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 BlueSM and Medicare PPO BlueSM Members

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.

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 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.

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.

<table>
<thead>
<tr>
<th>Product</th>
<th>Coverage Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>This is not a covered service.</td>
</tr>
</tbody>
</table>

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.

CPT Codes

There are no specific CPT codes for this testing.

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.\textsuperscript{3,4}

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.\textsuperscript{5} 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
<th>Stage 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Pre-clinical</td>
<td>Pre-clinical</td>
<td>MCI due to Alzheimer disease</td>
<td>Mild Dementia</td>
<td>Moderate Dementia</td>
<td>Severe Dementia</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Performance within expected range on objective cognitive tests. No evidence of recent cognitive decline or new neurobehavioral symptoms</td>
<td>Normal performance within expected range on objective cognitive tests.</td>
<td>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.</td>
<td>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.</td>
<td>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.</td>
<td>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.</td>
</tr>
</tbody>
</table>

Adapted from Table 6, Jack et al (2018)\textsuperscript{5}
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 Aβ42, or Aβ42/Aβ40 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. Other potential CSF, urinary, and blood 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. Neurogranin is a dendritic protein and CSF measurement may serve as a biomarker for dendritic instability and synaptic degeneration. 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. 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. 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. 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.

Summary
Biochemical changes associated with the pathophysiology of Alzheimer disease (AD) are being evaluated to aid in the diagnosis of AD. 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 may assist 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 Alzheimer disease (AD) 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 diagnosis 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 AD 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 AD 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 considered for initial treatment with an approved amyloid beta plaque targeting therapy, 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. Overall, the diagnostic accuracy of CSF biomarkers versus amyloid PET scans to identify MCI-AD was found to be similar but there are no data to support the clinical utility of CSF biomarker use as a component of determining appropriate initiation of amyloid beta targeting therapy. Prior to the availability of amyloid beta targeting therapy, additional data exist suggesting that amyloid beta PET scan results impacted diagnosis of dementias and patient management including use of symptomatic treatment. Further research is required to determine whether use of CSF biomarkers alone or in conjunction with amyloid PET scans is associated with improved clinical outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or mild dementia due to AD who are being treated with an amyloid beta plaque targeting therapy and are being evaluated for therapy continuation, the evidence includes multisite longitudinal studies and an analysis of a mixed cohort. Two of these studies assess the correlation between CSF biomarkers and PET amyloid scans and another assesses the clinical utility of amyloid PET in cognitively impaired 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. Prior to the availability of amyloid beta targeting therapy, additional data exist suggesting that amyloid beta PET scan results impacted diagnosis of dementias and
patient management including use of symptomatic treatment. Further research is required to determine whether use of CSF biomarkers alone in conjunction with amyloid beta PET scans are 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

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/2022</td>
<td>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.</td>
</tr>
<tr>
<td>12/2021</td>
<td>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.</td>
</tr>
<tr>
<td>2/2021</td>
<td>Annual policy review. Edits made to the second policy statement; intent of policy statements unchanged. Title changed to “Evaluation of Biomarkers for Alzheimer Disease.”</td>
</tr>
<tr>
<td>1/2020</td>
<td>Annual policy review. Description, summary, and references updated. Policy statements unchanged.</td>
</tr>
<tr>
<td>2/2017</td>
<td>Annual policy review. Title changed to “Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease.” New references added. 2/1/2017</td>
</tr>
<tr>
<td>10/2014</td>
<td>Annual policy review. New references added.</td>
</tr>
</tbody>
</table>

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

References


