LifeWise
Health Plan of Washington

# MEDICAL POLICY – 2.04.521

# Evaluation of Cerebrospinal Fluid, Urine, and Plasma Tests for Alzheimer Disease

BCBSA Ref. Policy: 2.04.14

| | |
|---|---|
| Effective Date: | **Nov. 6, 2026*** |
| Last Revised: | Jul. 14, 2026 |
| Replaces: | N/A |
| *View the current policy here. | |

RELATED MEDICAL POLICIES:

| | |
|---|---|
| 5.01.626 | Amyloid Antibodies for the Treatment of Alzheimer's Disease |
| 10.01.526 | Molecular Genetic Testing: Services Reviewed by Carelon Medical Benefits Management |
| 10.01.528 | Imaging: Services Reviewed by Carelon Medical Benefits Management |

**Select a hyperlink below to be directed to that section.**

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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## Introduction

Alzheimer's disease (AD) is a progressive and degenerative brain disorder that primarily affects memory, thinking and behavior. It is the most common cause of dementia in older adults. Progression of AD is associated with certain indicators, or biomarkers which are believed to assist with diagnosis and disease monitoring. These biomarkers can be measured in fluids such as blood, urine, saliva, serum and plasma. Measurement of these biomarkers is considered investigational (unproven). There's not enough medical evidence to show if measuring these biomarkers improves individual health or contributes to medical management.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

| Test | Medical Necessity |
|---|---|
| **Cerebrospinal fluid testing as part of an evaluation for the initiation of amyloid beta targeting therapy (CPT 0358U, 0445U, 0459U)** | **Cerebrospinal fluid testing of amyloid beta peptides and tau protein 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 may be considered medically necessary (i.e., lecanemab-irmb [Leqembi], donanemab-azbt [Kisunla]) (See Related Policies)**<br>• FDA approved or cleared tests that have proven to confirm amyloid pathology (through establishing clinical equivalency to amyloid PET imaging) for selecting amyloid beta targeting therapy are as follows:<br>○ Aβ42:Aβ40 ratio (Lumipulse G Amyloid Ratio 1-42/1-40)<br>**OR**<br>○ Aβ42:phosphorylated-tau181 (p-tau181) (Elecsys B-Amyloid 1-42 CSF II, Elecsys Phospho-Tau 181P) CSF)<br>**OR**<br>○ Aβ42:total-tau (Elecsys ß-Amyloid 1-42 CSF II, Elecsys Total-Tau CSF) |

| Test | Investigational |
|---|---|
| **Laboratory testing for Alzheimer's disease** | **Laboratory testing for Alzheimer's disease is considered investigational in any of the following:**<br>• 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<br>**OR**<br>• Cerebrospinal fluid testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease<br>**OR** |

| Test | Investigational |
|---|---|
| | • 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.<br>**OR**<br>• Plasma testing for Alzheimer disease, including but not limited to, tau protein, amyloid beta peptides, or neural thread proteins as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease<br>**OR**<br>• 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.<br>**OR**<br>• Measurement of urine analytes as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease<br>**OR**<br>• Multianalyte assays, algorithmic analysis, skin biopsies, CSF testing for alpha-synuclein, or other tests not mentioned above used as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease. |

## Coding

| Code | Description |
|---|---|
| **CPT** | |
| 0206U | Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment |

