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## Medical Coverage Policy

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# Beta-Amyloid and Phosphorylated-Tau Biomarker Testing for Alzheimer's Disease

## Table of Contents



## Related Coverage Resources

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Neurology – Kisunla
Neurology – Leqembi

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## Overview

This Coverage Policy addresses beta-amyloid (b-amyloid), also known as Aβ and amyloid beta and phosphorylated tau (p-tau) biomarker testing for the diagnosis and treatment of Alzheimer's disease.

## Coverage Policy

**Beta-amyloid biomarker testing using plasma or cerebrospinal fluid (CSF) is considered experimental, investigational or unproven for the diagnosis or management of Alzheimer's disease.**

**Phosphorylated tau (p-tau) biomarker testing using plasma or CSF is considered experimental, investigational or unproven for the diagnosis or management of Alzheimer's disease.**

**Multianalyte biomarker panel testing for beta-amyloid and/or p-tau using plasma or CSF is considered experimental, investigational or unproven for the diagnosis or management of Alzheimer's disease.**

## Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

Alzheimer's disease has an estimated dementia prevalence of about 50 million people worldwide, projected to triple in 2050, with two-thirds living in low-income and middle-income countries (National Institutes of Neurological Disorders and Stroke [NINDS], 2024).

According to a special report published by the AA (2024), an estimated 6.9 million Americans age 65 and older are living with Alzheimer's Disease (AD) in 2024. Seventy-three percent are age 75 or older. About 1 in 9 people aged 65 and older (10.9%) has AD. Almost two-thirds of Americans with AD are women. Older Black Americans are about twice as likely to have AD or other dementias as older Whites. Older individuals with Latinx ancestry are about one and one-half times as likely to have AD or other dementias as older Whites. Regarding morbidity and mortality,

among people aged 70, 61% of those with AD dementia are expected to die before age 80 compared with 30% of people without AD dementia.

The higher prevalence of AD dementia in Black and Latino populations compared with the White population appears to be due to a higher risk of developing dementia in these groups compared with the White population of the same age. There is some research into how the influence of genetic risk factors on AD and other dementias may differ by race, for example, the influence of the APOE-e4 allele on AD's risk may be stronger for White Americans than Black Americans. The AA also notes a systematic review of the literature found that Japanese Americans were the only Asian American subgroup with reliable prevalence data, and that they had the lowest prevalence of dementia compared with all other ethnic groups.

An older adult who is a member of an underrepresented sexual and gender group may face an increased dementia risk, through pervasive exposure to systematic discrimination, marginalization, disadvantage and/or exclusion from social organizations and enterprises.

## General Background

Alzheimer's disease (AD) is a neurological disorder that involves irreversible worsening changes in the ability to reason, learn new skills and plan and prioritize. It is currently the most common cause of dementia in older adults.

Sporadic AD is the most common cause of dementia with age being the principal risk factor. The incidence of AD increases with age. Symptoms typically begin with memory deficits, progressing to other cognitive domains with death, usually in 10 years from diagnosis (Rukmangadachar and Bollu, 2023).

A subset of AD known as familial or younger/early-onset Alzheimer disease accounts for 2% to 3% of Alzheimer disease cases. It tends to occur early in life, before age 60, as opposed to sporadic Alzheimer disease (Rukmangadachar and Bollu, 2023; Alzheimer's Association [AA], 2025).

The brain changes of AD include the excessive accumulation of the protein fragment beta-amyloid and an abnormal form of the protein tau, as well as damage to and destruction of neurons (AA, 2024).

Extracellular deposits of amyloid beta build up in the spaces between nerve cells. Tau protein tangles are twisted fibers that build up inside cells. This damage initially takes place in parts of the brain involved in memory, including the entorhinal cortex and hippocampus. It later affects areas in the cerebral cortex, such as those responsible for language, reasoning, and social behavior. Autopsy studies show that most people develop some plaques and tangles as they age, those with AD tend to develop far more and in a predictable pattern, beginning in the areas important for memory before spreading to other regions. The exact role plaques and tangles play in AD is unknown. Most experts believe they somehow play a critical role in blocking communication among nerve cells and disrupting processes that cells need to survive (AA, 2024).

The diagnosis of AD requires a combination of multiple modalities, including clinical evaluation, neuropsychological assessment, neuroimaging techniques, such as PET scan and other measurements of brain function. Neuropsychological exam is the cornerstone for clinical diagnosis and can determine whether individuals have normal cognition, cognitive impairment, and/or dementia while (Bouwman et al., 2023), post-mortem histological identification of extracellular plaque deposits of beta-amyloid peptide and neurofibrillary tangles of tau protein is considered the

gold standard for identification of AD pathology and definitive diagnosis. Amyloid PET is considered the gold standard for quantifying in vivo Aβ deposits in the brain (Meeker et al., 2024).

