MEDICAL POLICY

Medical Policy Title	**Lab Testing for Alzheimer's Disease**
Policy Number	**2.02.16**
Current Effective Date	October 15, 2025
Next Review Date	June 2026

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

Genetic Testing

Asymptomatic Individuals

I. Targeted genetic testing for a known familial variant in the presenilin (PSEN) genes or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease (EOAD) may be considered medically appropriate in an asymptomatic individual to determine future risk of disease when ANY of the following criteria are met:

   A. The individual has a close relative (i.e., first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease;

   B. The individual has a family history of dementia consistent with autosomal dominant Alzheimer disease, and the genetic status of the affected family members is unavailable;

   C. Results of testing will inform reproductive decision making.

Symptomatic Individuals

II. Targeted genetic testing for a known familial variant in the presenilin (PSEN) genes or amyloid-beta precursor protein (APP) may be considered medically appropriate in a symptomatic individual to determine future risk of disease when ANY of the following criteria are met:

   A. Patients with early onset Alzheimer's Disease (and other etiologies have been excluded);

   B. A family history of dementia or unknown family history;

   C. Autosomal dominant family history of dementia with one or more cases of EOAD;

   D. A relative with a pathological variant consistent with EOAD.

   E. Results of testing will inform reproductive decision making.

Apolipoprotein E (APOE) gene

III. Genetic testing for the apolipoprotein E (APOE) gene to guide initiation or management of a U.S. Food and Drug Administration-approved amyloid-beta targeting therapy is considered medically appropriate in individuals with mild cognitive impairment or mild dementia associated with Alzheimer disease.

Fluid Biomarker Testing

IV. CSF Biomarker testing is considered medically appropriate when ALL of the following criteria have been met:
    A. As part of the evaluation for the initiation of amyloid beta targeting therapy;
    B. Individuals with mild cognitive impairment or mild dementia due to Alzheimer's disease;
    C. Utilizing ONE of the following tests:
        1. Phospho-Tau (pTau181) and ß-Amyloid (1-42) assay, (Tau181/ Aβ42) (e.g., Elecsys Phospho-Tau);
        2. Total Tau (tTau) with Aβ42 assay, (tTau/Aβ42) (e.g., Elecsys Total Tau);
        3. ß-Amyloid Ratio (1-42/1-40) Test, (Aβ42/40) (e.g., Lumipulse G);
        4. pTau protein (e.g., ALZpath pTau217);

V. CSF Biomarker testing, including but not limited to amyloid beta, tau, or neural thread proteins (NTP) is considered investigational for EITHER of the following indications:
    A. As an adjunct to clinical diagnosis in individuals with mild cognitive impairment;
    B. As part of an evaluation for the continuation of amyloid beta targeting therapy;

VI. Biomarker testing for the diagnosis and/or assessment of Alzheimer disease using ANY of the following tests is considered investigational, including, but not limited to:
    A. Triggering receptor expressed on myeloid cells 2 (TREM2);
    B. MindX Memory Alzheimer test;
    C. Neural Thread Proteins (NTP);
    D. Urine biomarkers- (e.g., Urinary AD7c-NTP);
    E. PrecivityAD2 test;
    F. Elecsys Amyloid Plasma Panel Test;
    G. CSF testing for alpha-Synuclein (e.g., SYNTap biomarker test);
    H. Neurofilament Light Chain (NfL);
    I. Skin biopsy biomarkers (e.g., DISCERN).

RELATED POLICIES

Corporate Medical Policy

2.02.03 Genetic Testing for Inherited Disorders

6.01.07 Positron Emission Tomography (PET)- Non-Oncologic Applications

11.01.03 Experimental or Investigational Services

Pharmacy Policy

100 Anti-Amyloid Directed Therapies

POLICY GUIDELINE(S)

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Supporting documentation required:

   A. The following factors will be considered when determining the medical appropriateness of a genetic test:

      1. There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.

      2. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.

      3. The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).

      4. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.

      5. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any panel testing. If targeted testing has not been performed, rationale as to why panel testing is medically necessary should be documented.