| Code | Description |
|---|---|
| | by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease (use to report: DISCERN) |
| 0207U | Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure) (use to report: DISCERN) |
| 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 (Lumipulse) |
| 0361U | Neurofilament light chain, digital immunoassay, plasma, quantitative (use to report: Neurofilament Light Chain/Mayo Clinic) (code termed 01/01/26) |
| 0393U | Neurology (e.g., Parkinson disease, dementia with Lewy bodies), cerebrospinal fluid (CSF), detection of misfolded α-synuclein protein by seed amplification assay, qualitative (use to report: SYNTap Biomarker Test) |
| 0412U | Beta amyloid, Aβ42/40 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 (use to report: PrecivityAD) |
| 0443U | Neurofilament light chain (NfL), ultra-sensitive immunoassay, serum or cerebrospinal fluid (use to report: Neurofilament Light Chain/Washington University Neuromuscular Clinical Laboratory) |
| 0445U | B-amyloid (Abeta42) and phospho tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology (Elecsys Phospho-Tau CSF and B-Amyloid CSF II Ratio) |
| 0459U | B-amyloid (Abeta42) and total tau (tTau), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology (Elecsys Total Tau CSF and B-Amyloid CSF II Ratio) |
| 0479U | Tau, phosphorylated, pTau217 |
| 0503U | Neurology (Alzheimer disease), beta amyloid (AB40, AB42, AB42/40 ratio) and tau-protein (ptau217, np-tau217, ptau217/np-tau217 ratio), blood, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS), algorithm score reported as likelihood of positive or negative for amyloid plaques (use to report Precivity AD2) |
| 0547U | Neurofilament light chain (NfL), chemiluminescent enzyme immunoassay, plasma, quantitative (use to report Neurofilament Light Blood Test) |
| 0551U | Tau, phosphorylated, pTau217, by single-molecule array (ultrasensitive digital protein detection), using plasma (code termed 01/01/26) |
| 0568U | Neurology (dementia), beta amyloid (AB40, AB42, AB42/40 ratio), tau-protein phosphorylated at residue (e.g., pTau217), neurofilament light chain (NfL), and glial |

| Code | Description |
|---|---|
| | fibrillary acidic protein (GFAP), by ultra-high sensitivity molecule array detection, plasma, algorithm reported as positive, intermediate, or negative for Alzheimer pathology (use to report Lucent AD Complete) |
| 0596U | Neurology (Alzheimer disease), plasma, 3 distinct isoform-specific peptides (APOE2, APOE3, and APOE4) by liquid chromatography with tandem mass spectrometry (LC-MS/MS), reported as an APOE prototype (use to report Precivity-ApoE) |
| 81099 | Unlisted urinalysis procedure (use to report: AlzheimAlert) |
| 82233 | Beta-amyloid; 1-40 (Abeta 40) |
| 82234 | Beta-amyloid; 1-42 (Abeta 42) |
| 84393 | Tau, phosphorylated (e.g., pTau 181, pTau 217), each) |
| 84394 | Tau, total (tTau) |
| 86849 | Unlisted immunology procedure (use to report: Innotest, AlzoSure Predict) |

**Note**: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information

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, Alzheimer disease (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.'

## Evidence Review

### 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.

# 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 two 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 two 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 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| **Severity** | Pre-clinical | Pre-clinical | MCI due to Alzheimer disease | Mild Dementia | Moderate Dementia | Severe Dementia |
| **Clinical Features** | Performance within expected range on objective cognitive tests.<br><br>No evidence of recent cognitive decline or new neurobehavioral symptoms. | Normal performance within expected range on objective cognitive tests.<br><br>Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months).<br><br>Mild neurobehavioral changes may coexist or may be the primary complaint rather than cognitive.<br><br>No functional impact on daily life activities. | Performance in the impaired/abnormal range on objective cognitive tests.<br><br>Evidence of decline from baseline.<br><br>Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life | Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance.<br><br>Clearly evident functional impact on daily life, affecting mainly instrumental activities.<br><br>No longer fully independent/requires occasional assistance with daily life activities. | Progressive cognitive impairment or neurobehavioral changes.<br><br>Extensive functional impact on daily life with impairment in basic activities.<br><br>No longer independent and requires frequent assistance with daily life activities. | Progressive cognitive impairment or neurobehavioral changes.<br><br>Clinical interview may not be possible.<br><br>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 $Aβ_{42}$, or $Aβ_{42}/Aβ_{40}$ 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.

Skin fibroblast testing is being explored as a means to diagnose and differentiate AD from other dementias. The Discern Alzheimer's disease test (NeuroDiagnostics, Rockville, MD) examines skin fibroblast cells to identify and quantify three biomarkers (the phosphorylated extracellular signal-related kinases, Erk1 and Erk2, measure protein kinase C€ levels [PKCe], and measure skin fibroblast networks). At this time, peer-reviewed studies assessing the clinical validity or utility of this test are limited. This test currently does not have FDA clearance or approval. Large, randomized, controlled trials demonstrating this test is as accurate as autopsy results (the gold standard in the definitive diagnosis of AD) are needed.