Timely and accurate diagnosis of AD in clinical practice is currently challenging, with misdiagnosis in the range of 20–25% when cerebrospinal fluid (CSF) or positron emission tomography (PET) biomarkers are not utilized. Suboptimal treatment and care, delayed or incorrect therapies and inaccurate information about the disease and its prognosis are frequent (Timolo et al., 2024).

With the ability to measure amyloid and tau in cerebrospinal fluid (CSF) and plasma there has been an interest in the development of a biological definition of AD. More recently, researchers have proposed measurement of blood-based biomarker and cerebrospinal tests for beta-amyloid and tau as a means to diagnose and treat AD. Regarding a purely biological definition of Alzheimer's disease, Dubois et al. (2021) noted that its low predictive accuracy is a limitation. The presence of both tau and amyloid β positivity is insufficient to definitively predict the occurrence of symptoms (mild cognitive impairment or dementia) in individuals without clinical impairment. Individuals who have evidence of other brain pathology in addition to Alzheimer's disease lesions should not be considered as having a primary diagnosis of Alzheimer's disease.

On behalf of the Alzheimer's Association (AA) Workgroup and as an update to a previous research framework, Jack et al. (2024) proposed revised criteria for the diagnosis and staging of AD, including defining AD as a biological process that begins with the appearance of neuropathic changes while an individual is asymptomatic. Jack notes these criteria are not intended to provide step-by-step clinical practice guidelines for clinical workflow or specific treatment protocols; but rather serve as general principles to inform diagnosis and staging of AD that reflect current science.

Clinical trials are ongoing to develop treatments which will slow or reverse AD progression. At present, no blood tests can definitively diagnose Alzheimer's before symptoms develop (National Institute of Neurological Disease and Stroke [NINDS], 2024).

Although the use of cerebrospinal fluid (CSF) and blood-based biomarkers to diagnose and manage AD is promising, there is insufficient evidence in the peer-reviewed published literature to establish the clinical utility of biomarkers as the standard for diagnosis of AD or support for such testing in routine clinical practice. Studies are observational in design and a high level of heterogeneity is noted related to inclusion criteria for populations within studies and testing methodology used to establish diagnosis of AD. Published professional society guidelines recommending biomarker testing to diagnose or manage AD as a single diagnostic tool or in conjunction with other assessment methods in routine clinical practice are limited.

**Literature Review**
A systematic review of clinical practice guidelines for mild cognitive impairment (MCI) and Alzheimer's disease (AD) was published by Tahami Monfared et al. (2023). Fifty-three guidelines were identified; 15 guidelines were published between 2018-2022. Seven guidelines provided recommendations for populations with AD dementia; seven guidelines reviewed recommendations for both MCI and AD. The methods used to develop the guidelines varied. Seven used an evidence-based approach from the latest literature, although the methods were not clearly stated. The systematic literature review aimed to identify and summarize current clinical practice guidelines for screening, diagnosis, monitoring and treatment in the AD continuum. Screening refers to routine assessment for AD in populations at risk of AD dementia who either do not have a formal diagnosis of cognitive impairment or have neurocognitive disorders but without a diagnosis of dementia.

No guideline recommended biomarker testing for diagnosis in routine clinical practice. The rationale for the recommendations noted there are currently no biomarkers that have been conclusively demonstrated to predict progression in individuals with MCI and the specificity of these biomarkers is relatively low, entailing many false positive cases.

**Literature Review**
**Biomarker Testing**
There is insufficient evidence in the peer-reviewed published literature regarding the positive and negative predictive values of CSF levels of amyloid and tau to establish the diagnosis of AD in patients with clinical symptoms consistent with possible AD.

The Agency for Health Care Policy and Research ([AHCPR], 2020) published a systematic review evaluating tests to aid in the evaluation of clinical Alzheimer's-type dementia. Regarding the accuracy of biomarkers for distinguishing autopsy-confirmed AD from non-AD dementia, AHCPR noted:

- Individual CSF tests and ratios were moderately sensitive and specific; in the few direct comparisons, beta amyloid 42 (Aß42)/p-tau ratio, t-tau/Aß42 ratio and p-tau appeared more accurate and Aß42 and t-tau appeared least accurate.
- Combinations of CSF tests may have the highest mix of sensitivity and specificity and may increase accuracy for distinguishing AD from frontotemporal lobar degeneration (FTLD) when added to clinical evaluation.
- There was minimal evidence addressing whether the accuracy of biomarker testing for identifying AD varied by study participant characteristics.
- No studies reported data on the accuracy of blood tests for identifying autopsy-confirmed AD.
- Evidence regarding whether certain individual CSF tests or combinations of CSF tests are better than others for distinguishing neuropathologically confirmed AD from non-AD is inconclusive.
- Few studies evaluated the accuracy of brain imaging and CSF tests compared with autopsy-confirmed diagnoses, and none examined blood tests.
- Studies for both cognitive and biomarker tests were limited by small sample sizes.