V. In the appropriate use recommendations for Lecanemab it states that either elevated amyloid on PET or elevated phosphorylated tau and low Aβ42 level (increased p-tau/ Aβ42 ratio) in the CSF is required prior to initiating treatment with Lecanemab, currently blood based biomarkers are not a reliable and fully validates and are not considered adequate to identify appropriate patients for treatment. To guide safety and risk discussions, it is recommended that APOE genotyping

testing of all treatment candidates be completed before initiating therapy (Cummings et al., 2023).

In the prescribing information for LEQEMBI it suggests that testing should be performed prior to initiation of treatment to better determine the risk if ARIA. Stating that, individuals treated with LEQEMBI or other drugs in this class of medications who are ApoE ε4 homozygotes (two identical pairs of genes for a specific trait) have a higher incidence of amyloid related imaging abnormalities (ARIA).

VI. In the appropriate use criteria for Donanemab it states that biomarker confirmation of Aβ pathology by PET or CSF is required for patients to be eligible for treatment. To date, three CSF tests have been approved by the FDA for determination of amyloid status: Aβ42/Aβ40 ratio measured on the Lumipulse platform, and p-tau181/Aβ42 or total tau/Aβ42 ratios measured on the Elecsys platform (Rabinovici et al., 2025).

DESCRIPTION

Alzheimer's disease (AD) is the leading cause of dementia in the elderly, accounting for 50 to75% of all cases of dementia. AD can be associated with a family history (40% of patients with AD have at least one other afflicted first-degree relative) or idiopathic. More than 90% of AD occurs after age 65 years (late-onset AD) and is characterized by gradual onset and progressive and irreversible decline in cognitive function. There is also a less common early-onset form of AD, which appears before the age of 60 and is associated with a rapid decline and severe neurochemical and neuron-pathological changes. The estimated lifetime risk of AD in the general population is about 15%. Over 100 genes, particularly on chromosomes 9, 10, and 12 have been associated with late-onset AD, while mutations in chromosomes 1, 14, and 21 have been associated with early onset familial AD. Genetic testing has been investigated both in patients with probable AD and in asymptomatic family members.

Susceptibility Polymorphism at the Apolipoprotein E (APOE) Gene

The APOE lipoprotein gene is a carrier of cholesterol and is produced in the liver and brain glial cells. The APOE gene has three alleles - epsilon 2, 3, and 4 - with the epsilon 3 allele being the most common. Every person carries two APOE alleles. The presence of at least one epsilon 4 allele is associated with an increased risk of AD in the range of 1.2- to 3-fold, depending on the ethnic group. For those homozygous for epsilon 4 (about 2% of the population), the risk of AD is higher than for those heterozygous for epsilon 4. The mean age of onset of AD is about 68 years for epsilon 4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no epsilon 4 allele. It should be noted that the epsilon 4 allele represents a risk factor for AD rather than a disease-causing mutation.

Genetic Mutations

Patients with early-onset AD (e.g., before age 65 but as early as 30 years) are a small subset of patients. The families of these patients may show an autosomal dominant pattern of inheritance. Three genes have been identified by linkage analysis of affected families: amyloid-beta precursor protein (APP) gene, presenilin 1 (PS1) gene, and presenilin 2 (PS2) gene. These genes have nearly 100% penetrance, absent death from other causes; however, rare cases of lack of penetrance in

elderly individuals have been reported. A variety of mutations within these genes have been associated with AD; mutations in PS1 appear to be the most common. However, only 2% to 10% of all patients with AD have early onset AD, and genetic mutations have only been identified in 30% to 50% of these patients. Therefore, overall, identifiable genetic mutations are rare causes of AD.

Biomarker Tests

The Elecsys Amyloid Plasma Panel (Roche, a biotech company) measures phosphorylated Tau (pTau) 181 protein assay and apolipoprotein (APOE) E4 assay in human blood plasma. Positive results indicate the need for further confirmatory testing for AD. The panel test is intended to be used in conjunction with other clinical information in symptomatic patients who are being evaluated for AD and other causes of cognitive decline.

Roche also has Elecsys β-Amyloid (1-42) CSF and Elecsys Phospho-Tau (181P) CSF in vitro diagnostic immunoassays measuring β-Amyloid (1-42) and Phospho-Tau concentrations in CSF in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of dementia.

Lumipulse G β-Amyloid Ratio (1-42/1-40) immunoassay (Fujirebio Diagnostics, Inc.), the first in vitro diagnostic test for early detection of amyloid plaques with AD. The test uses CSF and is intended to be used in adult patients greater than or equal to 55 years, presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.

