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MEDICAL POLICY – 2.04.521

Evaluation of Biomarkers for Alzheimer Disease

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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 biomarker testing as part of an evaluation for the initiation of amyloid beta targeting therapy	**Cerebrospinal fluid biomarker testing of amyloid beta peptides and tau protein 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 medically necessary (e.g., lecanemab-irmb [Leqembi], donanemab-azbt [Kisunla]). (See Related Policies)**

Test	Investigational
Biomarker testing of Alzheimer's disease	**Measurement of biochemical markers of Alzheimer's disease is considered investigational in any of the following:** • 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 • 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. • 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. • Measurement of plasma, and/or serum biomarkers of Alzheimer disease, including but not limited to, tau protein, amyloid beta peptides, neural thread proteins as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease **OR** • Measurement of urinary biomarkers of Alzheimer disease, including but not limited to, neural thread proteins, amyloid beta peptides, and urinary extracellular vesicle analysis as an

Test	Investigational
	adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease **OR** • 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 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)
0346U	Beta amyloid, AB40 and AB42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma (use to report: Quest AD-Detect, Beta-Amyloid 42/40 Ratio) (code terminated 1/01/25)
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)
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)

Code	Description
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 (new code effective 10/01/24)
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 (new code effective 10/01/24)
0547U	Neurofilament light chain (NfL), chemiluminescent enzyme immunoassay, plasma, quantitative (new code effective 04/01/25)
0551U	Tau, phosphorylated, pTau217, by single-molecule array (ultrasensitive digital protein detection), using plasma (new code effective 04/01/25)
0568U	Neurology (dementia), beta amyloid (AB40, AB42, AB42/40 ratio), tau-protein phosphorylated at residue (e.g., 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 pathology (new code effective 07/01/25)
81099	Unlisted urinalysis procedure (use to report: AlzheimAlert)
82233	Beta-amyloid; 1-40 (Abeta 40) (new code effective 01/01/25)
82234	Beta-amyloid; 1-42 (Abeta 42) (new code effective 01/01/25)
84393	Tau, phosphorylated (eg, pTau 181, pTau 217), each) (new code effective 01/01/25)
84394	Tau, total (tTau) (new code effective 01/01/25)
86849	Unlisted immunology procedure (use to report: Innotest, AlzoSure Predict)

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].'"

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 blood. Additionally, the potential correlation between CSF biomarkers and 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

The pathologic hallmarks of AD are extracellular deposits of amyloid beta, referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. 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.[5,6]

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.[7] 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.

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. No evidence of recent cognitive decline or new neurobehavioral symptoms.	Normal performance within expected range on objective cognitive tests. Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months). Mild neurobehavioral changes may coexist or may be the primary complaint rather than cognitive. No functional impact on daily life activities.	Performance in the impaired/abnormal range on objective cognitive tests. Evidence of decline from baseline. Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life	Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Clearly evident functional impact on daily life, affecting mainly instrumental activities. No longer fully independent/requires occasional assistance with daily life activities.	Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities.	Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible. Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

Adapted from Table 6, Jack et al (2018)[8]

[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.[9] Other potential CSF[10,11], urinary, and blood[12], peptide markers have been explored. 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.[13] Neurogranin is a dendritic protein and CSF measurement may serve as a biomarker for dendritic instability and synaptic degeneration.[9] 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.[14,15] 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 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.[9] 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.[16] 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 pTau has shown analytical validity and initial evidence of clinical validity, whereas the maturity level for amyloid beta remains to be partially achieved.[17]

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 CSF biomarker testing for 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 urinary 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 blood biomarker testing for AD, the evidence includes a systematic review 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 the biomarker, plasma pTau, and have shown that this biomarker may be beneficial in screening for and diagnosing AD. 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, the evidence includes randomized controlled trials, multisite longitudinal studies, and an analysis of a mixed cohort. These studies assess the correlation between CSF biomarkers and PET amyloid scans and the clinical utility of amyloid PET or 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 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 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			
NCT05020106	Study on the Diagnostic Cut-off Value for Core Biomarkers in Cerebrospinal Fluid and Blood of Alzheimer's Disease	3200	Sep 2025 (recruiting)
NCT02612376	Rocky Mountain Alzheimer's Disease Center at the University of Colorado School of Medicine (RMADC at UCSOM) Longitudinal Biomarker and Clinical Phenotyping Study	800	Jan 2025 (recruiting)
NCT04575337	Study on Body Fluid, Gene and Neuroimaging Biomarkers for Early Diagnosis of Alzheimer's Disease	6000	Jun 2025 (recruiting)
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)

NCT: national clinical 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:[20]

"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."[20] 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."[20]

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."[22] 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.[56]