Evidence is insufficient to establish an improvement in health outcomes by use of CSF or blood biomarkers in distinguishing autopsy-confirmed AD from non-AD dementia.

Krishna et al. (2024) the accuracy of plasma biomarkers of amyloid 42 (A42), t-tau, p-tau 181, and neurofilament (NfL) to classify AD, Non-AD (NAD), and healthy controls (HC) were measured in 105 study participants (n=35 HC, 35 AD, 33 NAD). Biomarker results were correlated with the scores of clinical assessment scales such as Clinical Dementia Rating (CDR), Hindi Mental State Examination (HMSE), Neuropsychiatry Inventory (NPI), and Everyday abilities Scale for India (EASI). Participants with NAD were diagnosed with frontotemporal dementia (FTD), vascular dementia (VaD), Lewy body dementia (LBD), or mixed dementia (MD).

The median concentration of A42 in the AD, NAD and HC groups were statistically similar. The median concentration of p-tau 181 in AD ($p < 0.0001$) and NAD ($p < 0.001$) groups were significantly higher than that of the HC group. The median concentration of t-tau in AD ($p < 0.05$) was higher than that of the HC group; there was no significant difference between the NAD group and the HC group.

The performance of biomarkers in discriminating the groups were studied by ROC analysis. Among them, NfL had the highest AUC (0.88) for AD versus HC, closely followed by p-tau 181 (AUC= 0.83) and t-tau (AUC= 0.74). Aβ42 showed the least discriminatory power when compared to

other biomarkers. An increase in AUC was observed when the biomarkers were combined. The AUC increased with the addition of p-tau 181 (0.89). The discriminatory power between AD and HC with was increased with the addition of t-tau (AUC 0.98) and MfL/Aβ42 (AUC 0.99), respectively. On ROC analysis between AD and NAD groups, none of the standalone biomarkers could reliably distinguish between the two groups.

Small sample size was noted as a limitation The authors noted several limitations to the study. Supporting data from CSF measurements and neuroimaging of biomarkers regarding the diagnosis of AD or other dementias was lacking. Validation of the proposed biomarkers in larger cohorts and longitudinal studies is warranted.

Bethelmey et al. (2024) evaluated whether a blood-based biomarker test could perform as well as established cerebrospinal fluid (CSF) tests in detecting amyloid-β (Aβ) plaques and tau tangles. Plasma %p-tau217 (ratio of phosporylated-tau217 to non-phosphorylated tau) was analyzed by mass spectrometry in two cohort studies for a total of 1799 participants. Matched CSF samples were analyzed with clinically used and FDA-approved automated immunoassays for Aβ42/40 and p-tau181/Aβ42. The primary and secondary outcomes were detection of brain Aβ or tau pathology, respectively, using positron emission tomography (PET) imaging as the reference standard.

Plasma %p-tau217 was clinically equivalent to CSF tests in classifying Aβ PET status, with an area under the curve (AUC) for both between 0.95 and 0.97. Plasma %p-tau217 was generally superior to CSF tests in classification of tau-PET with AUCs of 0.95–0.98. In cognitively impaired subcohorts (BioFINDER-2: n = 720; Knight ADRC: n = 50), plasma %p-tau217 had an accuracy, a positive predictive value and a negative predictive value of 89–90% for Aβ PET and 87–88% for tau PET status, which was clinically equivalent to CSF tests. Blood plasma %p-tau217 demonstrated performance that was clinically equivalent or superior to clinically used FDA-approved CSF tests in the detection of AD pathology.

Fink et al. (2020) performed a systematic literature review to determine the accuracy of biomarker testing neuropathologically defined AD in older adults with dementia. Fifteen brain imaging studies and nine CSF studies met analysis criteria. Median sensitivity and specificity, respectively, were 0.91 and 0.92 for amyloid positron emission tomography (PET), 0.89 and 0.74 for 18F-labeled fluorodeoxyglucose (18F-FDG) PET, 0.64 and 0.83 for single-photon emission computed tomography, and 0.91 and 0.89 for medial temporal lobe atrophy on magnetic resonance imaging (MRI). Individual CSF biomarkers and ratios had moderate sensitivity (range, 0.62 to 0.83) and specificity (range, 0.53 to 0.69); in the few direct comparisons, β-amyloid 42 (Aβ42)/phosphorylated tau (p-tau) ratio, total tau (t-tau)/Aβ42 ratio, and p-tau appeared more accurate than Aβ42 and t-tau alone. Limitations include small study populations, neuropathologic AD were inconsistently defined and methods with uncertain applicability to typical clinical settings were used. Few studies directly compared biomarkers, assessed test combinations, evaluated whether biomarkers improved classification accuracy when added to clinical evaluation, or reported harms. Data are insufficient to establish the accuracy of CSF biomarkers to identify AD in older patients with dementia.