## 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 multi-site 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.

## Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 2**.

## Table 2. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| **Ongoing** | | | |
| 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) |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| NCT06304129 | Threshold Values and Diagnostic Performance of Plasma Biomarkers of Alzheimer's Disease Compared With CSF Markers (PLASM-ALZ) | 189 | Sep 2026 |
| NCT06661564 | Identification of Diagnosis Biomarkers in the Tears of Alzheimer's Disease Patients: the COG-EYE Pilot Study (COG-EYE) | 90 | Jan 2027 |
| NCT05531526 | 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 (recruiting) |
| NCT06561906 | Establish Diagnostic and Prognostic Models for Preclinical AD Patients Based on Multimodal MRI, Behavioral, Genetic, and Plasma Biomarkers | 1000 | Dec 2027 (recruiting) |
| NCT06856681a | 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.

## 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 three respondents; one physician-level response identified through a specialty society; two 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.

## Practice Guidelines and Position Statements

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

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or the 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.

## *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:

- Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
- Clear-cut history of worsening of cognition by report or observation; and
- The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
    - 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 one other cognitive domain, as defined earlier in the text.
    - 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.
- The diagnosis of probable AD dementia should not be applied when there is evidence of:
    - 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
    - Core features of dementia with Lewy bodies other than dementia itself; or
    - Prominent features of behavioral variant frontotemporal dementia; or
    - Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or

- 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:

- 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
- 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 policy 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 one 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 three circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician."[24]

## *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 (e.g., 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 (e.g., 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 3** 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 3. Indications for Appropriate Use of Lumbar Puncture and CSF Testing in Diagnosing AD

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

| Appropriate Indications | Inappropriate Indications |
|---|---|
| • Meeting core clinical criteria for probable AD with typical age of onset<br>• Individuals whose dominant symptom is a change in behavior and where AD diagnosis is being considered | • Individuals with SCD who are not considered to be at increased risk for AD<br>• Use to determine disease severity in patients having already received a diagnosis of AD<br>• Individuals who are apolipoprotein E (APOE) ε4 carriers with no cognitive impairment<br>• Use of lumbar puncture in lieu of genotyping for suspected ADAD mutation carriers<br>• 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 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 4** 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, "T1" are early changing phosphorylated mid-region tau fragments (p-tau 217, 181, and 231), "T2" 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 4. 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 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.

## US Preventive Services Task Force Recommendations

In 2020, the US 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.

## 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 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 5**.

## Table 5. 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<br><br>Intended to be used in adult patients, aged 55 years and older, presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.<br><br>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 patient's cognitive impairment is due to AD.<br><br>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.<br><br>A test result between 0.059 and 0.072 is considered as a likely positive result as it is |

| Test | Manufacturer | Location | Date Cleared | De Novo or 510(k) Number | Indication(s) |
|---|---|---|---|---|---|
| | | | | | 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.<br><br>The Lumipulse G P-Amyloid Ratio ( 1-42/ 1-40) results must be interpreted in conjunction with other patient clinical information. This test is not intended as a screening or stand-alone diagnostic test. |
| Lumipulse G p-tau217/β-Amyloid 1-42 Plasma Ratio[a] | Fujirebio Diagnostics, Inc | Malvern, PA | May 2025 | K242706 | Plasma test<br><br>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.<br><br>A test result ≤ 0.00370 is a negative result which is consistent with individuals who are unlikely to have amyloid pathology. These |

| Test | Manufacturer | Location | Date Cleared | De Novo or 510(k) Number | Indication(s) |
|---|---|---|---|---|---|
| | | | | | individuals should be investigated for other causes of cognitive decline.<br><br>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.<br><br>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.<br><br>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<br><br>Intended to be used in adult patients, aged 55 years and older, being evaluated for AD and |

