Medical Coverage Policy | Evaluation of Biomarkers for Alzheimer Disease

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OVERVIEW

Biochemical changes associated with the pathophysiology of Alzheimer disease (AD) are being evaluated to aid in the diagnosis of AD. Some of the most commonly studied biomarkers are amyloid-β peptide 1-42 and total or phosphorylated tau protein in cerebrospinal fluid (CSF), urine and blood.   This policy documents whether testing cerebrospinal fluid and urinary biomarkers improves outcomes in individuals with mild cognitive impairment or Alzheimer disease

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products, as the evidence is insufficient to determine the effects of the technology on health outcomes for the following indications:

- as an adjunct to clinical diagnosis in individuals with mild cognitive impairment
- as an adjunct to clinical diagnosis in individuals with mild dementia due to Alzheimer disease
- 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
- 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 urinary and blood biomarkers as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for not medically necessary/not covered services.

BACKGROUND

The diagnosis of Alzheimer disease (AD) is divided into 3 categories: possible, probable, and definite AD. A diagnosis of possible AD is made when the patient meets core clinical criteria for AD but has an atypical course or an etiologically mixed presentation. Probable AD is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. A typical clinical course is defined as an insidious onset, with the initial and most prominent cognitive deficits being either amnestic or non-amnestic (eg, language, visuospatial, or executive function deficits), and a progressively worsening cognition over time. A diagnosis of definite AD requires postmortem confirmation of AD pathology, including the presence of extracellular β-amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex.[7]

Mild cognitive impairment (MCI) may be diagnosed when a dementia diagnosis cannot be made yet there is a significant change in cognition.[6] MCI is characterized by impairment in 1 or more cognitive domains yet there remains preserved functional independence. In some patients, MCI may be a predementia phase of AD. Patients with MCI or suspected AD may undergo ancillary testing (eg, neuroimaging, laboratory tests, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. Because clinical diagnosis can be difficult, particularly early in the course of the disease, there has been considerable interest in developing an accurate laboratory test for AD.

Biomarkers
Several potential biomarkers of Alzheimer disease (AD) are associated with AD pathophysiology (eg, β-amyloid plaques, neurofibrillary tangles). Elevated 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, or an amyloid-β peptide such as 1-42 (Aβ42). Other potential CSF[1,2] and serum[3] 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. Aβ42 is a subtype of amyloid-β peptide produced from the metabolism of the amyloid precursor protein. Aβ42 is the key peptide deposited in amyloid plaques characteristic of AD. Low levels of Aβ42 in the CSF have been associated with AD, perhaps because Aβ42 is deposited in amyloid plaques instead of remaining in the fluid. Investigators have suggested the tau/Aβ42 ratio may be a more accurate diagnostic marker than either alone.[4] A variety of kits are commercially available to measure Aβ42 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.

For individuals who have AD or mild cognitive impairment (MCI) who receive cerebrospinal fluid (CSF) biomarker testing for AD, the evidence includes systematic reviews and prospective and retrospective studies. These studies assess using CSF biomarkers for diagnosis of AD or for the prognosis of progression of MCI to AD. Relevant outcomes include diagnosis accuracy, 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 outcomes.

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 AD or MCI who receive urinary biomarker testing for AD, the evidence includes a systematic review and prospective and retrospective studies. Relevant outcomes include diagnosis accuracy, 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 outcomes.

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

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 U.S. Food and Drug Administration (FDA) for review as an in-vitro diagnostic. The test uses a proprietary mass spectrometry platform that combines quantitative measurement of amyloid beta 42 and 40 peptides in plasma along with apolipoprotein E proteotype (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.

In May 2022, the FDA permitted marketing for the first in vitro diagnostic test for early detection of amyloid plaques with AD. The cerebrospinal fluid immunoassay was granted breakthrough device designation and was reviewed through the De Novo premarket review pathway. The Lumipulse G ß-Amyloid Ratio (1-42/1-40) immunoassay (Fujirebio Diagnostics, Inc.) is intended to be used in adult patients, ≥ 55 years, presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. A positive test result is consistent with the presence of amyloid plaques, similar to what would be seen in a PET scan.

In July 2022, the FDA granted breakthrough device designation to the Elecsys Amyloid Plasma Panel (Roche). The Elecsys Amyloid Plasma Panel 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 has also received a Breakthrough Device Designation for the Elecsys® ß-Amyloid (1-42) CSF and Elecsys® Phospho-Tau (181P) CSF in vitro diagnostic immunoassays measuring ß-Amyloid (1-42) and Phospho-Tau concentrations in cerebrospinal fluid (CSF) in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of dementia.

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.

CODING
Medicare Advantage Plans and Commercial Products
There are no specific code(s) for the tests referenced in this policy. The following CPT code(s), when filed with one of the ICD-10 Diagnosis Code(s)* listed below, are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

The following CPT code may be used to test urine:
81099   Unlisted Urinalysis Procedure

The following CPT code may be used to test cerebrospinal fluid:
86849   Unlisted Immunology Procedure

The following CPT code(s) may be used to report testing for tau protein and amyloid-β peptides:
83520   Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

*ICD-10 Diagnosis Code(s)
F03.90-F03.91 Unspecified dementia

G30.0-G30.9   Alzheimer 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

RELATED POLICIES
Unlisted Procedures

PUBLISHED
Provider Update, January 2023
Provider Update, April 2021
Provider Update, January 2020
Provider Update, November/December 2018
Provider Update, June 2017

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