On behalf on a workgroup convened by the Alzheimer's Association, results of a systematic review of observational and cohort studies were reported by Shaw et al. (2023). The workgroup used the findings to develop criteria to support clinicians in consistently identifying appropriate patient populations for lumbar puncture (LP) and cerebrospinal fluid (CSF) testing to aid in the diagnosis of AD. A limitation of the study identified by the authors: most studies on diagnostic accuracy CSF biomarker accuracy to the reference standard of clinical diagnosis instead of amyloid PET or neuropathology, thus likely reducing the accuracy of controls.

When amyloid PET was the reference standard for detection of brain neuritic plaque burden (i.e., presence or absence), in persons experiencing cognitive impairment the sensitivity and specificity of CSF amyloid (Aβ2) and tau levels (total tau and p-tau) or ratios of analytes were (0% and 84%, pooled values, respectively. Studies reflected a concordance of 85%–95% for CSF Aβ42, alone or combined with t-tau or p-tau, and amyloid PET.

The study also evaluated the sensitivity and specificity of LP and CSF testing of Aβ42 and tau levels as indicators of AD presence or absence. The sensitivity and specificity values for CSF Aβ42 or the ratios Aβ42/Aβ40 and t-Tau/Aβ42 or p-tau/Aβ42 in these two study groups fell within the range of the previously reported values.

The authors noted if there is significant uncertainty as to the etiology of cognitive impairment, the decision to use CSF testing is based on the clinical judgement of the provider and the patient's individual situation. Where diagnostic confidence of the physician is high, the use of advanced biomarker testing may not be needed.

Prolonged follow-up studies for at least five years, and ideally longer, are needed to provide robust estimates of the predictive performance of biomarkers in clinical practice, and for research studies such as clinical trials.

**Beta-Amyloid Peptide (Aβ, Amyloid beta)**
Beta-amyloid peptide, also known as amyloid-beta and Aβ, appears to play a role in the pathogenesis of Alzheimer disease. It is a 42-amino acid peptide and derives from the precursor protein, amyloid beta precursor protein (APP).

According to amyloid cascade theory, the cerebral accumulation of Aβ peptide, resulting from the imbalance between production and clearance of this protein, is the main event causing the disease (Silva, 2019). Free amyloid peptide levels are measurable in cerebrospinal fluid (CSF) and plasma. Low levels of amyloid beta and abnormally high tau protein in CSF are being studied as biomarkers of AD in clinical trials.

Although some studies suggest that CSF Aβ42 levels may be a surrogate marker of underlying brain amyloidosis, the correlation between serum Aβ42 levels and cerebral amyloidosis is not yet demonstrated. A decrease in Aβ42 levels is observed in cerebrospinal fluid of AD subjects, which can be explained in part by higher deposition of β-amyloid plaques.

The Aβ42 peptide is more prone to aggregation than Aβ40. Immunohistochemical analyses indicate that Aβ42 is initially deposited and found at higher concentrations in the amyloid plaques observed in AD patients (Silva, 2019).

There is insufficient evidence in the published, peer-reviewed medical literature to establish the clinical utility of beta-amyloid testing as a standard in routine clinical practice. There is a lack of randomized controlled trials and studies are heterogeneous in design and study populations.

**Literature Review**
Ebbeson et al. (2023) published results of a systematic review and metanalysis to investigate the biomarker potential of plasma Aβ. The focus of the review was on Aβ42, Aβ40 and the Aβ42/40 ratio and their respective association with aPET positivity and CSF Aβ levels. The reviewer noted that increased standardized uptake value ratio of the Aβ binding isotope demonstrated by aPET is a gold standard biomarker of amyloid.

The authors note that plasma Aβ42/40 ratio is positively correlated with CSF Aβ42/40 ratio and negatively correlated with aPET. However, the studies included in the meta-analysis exhibited substantial heterogeneity, which limits the generalizability of the results and lowers the confidence in the meta-analytic model estimates. This may be due to the considerable variance in cognitive level of participants: cognitively unimpaired, MCI and those with a diagnosis of AD. Robustness of Aβ42/40 ratio as a marker for AD pathology may be questioned due to the small fold changes between amyloid positivity versus negativity. More research is warranted, including validation studies, longitudinally clinical studies, studies comparing measurement methods and studies of Aβ kinetics.