The Precivity mass-spec amyloid beta assay uses plasma and a proprietary mass spectrometry platform that combines quantitative measurement of amyloid beta 42 and 40 peptides in plasma along with apolipoprotein E prototype (equivalent to ApoE genotype) to calculate an individual's likelihood of amyloid plaques in the brain. The test is currently not intended to be used as a stand-alone diagnostic.

SUPPORTIVE LITERATURE

Ren et al. (2025) conducted a meta-analysis looking for the association of APOE ε4 status in AD patients. Included in the meta-analysis were, 22 eligible articles involving 571,800 cases published between 2001 and 2023. There was heterogeneity in the ability to APOE ε4 status to predict AD risk, they performed a sensitivity analysis to predict whether one study impacted the pooled hazard ratios; and the results did not change when a study was eliminated. They did conduct a subgroup analysis on the basis of region, study design, and cutoff method to investigate the source of the heterogeneity. There was not a reduction in the heterogeneity in the basis of region stratification and the study design. It remains unclear on of the source of heterogeneity, but this meta-analysis suggests that there is an increased risk of AD in individuals with different APOE ε4 statuses; future high quality, larger sample, randomized control trials are needed.

Safransky et al. (2024) conducted a retrospective study of brain donors from the national Alzheimer's Coordinating Center who had normal cognition at the time of the lumbar puncture, and CSF Aβ42 and p-tau181 performed with Lumipulse assays. The primary objective of the study investigated the association between CSF biomarkers and AD and AD neuropathologic changes among those brain donors. The National Institute on Aging-Alzheimer's Association criteria was used to stage ADNC.

Participants were divided into 2 categories: AD negative (no AD/low ADNC) and AD positive (intermediate /high ADNC). At autopsy confirmed AD in 20 (40.8%) individuals. The average span from LP until death was 7.76 years. CSF p-tau181/Aβ42 was the optimal predictor of AD, having excellent discrimination accuracy (AUC = 0.97), followed by CSF p-tau181 (AUC = 0.92), CSF Aβ42 alone (AUC = 0.92) and CSF t-tau having the lowest accuracy (AUC = 0.87). CSF p-tau181/Aβ42 was associated with the Consortium to Establish a Registry for Alzheimer's (CERAD)ratings of neuritic amyloid plaque scores, and Braak staging (refers to two methods used to classify the degrees of pathology in Parkinson's and Alzheimer's disease) of the neurofibrillary tangle (NFT's).

Schraen-Maschke et al. (2024) reported results from a subgroup (n=106) of the BALTAZAR study evaluating whether plasma levels of the free amyloid peptides Aβ1–42 and Aβ1–40 and the free plasma Aβ1–42/Aβ1–40 ratio is associated with the conversion of MCI to dementia over three years of follow-up total of 50 participants converted to dementia during follow-up. The risk of conversion was lower for participants in the highest quartile of free plasma Aβ1–42/ Aβ1–40 compared to those in the three lower quartiles. The risk of conversion in the highest quartile of total plasma Aβ1–42/Aβ1–40 compared to the lower quartiles was similar. The results show the relevance of the free plasma Aβ1–42/Aβ1–40 ratio for identifying MCI patients at lower risk of conversion to dementia (mainly AD) within three years. Using the threshold of 25.8% for the free plasma Aβ1–42/Aβ1–40 ratio, it was possible to identify MCI patients with an at least 60% lower risk of conversion to dementia. The performance of the free Aβ1–42/Aβ1–40 ratio in predicting conversion to dementia was similar to that of the total Aβ1–42/Aβ1–40 ratio. The study limitations were, the diagnosis of AD was only based on clinical and MRI; the results of the CSF biomarkers were not taken into consideration for the AD diagnosis; they excluded participants with Lewy Body, Parkinsonian, frontotemporal, or vascular dementia; and small sample size.

