofilament Light Chain (NfL), Neuromuscular Clinical Laboratory at Washington University in St. Louis School of Medicine, Neuromuscular Clinical Laboratory at Washington University in St. Louis School of Medicine
	0445U	B-amyloid (Abeta42) and phospho tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology Includes Elecsys® Phospho-Tau (181P) CSF (pTau181) and ß-Amyloid (1-42) CSF II (Abeta 42) Ratio, Roche Diagnostics Operations, Inc (US owner/operator)
	0459U	B-amyloid (Abeta42) and total tau (tTau), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology Includes Elecsys® Total Tau CSF (tTau) and ß-Amyloid (1-42) CSF II (Abeta 42) Ratio, Roche Diagnostics Operations, Inc (US owner/operator)
HCPCS	N/A	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/02/2010	New policy Policies combined: • Apolipoprotein E Epsilon (apoE) 4 Allele and Alzheimers Disease: Role for Genetic Testing for Diagnosis and Risk Management Cerebrospinal Fluid and Urinary Assays of Neuronal (Neural) Thread Protein in the Diagnosis of Alzheimers Dementia
04/19/2012	Added documentation required for clinical review
02/22/2013	Coding update.
02/27/2015	Policy title change from Alzheimer's Disease - Genetic and Biochemical Testing Policy revision without position change
02/01/2017	Policy title change from Biochemical Markers of Alzheimer Disease Policy revision without position change
02/01/2018	Policy revision without position change
02/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated.
12/01/2020	Coding update.
02/01/2021	Annual review. No change to policy statement. Literature review updated. Policy title changed from Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease to current one.
12/01/2021	Annual review. Policy statement, guidelines and literature review updated.
11/01/2022	Coding update.
12/01/2022	Annual review. Policy statement, guidelines and literature review updated.
03/01/2023	Coding update.
08/01/2023	Coding update.
11/01/2023	Coding update.
12/01/2023	Annual review. No change to policy statement.

Effective Date	Action
05/01/2024	Coding update.
09/01/2024	Annual review. No change to policy statement.
08/01/2026	Policy reactivated. Previously archived from 02/01/2025 to 07/31/2026. Policy title changed from Evaluation of Biomarkers for Alzheimer Disease to current one. Policy statement, guidelines and literature updated. Coding update.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Evaluation of Cerebrospinal fluid, Urine, and Plasma Tests for Alzheimer Disease 2.04.14** **Policy Statement:** **Tests as an Adjunct to Clinical Diagnosis** I. Cerebrospinal fluid testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins is considered **investigational** for **EITHER** of the following situations: A. As an adjunct to clinical diagnosis in individuals with mild cognitive impairment B. As an adjunct to clinical diagnosis individuals with mild dementia due to Alzheimer disease II. Plasma testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins is considered **investigational** for **EITHER** of the following situations: A. As an adjunct to clinical diagnosis in individuals with mild cognitive impairment B. As an adjunct to clinical diagnosis individuals with mild dementia due to Alzheimer disease **Tests as Part of an Evaluation for the Initiation of Amyloid Beta Targeting Therapy** III. Cerebrospinal fluid testing of amyloid beta peptides and tau protein using tests that confirm amyloid pathology may be considered **medically necessary** for **ALL** of the following situations: A. One of these three FDA approved or cleared tests that have proven to confirm amyloid pathology (through establishing clinical equivalency to amyloid PET imaging): 1. Aβ42:Aβ40 ratio (Lumipulse G Amyloid Ratio 1-42/1-40); or

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
	2. Aβ42:phosphorylated-tau181 (p-tau181) (Elecsys B-Amyloid 1-42 CSF II, Elecsys Phospho-Tau 181P) CSF); or 3. Aβ42:total-tau (Elecsys ß-Amyloid 1-42 CSF II, Elecsys Total-Tau CSF). B. As part of an evaluation for the initiation of amyloid beta targeting therapy C. in individuals with mild cognitive impairment or individuals with mild dementia due to Alzheimer disease IV. Plasma testing of amyloid beta peptides and tau protein using tests that confirm amyloid pathology as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**. V. Cerebrospinal fluid testing of neural thread proteins as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**. VI. Plasma testing of neural thread proteins as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**. **Tests as Part of an Evaluation for the Continuation of Amyloid Beta Targeting Therapy** VII. Cerebrospinal fluid testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as part of an evaluation for the continuation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**.

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
	Evaluation of Urine VIII. Measurement of urine analytes as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**.