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.[57] 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.[56] **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.[59]

Table 3. Indications for Appropriate Use of Lumbar Puncture and CSF Testing in Diagnosing AD

Appropriate Indications	Inappropriate Indications
• Patients with SCD who are considered at increased risk for AD • MCI that is persistent, progressing, and unexplained • Patients with symptoms that suggest possible AD • MCI or dementia with an onset at an early age (<65 y) • Meeting core clinical criteria for probable AD with typical age of onset • Patients whose dominant symptom is a change in behavior and where AD diagnosis is being considered	• Cognitively unimpaired and within normal range functioning for age as established by objective testing; no conditions suggesting high risk and no SCD or expressed concern about developing AD • Cognitively unimpaired patient based on objective testing, but considered by patient, family informant, and/or clinician to be at risk for AD based on family history • Patients with SCD who are not considered to be at increased risk for AD • Use to determine disease severity in patients having already received a diagnosis of AD • Individuals who are apolipoprotein E (APOE) ε4 carriers with no cognitive impairment • Use of lumbar puncture in lieu of genotyping for suspected ADAD mutation carriers • ADAD mutation carriers, with or without symptoms

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

In 2022, the Alzheimer's Association Global Workgroup released appropriate use recommendations for blood biomarkers in AD.[60] 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.

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.[61] 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.[62] 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.

The FDA has cleared AD biomarker tests for marketing via the De Novo and 510(k) pathways with product code QSE, see **Table 4**.

Table 4. FDA Cleared Biomarker Tests for Alzheimer Disease

Test	Manufacturer	Location	Date Cleared	De Novo or 510(k) Number	Indication(s)
Lumipulse G Amyloid Ratio (1-42/1-40)	Fujirebio Diagnostics, Inc	Malvern, PA	May 2022	DEN200072	CSF test Intended to be used in adult patients, aged 55 years and older, presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. A test result ≥0.073 is a negative result which is consistent with a negative amyloid PET scan result. A negative result reduces the likelihood that a patient's

Test	Manufacturer	Location	Date Cleared	De Novo or 510(k) Number	Indication(s)
					cognitive impairment is due to AD. A test result ≤0.058 is a positive result which is consistent with a positive amyloid PET scan result. A positive result does not establish a diagnosis of AD or other cognitive disorder. A test result between 0.059 and 0.072 is considered as a likely positive result as it is more likely consistent with a positive amyloid PET scan result. A likely positive result does not establish a diagnosis of AD or other cognitive disorders and has increased uncertainty in regard to amyloid PET positivity. The Lumipulse G P-Amyloid Ratio (1-42/ 1-40) results must be interpreted in conjunction with other patient clinical information. This test is not intended as a screening or stand-alone diagnostic test.
Elecsys B-Amyloid (1-42)	Roche Diagnostics	Indianapolis, IN	December 2022	K221842	CSF test

Test	Manufacturer	Location	Date Cleared	De Novo or 510(k) Number	Indication(s)
CSF II, Elecsys Phospho-Tau (181P) CSF					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 pTau181/Abeta42 ratio value. The adjusted ratio cutoff is 0.023. 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. 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. The pTau181/Abeta42 ratio result is used as an adjunct to other clinical diagnostic evaluations. The performance of the pTau181/Abeta42 ratio has not been established for predicting development of

Test	Manufacturer	Location	Date Cleared	De Novo or 510(k) Number	Indication(s)
					dementia or other neurologic conditions or monitoring responses to therapies
Elecsys ß-Amyloid (1-42) CSF II, Elecsys Total-Tau CSF	Roche Diagnostics	Indianapolis, IN	June 2023	K231348	CSF test Intended to be used in adult patients, aged 55 years and older, being evaluated for AD and other causes of cognitive impairment to generate a tTau/Abeta42 ratio value. The numerical ratio must be compared to the cutoff of 0.28. A negative result, defined as tTau/Abeta42 ratio value below cutoff or an Abeta42 value above the measuring range, is consistent with a negative amyloid PET scan result. A negative result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive result, defined as tTau/Abeta42 ratio value above cutoff, is consistent with a positive amyloid PET scan result. A positive result does not establish a diagnosis of AD or other cognitive disorder. The tTau/Abeta42 ratio result is used as an

Test	Manufacturer	Location	Date Cleared	De Novo or 510(k) Number	Indication(s)
					adjunct to other clinical diagnostic evaluations. The performance of the tTau/Abeta42 ratio has not been established for predicting development of dementia or other neurologic conditions or monitoring responses to therapies.

AD: Alzheimer disease; CSF: cerebral spinal fluid; FDA: Food and Drug Administration; PET: positron emission tomography.

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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; 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 CPT code 0568U following Q3 coding updates.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.