Cheng et al. (2022) performed a systematic review and meta-analysis on data related to plasma Aβ40 values in PET (−) subjects and PET (+) subjects. Objectives were to quantitatively determine (1) what are the differences in plasma Aβ markers between Aβ-PET (+) and Aβ-PET (−) people, (2) whether the plasma Aβ can be used as an independent biomarker for predicting Aβ-PET status and (3) which type of plasma Aβ isoform is suitable for predicting Aβ-PET status accurately.

Sixteen studies with 3047 participants were included in the meta-analysis. There were 1749 PET (−) subjects and 1298 PET (+) subjects. The pooled standardized mean difference (SMD) was 0.76. The overall effect was not significant (p=0.28), which implied there was no statistical distinction in plasma Aβ40 values between PET (+) and PET (−) subjects. In addition, high heterogeneity was found.

In a meta-analysis of reported data on plasma Aβ42 values the pooled SMD was −0.60 and the overall effect was significant (p<0.0001). Data suggest plasma Aβ42 values could be used as an independent biomarker for predicting Aβ-PET status. Heterogeneity was 73%. For Aβ42:Aβ40 ratio, the pooled SMD was −1.44. The overall was significant (p<0.0001). Heterogeneity was 97%.

Although data are promising to suggest that Aβ42 and Aβ42:Aβ40 ratio values can be used to predict people with PET (+) and PET (-); heterogeneity of study results prevents such an assessment.

Chatterjee et al. (2019) published results of a prospective trial comparing Aβ40 and Aβ42 concentrations were measured in 95 cognitively normal elderly individuals, who underwent PET to assess brain Aβ deposition. Plasma Aβ was compared between 32 participants assessed to have low brain Aβ load and 63 assessed to have high brain Aβ load. Plasma Aβ42/Aβ40 ratios were lower in the Aβ+ group compared to the Aβ–group. Plasma Aβ40 and Aβ42 levels were not significantly different between Aβ–and Aβ+ groups, although a trend of higher plasma Aβ40 was observed in the Aβ+ group. Authors note this method to measure plasma Aβ needs further development to increase the accuracy of this AD blood biomarker.

**Phosphorylated Tau (p-tau)**
Tau protein primarily provides stability to microtubules in axons and dendrites. In a pathological state tau becomes hyperphosphorylated, causing tau dysfunction and leading to synaptic impairment and degeneration of neurons. Six isoforms of tau protein are produced by alternate splicing of the MAPT gene, located on chromosome 17 (17q21) (Silva, 2019).

There is insufficient evidence in the published, peer-reviewed medical literature to demonstrate the clinical utility of p-tau biomarker testing in routine clinical practice. There is a lack of randomized controlled clinical trials and studies are heterogenous in design and study populations.

**Literature Review**

Hanes et al. (2020) evaluated whether a tau phosphorylated at Thr217 (p-tau T217) assay in CSF can distinguish individuals with AD from those other dementias and healthy controls. A new Simoa immunoassay was developed and validated to detect p-tau T217 in CSF for this study. Three cohorts participated: AD (n=77), other neurodegenerative disorders (n=69) and healthy controls (n=44).

The p-tau T217 assay identified individuals with AD with accuracy of 90%, with 78% positive predictive value (PPV), 97% negative predictive value (NPV), 93% sensitivity, and 88% specificity. Compared with p-tau T181 ELISA (52 pg/mL), the test demonstrated 78% accuracy, 58% PPV, 98% NPV, 71% specificity, and 97% sensitivity. The assay distinguished patients with AD from age-matched healthy controls 98% sensitivity, 93% specificity), similarly to p-tau T181 ELISA (96% sensitivity, 86% specificity). A correlation between p-tau T217 and p-tau T181, total tau and β-amyloid 40, but not β-amyloid 42 was found in individuals with AD.

Identified study limitations include small sample size. Authors note results should be replicated in larger cohorts characterized by both amyloid and tau PET imaging and validated in routine clinical practice. The technology should undergo a structured assessment to evaluate its benefit in terms of clinical utility.

Results of a systematic review and meta-analysis evaluating the role of blood p-tau isoforms 181, 217 and 231 in predicting conversion from mild cognitive impairment (MCI) to dementia due to AD were reported by Lombardi et al. (2024).

Twelve studies reported p-tau 181 levels for converters and non-converters to AD (n=895 and 3445, respectively; conversion rate 20.6%). There was a significant difference between baseline p-tau 181 values in MCI converters and non-converters to AD ($p < 0.001$), indicating higher p-tau 181 values in those converting to AD. The heterogeneity index I2 was 81.72%. Four studies reported p-tau 217 values, for converters and non-converters (n= 305 and 608, respectively; conversion rate 33.4%). For p-tau 217 the heterogeneity ratio was 0.85. One study reported p-tau 231 levels for converters and non-converters (n-45 and 90, respectively; conversion rate 33%). Insufficient results were available for p-tau 231. In this study the heterogeneity of studies limits the ability to draw definite conclusions regarding the role of p-tau isoforms in predicting conversion from MC to AD.