| Test | Manufacturer | Location | Date Cleared | De Novo or 510(k) Number | Indication(s) |
|---|---|---|---|---|---|
| | | | | | other causes of cognitive impairment to generate a pTau181/Abeta42 ratio value.<br><br>The adjusted ratio cutoff is 0.023.<br><br>A negative result, defined as pTau181/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 a patient's cognitive impairment is due to AD.<br><br>A positive result, defined as pTau181/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.<br><br>The pTau181/Abeta42 ratio result is used as an adjunct to other clinical diagnostic evaluations.<br><br>The performance of the pTau181/Abeta42 ratio has not been established for predicting development of dementia or other neurologic conditions or monitoring responses to therapies |

| Test | Manufacturer | Location | Date Cleared | De Novo or 510(k) Number | Indication(s) |
|---|---|---|---|---|---|
| Elecsys Phospho-Tau (181P) Plasma | Roche Diagnostics | Indianapolis, IN | October 2025 | K252163 | Plasma test<br><br>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.<br><br>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.<br><br>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.<br><br>The p-tau181 result is used as an adjunct to other clinical diagnostic evaluations. |

| Test | Manufacturer | Location | Date Cleared | De Novo or 510(k) Number | Indication(s) |
|---|---|---|---|---|---|
| | | | | | 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<br><br>Intended to be used in adult patients, aged 55 years and older, being evaluated for AD and other causes of cognitive impairment to generate a tTau/Abeta42 ratio value.<br><br>The numerical ratio must be compared to the cutoff of 0.28.<br><br>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 that a patient's cognitive impairment is due to AD.<br><br>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. |

| Test | Manufacturer | Location | Date Cleared | De Novo or 510(k) Number | Indication(s) |
|---|---|---|---|---|---|
| | | | | | The tTau/Abeta42 ratio result is used as an adjunct to other clinical diagnostic evaluations.<br><br>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.

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## History

| Date | Comments |
|---|---|
| 05/01/24 | New policy, approved April 9, 2024, effective for dates of service on or after August 2, 2024, following a 90-day provider notification. Measurement of biochemical markers of Alzheimer's disease is considered investigational. Added CPT codes 0206U, 0207U, 0346U, 0361U, 0393U, 0412U, 0443U, 81099 and 86849. |
| 10/01/24 | Coding update. Added new CPT codes 0479U and 0503U. |
| 01/01/25 | Interim Review, approved December 10, 2024. Added new CPT codes 82233, 82234, 84393, 84394 and removed termed CPT code 0346U. Policy updated with literature review through May 15, 2024; references added. The following policy changes are effective for dates of service on or after April 6, 2025, following 90-day provider notification. Added the following statements "Measurement of cerebrospinal fluid biomarker 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 and measurement of cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered investigational, and cerebrospinal fluid biomarker 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. Minor edit of updated amyloid targeted therapy example; |

| Date | Comments |
|---|---|
| | other policy statements remain unchanged. Added CPT codes 0358U. 0445U and 0459U to match updated criteria. |
| 04/01/25 | Coding update. Added new CPT codes 0547U and 0551U. |
| 07/01/25 | Coding update. Added new CPT code 0568U to match criteria. |
| 08/01/25 | Annual Review, approved July 7, 2025. Policy updated with literature review through April 18, 2025; references added. Policy statements unchanged. |
| 10/01/25 | Coding update. Added new CPT code 0596U. |
| 01/01/26 | Coding update. Notated that HCPCS codes 0361U and 0551U termed 01/01/26. Removed HCPCS code 0346U that termed 01/01/25. |
| 08/01/26 | Annual Review, approved July 14, 2026. Effective for dates of service on or after November 6, 2026, following 90-day provider notification. Title changed from "Evaluation of Biomarkers for Alzheimer Disease" to "Evaluation of Cerebrospinal Fluid, Urine, and Plasma tests for Alzheimer Disease." Policy updated with literature review through March 23, 2026; references added. Policy statements changed to include the specific CSF biomarker tests which may be considered medically necessary. Added investigational policy statement for plasma-based tests used to confirm amyloid pathology as part of an evaluation for the initiation of amyloid beta targeting therapy. |

**Disclaimer**: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

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