Bolsewig et al. (2024) conducted a cross-sectional multicenter cohort study with prospective component, it included individuals with dementia with Lewy bodies, Alzheimer's disease and healthy control. 562 Participants had annual follow up for 5 years. Plasma biomarkers were measured; amyloid status was determined by CSF Aβ42 concentrations and cognition evaluation by Mini-Mental State Examination (MMSE). Higher baseline glial fibrillary acidic protein (GFAP), neurofilament light (NfL), and phosphorylated-tau (P-tau) concentrations were associated with lower MMSE scores in DLB, and GFAP and NfL were associated with a faster cognitive decline. DLB participants with parkinsonism had higher concentrations of NfL (β = 0.08, 95% CI 0.02–0.14, p = 0.006) than those without. This study does suggest that the use of plasma biomarkers (Aβ42/40, P-tau181, and P-tau231) to assess amyloid copathology in DLB, and plasma GFAP and NfL as monitoring biomarkers for cognitive symptoms in DLB.

Krishna et al. (2024) reported results of a cross-sectional study of a single molecule array (Simoa) analysis of Aβ1–42, total tau (t-tau), phospho-tau (p-tau 181), and neurofilament L (NfL) in the plasma samples of AD patients (n=35), healthy controls (n=35), and non-AD (n=33) patients from a tertiary care center in India. The non-AD dementia patients included those with frontotemporal dementia (n=12), vascular dementia (n=5), Lewy body dementia (n=4), and mixed dementia (n=12). The cutoffs used for calculating sensitivity and specificity were unclear. A model including all 4 biomarkers had sensitivity of 94% and specificity of 96% for distinguishing AD versus healthy controls. The model including all 4 biomarkers had sensitivity of 40% and specificity of 93% for

distinguishing AD from non-AD dementia. Limitations included a small sample size, dissimilatory analysis between dementia types could not me assessed, supporting data from CSF measurements and neuroimaging of biomarkers regarding the diagnosis of AD or other dementias was lacking, and Aβ40 in plasma was not measured.

Van Dyck et al. (2023) conducted an 18-month multicenter, double blinded, phase 3 trial involving 1795 individuals with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron emission tomography (PET) or by cerebrospinal fluid (CSF) testing. Individuals were randomly assigned in a 1:1 ratio to receive intravenous lecanemab or a placebo. Primary endpoint was to see a change from the baseline at 18months in the score on the Clinical Dementia Rating. Secondary endpoint was to see a change on the PET imaging, and changes on other dementia evaluation tools. During the trial participants had the option of participating in sub studies that evaluated the longitudinal changes in brain amyloid burden as measured by PET, brain tau pathologic features as measured by PET, and CSF biomarkers of Alzheimer's disease. Amyloid-related imaging abnormalities-edema or effusion (ARIA-E) and amyloid-related imaging abnormalities-Hemorrhage (ARIA-H) were numerically less common among ApoE ε4 noncarriers than among carriers, with higher frequency among ApoE ε4 homozygotes than among ApoE ε4 heterozygotes.

Amft et al. (2022) conducted a retrospective study on 103 patients with known amyloid PET status. The study aimed to evaluate the performance of the amyloid beta (Aβ)42/40 ratio for predicting amyloid positivity by PET, compared with Aβ42 alone, and phosphorylated tau 181 (pTau181)/Aβ42 and total tau (tTau)/Aβ42 ratios, using the fully automated Elecsys CSF immunoassay test by Roche Diagnostics International Ltd. in patients with a range of cognitive disorders. Results for sensitivity and specificity of CSF biomarkers and biomarker ratios versus amyloid PET were 0.93 and 0.57 for Aβ42, 0.96 and 0.69 for pTau181/Aβ42, 0.92 and 0.69 for tTau/Aβ42, and 0.94 and 0.82 for Aβ42/40. For area under the curve point estimates (95% confidence intervals) versus amyloid PET were 0.78 (0.68−0.88) for Aβ42, 0.88 (0.81−0.95) for pTau181/Aβ42, 0.87 (0.80−0.95) for tTau/Aβ42, and 0.90 (0.83−0.97) for Aβ42/40. The study proved that Aβ42/40 ratio in detecting amyloid positivity by PET was higher than using Aβ42 alone and comparable with the performance of the pTau181/Aβ42 and tTau/Aβ42 ratios. Limitations of the study were, small sample size, use of a pre-analytical protocol not in accordance with the Elecsys CSF immunoassay method sheets, and the lack of a pre-defined cut-off for Aβ42/40.