Sperling et al. (2024) presented longitudinal data from a large cohort of cognitively unimpaired individuals enrolled in a Phase 3 clinical trial and companion observational study to evaluate whether biomarker indicators of higher levels of AD pathology at baseline predicted greater cognitive and functional decline. An additional objective was to compare the relative predictive power of amyloid PET imaging, tau PET imaging, and a plasma P-tau217 assay. Baseline tau PET scans were obtained in a subset of participants.

Participants with elevated amyloid (Aβ+) on screening PET who met inclusion/exclusion criteria were randomized to receive placebo or solanezumab in a double-blind phase of the A4 Study over 240+ weeks. Participants who did not have elevated amyloid (Aβ-) but were otherwise eligible for the A4 Study were referred to the companion observational LEARN Study with the same outcome assessments over 240+ weeks.

Higher baseline amyloid PET CL and P-tau217 levels were associated with faster rates of decline, and increased likelihood of progression to functional impairment, both across LEARN Aβ- and A4 Aβ+ (solanezumab and placebo arms). Plasma P-tau217 was the best predictor of decline in the overall sample, superior to baseline amyloid PET. Neocortical tau was the strongest predictor of

cognitive decline in the subgroup with tau PET, suggesting that tau deposition may be linked to clinical decline.

Zabala-Findlay et al. (2022) performed a systematic review and meta-analysis to determine the utility of blood-based total and phosphorylated tau biomarkers for MCI and AD. The meta-analyses (n=48 studies) assessed total tau (t-tau), tau phosphorylated at threonine 181 (p-tau181), and tau phosphorylated at threonine 217 (p-tau217), comparing the ratio of biomarker concentrations in MCI, AD, and cognitively unimpaired (CU) controls. Plasma/serum p-tau181 and t-tau were elevated in AD study participants compared to controls. Plasma/serum p-tau181 and t-tau were also elevated with moderate effect size in MCI study participants compared to controls. p-tau 217 was also assessed in a small number of eligible studies, for AD vs. CU and for MCI vs. CU groups.

Researchers note the findings of this meta-analysis need to be considered alongside the heterogeneity noted between each study. Factors contributing to heterogeneity are extensive and include but are not limited to, different and evolving diagnostic criteria, subjective clinical assessment and diagnosis, clinical and pathological heterogeneity of AD itself, the inclusion of familial and sporadic cases, sample handling, processing and pre-analytical variables, as well as different assays and technologies used to derive the data. The applicability of study results to routine clinical use of blood-based tau testing is limited by study heterogeneity.

**Professional Societies/Organizations**
**Alzheimer's Association [AA], 2024:** In the 2024 online publication of Alzheimer's Disease: Facts and Figures the AA noted that advances in the identification of biomarkers for Alzheimer's disease makes it possible to identify individuals who have beta-amyloid accumulation in the brain and who may qualify for clinical trials of experimental treatments that aim to reduce the accumulated beta-amyloid and in doing so prevent or delay the onset of symptoms. Biomarkers also enable earlier detection of the brain changes of Alzheimer's disease, giving those affected the opportunity to address modifiable risk factors that may slow or delay cognitive decline. Biomarkers are already accelerating the development of new treatments by making it possible for clinical trials to specifically recruit individuals with the brain changes those experimental therapies target.

**Alzheimer's Association DETeCD-ADRD CPG Expert Workgroup (2024)**: Atri et al. published clinical practice guidelines for the Diagnostic Evaluation, Testing, Counseling, and Disclosure of Suspected Alzheimer's Disease and Related Disorders (DETeCD-ADRD: Recommendations for Primary Care. Regarding laboratory testing, including biomarker testing, the guidelines included the following recommendations:

- When diagnostic uncertainty remains, the clinician can obtain additional (Tier 2–4) laboratory tests guided by the patient's individual medical, neuropsychiatric, and risk profile (Strength of Recommendation A).
- In a patient with an established cognitive–behavioral syndrome in whom there is continued diagnostic uncertainty regarding cause(s) after structural imaging with or without FDG PET, a dementia specialist can obtain CSF according to appropriate use criteria for analysis of amyloid beta (Aβ)42 and tau/phosphorylated tau (p-tau) profiles to evaluate for AD neuropathologic changes (Strength of Recommendation B).

Tier 3 laboratory tests include: CSF biomarker panel (Aβ42, tau, phospho-tau and ratios) (Rec. 17) *

Tier X laboratory tests include: Aβ, hyperphosphorylated tau

Subspecialty molecular biomarkers 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.

Tau PET is FDA approved but not yet widely available or reimbursed.

