MASSACHUSETTS

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Medical Policy

Evaluation of Biomarkers for Alzheimer Disease

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Policy Number: 581

BCBSA Reference Number: 2.04.14 (For Plan internal use only)
NCD/LCD: N/A

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Diagnosis

Cerebrospinal fluid biomarkers 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 is considered **INVESTIGATIONAL**.

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 dementia due to Alzheimer disease is considered **INVESTIGATIONAL**.

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** (see policy guidelines).

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**.

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**.

Measurement of urinary and blood biomarkers as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **INVESTIGATIONAL**.

Policy Guidelines
The labels for FDA-approved, amyloid beta targeting therapies, LEQEMBI® (lecanemab) and Kisunla™ (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]."

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue℠	Prior authorization is **not required**.
Medicare PPO Blue℠	Prior authorization is **not required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT codes:	Code 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
0445U	βamyloid (Abeta42) and Phospho Tau (181P) (pTau181), electrochemiluminescence immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
0459U	β-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

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:

ICD-10-CM Diagnosis codes:	Code Description
F01.A11	Vascular dementia, mild, with agitation
F01.A18	Vascular dementia, mild, with other behavioral disturbance
F01.A2	Vascular dementia, mild, with psychotic disturbance
F01.A3	Vascular dementia, mild, with mood disturbance
F01.A4	Vascular dementia, mild, with anxiety
F03.A0	Unspecified dementia, mild, without behavioral disturbance, psychotic disturbance, mood disturbance, and anxiety
F03.A11	Unspecified dementia, mild, with agitation
F03.A18	Unspecified dementia, mild, with other behavioral disturbance
F03.A2	Unspecified dementia, mild, with psychotic disturbance
F03.A3	Unspecified dementia, mild, with mood disturbance
F03.A4	Unspecified dementia, mild, with anxiety
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset
G30.8	Other Alzheimer's disease
G30.9	Alzheimer's disease, unspecified
G31.84	Mild cognitive impairment of uncertain or unknown etiology
R41.81	Age-related cognitive decline

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
0361U	Neurofilament light chain, digital immunoassay, plasma, quantitative
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
0443U	Neurofilament light chain (NfL), ultra-sensitive immunoassay , serum or cerebrospinal fluid
0503U	Neurology (Alzheimer disease), beta amyloid (A1340, A1342, A1342/40 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

Description

Alzheimer Disease

Alzheimer Disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 12 million by 2050.[1] Per the 2018 American Academy of Neurology practice guideline update

on mild cognitive impairment (MCI), the prevalence of MCI was 6.7% for ages 60 to 64, 8.4% for ages 65 to 69, 10.1% for ages 70 to 74, 14.8% for ages 75 to 79, and 25.2% for ages 80 to 84.[2] The cumulative dementia incidence was 14.9% in individuals with MCI >65 years of age followed for 2 years.
Data from the National Institute on Aging have shown that Black Americans are approximately 1.5 to 2 times more likely to develop AD and related dementias as compared to Whites.[3] Additionally, Black participants in AD research studies were 35% less likely to be diagnosed with AD and related dementias and were found to have more risk factors for the disease as well as greater cognitive impairment and symptom severity than White participants. Findings from 2 national surveys conducted by the Alzheimer's Association also found that people of color face discrimination when seeking health care for AD and related dementias with the highest level of discrimination in dementia health care reported by Black Americans (50%) followed by Native (42%), Asian (34%), and Hispanic (33%) Americans.[4] Non-Hispanic White Americans reported a discrimination rate of 9%.

Pathophysiology
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	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Severity	Pre-clinical	Pre-clinical	MCI due to Alzheimer disease	Mild Dementia	Moderate Dementia	Severe Dementia
Clinical Features	Performance within expected range on objective cognitive tests. No evidence of recent cognitive decline or new neurobeh	Normal performance within expected range on objective cognitive tests. Transitional cognitive decline (change from individual baseline within past 1 to 3	Performance in the impaired/abnormal range on objective cognitive tests. Evidence of decline from baseline. Performs daily life activities independently, but cognitive difficulty may	Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Clearly evident functional impact on	Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities.	Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible. Complete dependency due to

	avioral symptoms	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.	result in detectable but mild functional impact on the more complex activities of daily life.	daily life, affecting mainly instrumental activities. No longer fully independent /requires occasional assistance with daily life activities.	No longer independent and requires frequent assistance with daily life activities.	severe functional impact on daily life with impairment in basic activities, including basic self-care.

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

[a]Applicable only to individuals in the Alzheimer continuum that fall into 1 of the 4 biomarker groups: 1) A+T+N+ 2) A+T-N- 3) A+T+N- 4) A+T-N+ where A: Aggregated Aβ or associated pathologic state (CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio or Amyloid PET), T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau or Tau PET) and N: Neurodegeneration or neuronal injury (anatomic MRI, FDG PET or CSF total tau)
For stages 1 to 6: Cognitive test performance may be compared to normative data of the investigator's choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.
For stages 2 to 6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.
For stages 3 to 6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.
CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

Biomarkers
Several potential biomarkers of AD are associated with AD pathophysiology (eg, amyloid beta plaques, neurofibrillary tangles). Altered cerebrospinal fluid (CSF) levels of specific proteins have been found in patients 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]

Summary

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 patients for the initiation or discontinuation of amyloid beta plaque targeted therapy.

Summary of Evidence

For individuals who have mild cognitive impairment (MCI) or dementia who receive cerebrospinal fluid (CSF) biomarker testing for Alzheimer disease (AD), the evidence includes systematic reviews. These studies assess using CSF biomarkers for diagnosis of AD or for the prognosis of progression of MCI to AD. Relevant outcomes include test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life (QOL). Most clinical validity studies have been derived from select patient 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 both the correlation between CSF biomarkers and positron emission tomography (PET) amyloid scans and the clinical utility of amyloid PET or CSF biomarkers in cognitively impaired patients 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 patients 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 patients who met appropriate use criteria for clinical amyloid PET. Relevant outcomes include test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. The diagnostic accuracy of CSF biomarkers versus amyloid beta PET scans to identify MCI-AD was found to be similar. Further research is required to determine whether the use of CSF biomarkers alone in conjunction with amyloid beta PET scans is useful for determining whether or not amyloid beta targeting therapy should be continued. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Policy History

Date	Action
4/2025	Clarified coding information.
3/2025	Annual policy review. Policy updated with literature review through May 15, 2024; references added. Clinical input added. Policy statements changed to medically necessary specifically for indication related to use of CSF biomarkers to select individuals for treatment with FDA-approved amyloid targeting therapies. Other policy statements remain investigational. Effective 3/1/2025.
1/2025	Clarified coding information.
10/2024	Clarified coding information.
7/2024	Clarified coding information.
4/2024	Clarified coding information.
10/2023	Clarified coding information.
12/2022	Annual policy review. The policy statement was updated to further clarify biomarker testing in patients with mild cognitive impairment or dementia due to Alzheimer disease is investigational.
12/2021	Annual policy review. Additional evidence review added for use of CSF biomarkers in the management of MCI or mild dementia due to AD who are being evaluated for the initiation or continuation of amyloid beta targeting therapy. These indications are considered investigational.
2/2021	Annual policy review. Edits made to the second policy statement; intent of policy statements unchanged. Title changed to "Evaluation of Biomarkers for Alzheimer Disease."
1/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
2/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
3/2018	Annual policy review. New references added.
2/2017	Annual policy review. Title changed to “Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease.” New references added. 2/1/2017
10/2014	Annual policy review. New references added.
3/2014	New medical policy describing ongoing investigational indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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