Swanson et al. (2021) conducted a randomized double blinded clinical trial of 854 individuals with early Alzheimer's disease (AD), mild cognitive impairment due to AD and mild dementia. The study aimed to establish the simplest dose that achieves greater or equal to 90% of the maximum treatment effect. They were randomized to receive LEQEMBI or placebo, approximately 70% were ApoE4 carriers and 30% were ApoE4 non-carriers. The ApoE4 carriers were not randomized, as they were authorized to make sure that there were no ApoE4 carriers in the 10 mg/kg group. The incidence of ARIA-H on LEQEMBI was higher in ApoE4 carriers (13.1%) than in ApoE4 non-carriers (4.6%)

Fink et al. (2020) conducted a systematic review of biomarker accuracy for diagnosing neuropathologically defined AD in older patients with dementia. The analysis included literature

published between January 2012 and November 2019, with 9 cohort studies focusing on CSF biomarkers. Overall, CSF biomarkers and ratios had moderate sensitivity (range, 62% to 83%) and specificity (range, 53% to 69%). Biomarker accuracy was higher with amyloid beta-42/pTau ratio, tTau/amyloid beta-42 ratio, and pTau compared with tTau alone. The limitations were small study size, biomarker cut points and neuropathologic AD were inconsistently defined and methods with uncertain applicability to typical clinical settings were used.

Genetic testing for the APOE 4 allele in patients with late-onset AD and for APP, PS1, or PS2 mutations in the rare patient with early-onset AD has been investigated, as an aid in diagnosis of patients presenting with symptoms suggestive of AD, or as a technique for risk assessment in asymptomatic patients with a family history of AD.

PROFESSIONAL GUIDELINE(S)

The Joint Practice Guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors (Goldman et al., 2011; reaffirmed in 2018)

- Do not recommend pediatric testing for AD.
- Genetic testing for AD should only occur in the context of genetic counseling (in-person or through video conference) and support by someone with expertise in this area.
- Direct-to-consumer testing of APOE is not advised.
- At least a three-generation family history should be obtained, with specific information regarding diagnosis of AD in affected family members, along with age of onset and age of death.
- Testing for genes associated with early-onset autosomal dominant AD (EOAD) should be offered in the following situations:
    - Symptomatic patients with EOAD with a family history of dementia or unknown family history.
    - Autosomal dominant family history of dementia with one or more cases of EOAD.
    - A relative with a pathological variant consistent with EOAD.
- For families in which autosomal-dominant AD is unlikely:
    - Genetic testing for susceptibility loci (e.g., APOE) is not clinically recommended due to limited clinical utility.

National Institute for Health and Care Excellence 2018 guidelines on the assessment, management and support of people living with dementia state;

- APOE genotyping should not be used to diagnose Alzheimer disease.
- If the diagnosis is uncertain and Alzheimer's disease is suspected you may consider PET, or CSF testing 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

Jack et al. (2024) reported The National Institute of Aging and Alzheimer's Association, revised 2018

criteria for the diagnosis and staging of Alzheimer's disease. The workgroup divided biomarkers into three broad categories (below only addresses CSF or plasma samples).

Core biomarkers of AD neuropathologic change (ADNPC)

Core 1

- Aβ proteinopathy- Aβ 42
- phosphorylated and secreted AD tau- p-tau217, p-tau181, p-tau231.

Core 2

- AD tau proteinopathy- MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments.

Non-specific biomarkers that are important in AD pathogenesis but are also involved in other brain diseases

- Injury, dysfunction, or degeneration of neuropil- NfL
- Inflammation, Astrocytic activation- Glial Fibrillary Acidic Protein (GFAP)

Biomarkers of common non-AD copathologies

- α-synuclein- αSyn-SAA

They state:

"To date, clinical symptoms have not been used as the reference standard for regulatory approval of AD biomarkers. Our position is that AD is defined by its biology and therefore a biomarker that can accurately detect ADNPC or a validated surrogate is sufficient to establish the diagnosis of the disease."

"The clinical use of AD biomarkers is presently intended for the evaluation of symptomatic individuals, not cognitively unimpaired individuals. We highlight the distinction between can and should. AD can be diagnosed in asymptomatic individuals, but we do not believe this should be done for clinical purposes at this time".

"Although, the presence of abnormal Core 1 biomarkers is sufficient for confirming AD pathology in a symptomatic individual, it does not preclude the search for other contributors to the clinical symptoms, particularly other common copathologies."