Tests listed in Tier 2–4 are representative of tests that could be ordered with increasing selectively based on an individual's clinical characteristics. Tier X are clinically emerging in specialist/subspecialist settings but may not be validated in diverse real-world.

Rating System for Strength of Recommendations

A: In almost all circumstances, adherence to the recommendation will improve outcomes.
B: In most circumstances, adherence to the recommendation will likely improve outcomes.

**Alzheimer's Association Workgroup (2024):** On behalf of the Workgroup, Jack et al. (2024) published an update to the 2018 criteria for diagnosis and staging of AD. The Workgroup notes the intent is to present objective criteria for diagnosis and staging AD, incorporating recent advances in biomarkers, to serve as a bridge between research and clinical care. These criteria are not intended to provide step-by-step clinical practice guidelines for clinical workflow or specific treatment protocols, but rather serve as general principles to inform diagnosis and staging of AD that reflect current science.

Highlights include:

- We define Alzheimer's disease (AD) to be a biological process that begins with the appearance of AD neuropathologic change (ADNPC) while people are asymptomatic.
- Early-changing Core 1 biomarkers (amyloid positron emission tomography [PET], approved cerebrospinal fluid biomarkers, and accurate plasma biomarkers [especially phosphorylated tau 217]) map onto either the amyloid beta or AD tauopathy pathway; however, these reflect the presence of ADNPC more generally (i.e., both neuritic plaques and tangles).
- An abnormal Core 1 biomarker result is sufficient to establish a diagnosis of AD and inform clinical decision making throughout the disease continuum.
- Later-changing Core 2 biomarkers (biofluid and tau PET) can provide prognostic information, and when abnormal, will increase confidence that AD is contributing to symptoms.

Alzheimer's disease (AD) is defined by its biology with the following implications:

- AD is defined by its unique neuropathologic findings; therefore, detection of AD neuropathologic change by biomarkers is equivalent to diagnosing the disease.
- AD exists on a continuum. The disease is first evident in vivo with the appearance of disease-specific Core biomarkers while people are asymptomatic
- Early-changing Core 1 biomarkers (amyloid positron emission tomography [PET], approved cerebrospinal fluid biomarkers, and accurate plasma biomarkers [especially phosphorylated tau 217]) map onto either the amyloid beta or AD tauopathy pathway; however, these reflect the presence of AD neuropathologic changes more generally (i.e., both neuritic plaques and tangles).
- An abnormal Core 1 biomarker (i.e., amyloid PET, CSF Aβ 42/40, CSF p-tau 181/Aβ42, CSF t-tau/Aβ42) result is sufficient to establish a diagnosis of AD and to inform clinical decision making throughout the disease continuum. Core biomarkers are noted as follows:

| Core 1 biomarkers | CSF or plasma analytes | Imaging |
|---|---|---|
| A (Aβ proteinopathy) | Aβ 42 | Amyloid PET |
| T1 (phosphorylated and secreted AD tau | p-tau217, ptau 181, p-tau 231 | |

- Later-changing Core 2 biomarkers (biofluid and tau PET) can provide prognostic information, and when abnormal, will increase confidence that AD is contributing to symptoms but most often would not be used as standalone diagnostic tests for AD
- Combinations of Core 1 biomarkers may also be used for diagnosis.
- Only biomarkers that have been proven to be accurate with respect to an accepted reference standard should be used for clinical diagnostic purposes, and the same criteria apply to PET, CSF, or blood-based biomarkers.
- We recommend, as a minimum requirement, an accuracy of 90% for the identification of moderate/frequent neuritic plaques at autopsy (or an approved surrogate, which, at this point, would be amyloid PET or CSF) in the intended-use population.
- For blood-based biomarker assays, this translates to an accuracy equivalent to that of approved CSF assays.
- P-tau205, MTBR-tau243, and non-phosphorylated tau fragments have not undergone the same level of validation testing as has tau PET.

**American Academy of Neurology ([AAN], 2018):** In an update of the AAN guideline on mild cognitive impairment Peterson et al. recommends the inclusion of patient cohorts with specific biomarker data in treatment studies targeted at specific pathologies (e.g., MCI due to AD). The Guidelines also recommends:

- For patients diagnosed with MCI, clinicians should counsel the patients and families that there are no pharmacologic or dietary agents currently shown to have symptomatic cognitive benefit in MCI and that no medications are FDA-approved for this purpose (Level B).
- For patients and families asking about biomarkers in MCI, clinicians should counsel that there are no accepted biomarkers available at this time (Level B).
- For interested patients, clinicians may discuss the option of biomarker research or refer patients, or both, if feasible, to centers or organizations that can connect patients to this research (e.g., subspecialty centers, Trial Match, ClinicalTrials.gov) (Level C)