"AD biomarkers are fundamental to making an accurate diagnosis and determining likely contributions to the patient's symptoms. Although it is expected that clinicians will use AD biomarkers to determine potential eligibility for recently approved Aβ-specific therapies, clinical applications also include counseling and tailoring medications for symptomatic treatment."

- The National Institute on Aging (NIA) In 2019, the NIA published a fact sheet noting that although a blood test can identify which APOE alleles a person has, it cannot predict who will or will not develop Alzheimer's disease. Per the NIA, it is unlikely that genetic testing will ever be able to predict the disease with 100% accuracy because too many other factors may influence its development and progression. Further, the NIA noted APOE testing is used in research settings

to identify study participants who may have an increased risk of developing Alzheimer's.

National Institute on Aging (NIA)/Alzheimer's Association (AA) issued consensus recommendations regarding the diagnosis of AD:

- For probable AD dementia in a carrier of a causative genetic mutation the recommendations note that in persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2), increases the certainty that the condition is caused by AD pathology. Carriage of the 3/4 allele of the apolipoprotein E gene is not sufficiently specific to be considered in this category (McKhann, et al., 2011).

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's and Related Disorders Association (ADRDA) developed clinical criteria for the diagnosis of AD in 1988, since then great advancements in understanding Alzheimer's Disease process have occurred. Dubois et al. (2007) researched criteria for the diagnosis of AD, revising the NINCDS-ADRDA criteria. The proposed criteria move away from the traditional two-step approach (degree of functional disability and specifying its cause), they aimed to define the clinical, biochemical, structural and metabolic presence of AD, their usefulness will be determined in future studies.

In 2018, the Alzheimer's Association published appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis or Alzheimer's disease. The recommendation is that "there should be an initial clinical diagnosis or differential diagnosis, followed by a determination of how the CSF biomarkers might contribute to the diagnosis and to the clinical decision making." They do discuss the need for further studies that include, long-term follow-up, comparing against pathological standards, effects on decision making, and elevated amyloid in cognitively normal individuals.

In 2022, the Alzheimer's Association appropriate use recommendations for blood-based biomarkers in Alzheimer's disease was published. They state that "blood-based markers (BBM)should not yet be used as a primary end point in pivotal trials" and "recommend to cautiously start using BBM's in specialized memory clinics as part of the diagnostic work-up of patients with cognitive symptoms and the results should be confirmed whenever possible with CSF or PET." More data is needed before BBMs are used as a stand-alone diagnostic test for AD or using in primary care.

REGULATORY STATUS

Refer to the FDA Medical Device website. Available from: https://www.fda.gov/medical-devices [accessed 2025 May 28]

In May of 2022, the U.S. Food and Drug Administration (FDA) permitted marketing for Lumipulse G β-Amyloid Ratio (1-42/1-40) immunoassay (Fujirebio Diagnostics, Inc.), The CSF fluid immunoassay was granted breakthrough device designation.

In July 2022, the FDA granted breakthrough device designation to the Elecsys Amyloid Plasma Panel (Roche). Roche has also received a Breakthrough Device Designation for the ElecsysR s-Amyloid (1-42) CSF and Elecsys Phospho-Tau (181P) CSF in vitro diagnostic immunoassays.

In November 2020, C2N Diagnostics gained CLIA certification for its Precivity mass-spec amyloid beta assay. This plasma test has received breakthrough device designation from the FDA for review as an

in-vitro diagnostic.

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. AlzheimAlert and AdMark CSF analysis are examples of tests that may be available in CLIA certified labs.

Additional diagnostic blood tests that have received FDA breakthrough device designation include AlzoSure Predict (Diadem) in January, 2022 and SOBA-AD (AltPep Corporation) in March 2022.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
81401	Molecular pathology procedure level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat). Includes APOE (apolipoprotein E) (e.g., hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (e.g., *2, *3, *4)
81405	Molecular pathology procedure level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis). Includes PSEN1 (presenilin 1) (e.g., Alzheimer's disease), full gene sequence
81406	Molecular pathology procedure level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons). Includes PSEN2 (presenilin 2 [Alzheimer's disease 4]) (e.g., Alzheimer's disease), full gene sequence and APP (amyloid beta [A4] precursor protein) (eg, Alzheimer's disease), full gene sequence
82172	Apolipoprotein, each
82233	Beta-amyloid; 1-40 (Abeta 40) (effective 01/01/2025)

Code	Description
82234	Beta-amyloid; 1-42 (Abeta 42) (effective 01/01/2025)
83884 (E/I)	Neurofilament light chain (NfL) (effective 01/01/2025)
84393	Tau, phosphorylated (e.g., pTau 181, pTau 217), each (effective 01/01/2025)
84394	Tau, total (tTau) (effective 01/01/2025)
0206U (E/I)	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease (DISCERN, NeuroDiagnostics)
0207U (E/I)	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) (DISCERN, NeuroDiagnostics)
0289U (E/I)	Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score (MindX Blood Test-Memory/Alzheimer's, MindX Sciences Laboratory)
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 G ß-Amyloid Ratio (1-42/1-40) Test, Fujirebio Diagnostics, Inc)
0361U (E/I)	Neurofilament light chain, digital immunoassay, plasma, quantitative (Neurofilament Light Chain (NfL), Mayo Clinic)
0393U (E/I)	Neurology (e.g., Parkinson disease, dementia with Lewy bodies), cerebrospinal fluid (CSF), detection of misfolded a-synuclein protein by seed amplification assay, qualitative

Code	Description
	(SYNTap Biomarker Test, Amprion Clinical Laboratory)
0412U (E/I)	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. (PrecivityAD blood test)
0443U (E/I)	Neurofilament light chain (NfL), ultra-sensitive immunoassay, serum or cerebrospinal fluid (Neurofilament Light Chain (NfL), Neuromuscular Clinical Laboratory at Washington University in St. Louis School of Medicine)
0445U	B-amyloid (Abeta42) and phospho tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology (Elecsys Phospho-Tau CSF [pTau181] and ß-Amyloid [1-42] CSF II [Abeta 42] Ratio, Roche Diagnostics Operations)
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 (tTau) and ß-Amyloid CSF II Ratio, Roche Diagnostics Operations, Inc) (effective 07/01/2024)
0479U	Tau, phosphorylated, pTau217 (ALZpath pTau217, Neurocode USA, Inc, Quanterix/ALZpath) (effective 10/01/2024)
0503U (E/I)	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 (PrecivityAD2, C2N Diagnostics, LLC) (effective 10/01/2024)
0568U (E/I)	Neurology (dementia), beta amyloid (AB40, AB42, AB42/40 ratio), tau-protein phosphorylated at residue (eg, pTau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP), by ultra-high sensitivity molecule array detection, plasma, algorithm reported as positive, intermediate, or negative for Alzheimer

Code	Description
	pathology (effective 07/01/25)

HCPCS Codes

Code	Description
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

ICD10 Codes

Code	Description
F03.90-F03.91	Unspecified dementia, unspecified severity, without behavioral disturbance, psychotic disturbance, mood disturbance, and anxiety
G30.0-G30.9	Alzheimer's Disease (code range)
G31.1	Senile degeneration of brain, not elsewhere classified
G31.84	Mild cognitive impairment of uncertain or unknown etiology
R41.81	Age-related cognitive decline

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Molecular Pathology Procedures (LCD L35000) [accessed 2025 Feb 10]

Article - Billing and Coding: Molecular Pathology Procedures (LCA A56199) [accessed 2025 Feb 10]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION

Committee Approval Dates

09/19/02, 07/17/03, 06/17/04, 06/16/05, 04/20/06, 02/15/07, 03/20/08, 05/28/09, 05/27/10, 05/19/11, 03/15/12, 03/21/13, 03/20/14, 03/19/15, 03/17/16, 03/16/17, 04/19/18, 05/16/19,

05/21/20, 05/20/21, 05/19/22, 05/18/23, 05/16/24, 06/26/25	
Date	**Summary of Changes**
06/26/25	• Annual Review, policy statements added for biomarkers for Alzheimer's disease as investigational. Codes added to policy 82233,82234,83884, 84393, 84394, 0206U, 0207U, 0358U, 0361U, 0393U, 0443U, 0445U, 0459U, 0479U, 0503U, 0568U and Deletion of code 0346U.
01/01/25	• Summary of changes tracking implemented.
12/20/01	• Original effective date