**International Working Group ([IWG], 2024):** On behalf of the IWG, Dubois et al. updated recommendations related to AD as a clinical-biologic construct and published the following statements:

- Amyloid β and tau biomarkers are not sufficient to confidently predict progression to prodromal Alzheimer's disease or Alzheimer's disease dementia, or to define a person's position on the Alzheimer's disease continuum, without clinical input.
- The relationship between the coexistence of tau and amyloid β pathology on the one hand, and the development of cognitive decline and neurodegeneration on the other hand, remain uncertain at an individual level.
- Besides the dominant amyloid cascade model, additional models of pathogenesis in Alzheimer's disease include those highlighting the roles of endosomal recycling deficiency, immunity, lipid metabolism, endocytosis deficiency, and vascular dysfunction.

- Overall, evidence for the use of biomarkers in clinical practice remains highly disputed and suffers from a dearth of evidence-based data to recommend biomarker assessments for cognitively unimpaired individuals.

Investigators note there is an important overlap between Alzheimer's disease pathological changes in cognitively unimpaired individuals and in patients with Alzheimer's disease dementia. Also noted as a major limitation of a biological definition of AD is its low predictive accuracy and that the presence of both tau and amyloid β positivity is insufficient to definitively predict the occurrence of symptoms (mild cognitive impairment or dementia) in individuals without clinical impairment. In a review of cross-sectional data, highlights include:

Post-mortem

- Numerous cognitively unimpaired and impaired individuals have a similar burden of Alzheimer's disease brain lesions, confirmed with large post-mortem cohorts using quantification and digital neuropathological methods

- All stages of Alzheimer's disease brain lesions (including amyloid β and tau lesions) are found in two-thirds of individuals aged at least 70 years in systematic post-mortem examination, regardless of clinical status, which far exceeds the expected prevalence (30%)18 of cognitive impairment

- Neurofibrillary tangles in the medial temporal regions are found in almost all cognitively unimpaired people aged 70 years or older

Molecular neuroimaging cohorts

- Numerous cognitively healthy and cognitively impaired individuals have similar amyloid and tau PET burden

- Both amyloid and diffuse (ie, outside the medial temporal lobe) tau pathologies were found in 140 (24%) of 576 cognitively unimpaired older individuals (mean age 71 years).

**National Institute for Healthcare Excellence ([NICE], 2018):** In guidance related to the assessment, management for people living with dementia, NICE notes:

- Alzheimer's disease
    - If the diagnosis is uncertain (see recommendation 1.2.14) and Alzheimer's disease is suspected, consider either:
        - FDG-PET (fluorodeoxyglucose-positron emission tomography-CT), or perfusion SPECT (single-photon emission CT) if FDG-PET is unavailable or
        - examining cerebrospinal fluid for: either total tau or total tau and phosphorylated-tau 181 and either amyloid beta 1–42 or amyloid beta 1–42 and amyloid beta 1–40.
    - If a diagnosis cannot be made after one of these tests, consider using the other one.

- Be aware that the older a person is, the more likely they are to get a false positive with cerebrospinal fluid examination.

**National Institute on Aging ([NIA], 2023):** The NIA notes in clinical practice, CSF biomarkers may be used to help diagnose Alzheimer's or other types of dementia. In research, CSF

biomarkers are valuable tools for early detection of a neurodegenerative disease and to assess the impact of experimental medications.

The NIA also notes it is now possible for scientists and some doctors, dependent on state-specific availability reflecting U.S. Food and Drug Administration guidelines, to order a blood test to measure levels of beta-amyloid. Several other similar tests are in development. Still, the availability of these diagnostic tests is limited: They are more common in research settings where scientists use blood biomarkers to study early detection, prevention, and the effects of potential treatments.

## Medicare Coverage Determinations

| | Contractor | Determination Name/Number | Revision Effective Date |
|---|---|---|---|
| NCD | National | N/A | |
| LCD | | N/A | |

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

## Coding Information

**Notes:**

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Experimental/Investigational/Unproven:**

| CPT®* Codes | Description |
|---|---|
| 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 |
| 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 |
| 0445U | B-amyloid (Abeta42) and phospho tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology |
| 0459U | B-amyloid (Abeta42) and total tau (tTau), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology |
| 0479U | Tau, phosphorylated, pTau217 |

# EFFECTIVE 7/15/2025

| CPT®* Codes | Description |
|---|---|
| 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 |
| 0551U | Tau, phosphorylated, pTau217, by single-molecule array (ultrasensitive digital protein detection), using plasma |



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## Revision Details

| Type of Revision | Summary of Changes | Date |
|---|---|---|
| New | New policy-Beta-amyloid and P-tau biomarker testing for Alzheimer’s Disease | 7/2025 |

# EFFECTIVE 7/15/2025