BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.14 Evaluation of Biomarkers for Alzheimer Disease

Effective Policy Date: January 1, 2023

Original Policy Date: June 2012

Related Policies:

6.01.55 - Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease

Evaluation of Biomarkers for Alzheimer Disease

Description

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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.

OBJECTIVE

The objective of this evidence review is to examine whether testing cerebrospinal fluid (CSF), urinary, and blood biomarkers improves the net health outcome in individuals with mild cognitive impairment or Alzheimer disease, with an additional focus on the correlation between CSF biomarkers and positron emission tomography (PET) amyloid scans in selecting patients for, and maintaining patients on, amyloid beta plaque targeted therapy.

POLICY STATEMENT

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 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.**

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

None.

FDA 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 - 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 -Amyloid (1-42) CSF and Elecsys Phospho-Tau (181P) CSF in vitro diagnostic immunoassays measuring -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.

RATIONALE

Summary of Evidence

For individuals who have mild cognitive impairment (MCI) or Alzheimer disease (AD) who receive cerebrospinal fluid (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 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 being 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 positron emission tomography (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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or 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:[40,]

"Meets criteria for dementia...and in addition has the following characteristics:

1. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
2. Clear-cut history of worsening of cognition by report or observation; and
3. The initial and most prominent cognitive deficits are evident on history and examination in 1 of the following categories.
    1. 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 1 other cognitive domain, as defined earlier in the text.
    2. 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.
4. The diagnosis of probable AD dementia should not be applied when there is evidence of:
    1. 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
    2. Core features of dementia with Lewy bodies other than dementia itself; or
    3. Prominent features of behavioral variant frontotemporal dementia; or
    4. Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or
    5. 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:

A. 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

B. 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 evidence review are in a category among the 2011 revisions to AD diagnostic criteria, "probable AD dementia with evidence of the AD pathophysiological process."[40,] 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 patients; 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 1 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 3 circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician."[40,]

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."[19,] In 2012, the Alzheimer's Biomarkers Standardization Initiative published consensus recommendations for standardization of preanalytical aspects (eg, fasting, tube types, centrifugation, storage time, temperature) of CSF biomarker testing.[47,]

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.[48,] 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 (eg, 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.[49,] Table 1 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.[50,]

Table 1. Indications for Appropriate Use of Lumbar Puncture and CSF Testing in Diagnosing AD

Appropriate 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
Inappropriate Indications
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.[51,] 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 patients 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.[52,] 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.

U.S. Preventive Services Task Force Recommendations

In 2020, the U.S. 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.[53,] 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. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2012	New policy	
December 2013	Replace policy	Policy updated with literature search; references 2, 3, 7, 12, 28, 31, 34-35, and 44 added; policy statements unchanged.
December 2014	Replace policy	Policy updated with literature review; references 5, 7, 12, 14- 15, 21, 24-25, 28, 44-45, 48, 53-54, and 56 added; references 1-2 and 57 updated; references 42, 44 deleted. No change to policy statement.
December 2015	Replace policy	Policy updated with literature review through July 30, 2015; no references added. Policy statements unchanged.
March 2018	Replace policy	Policy updated with literature review through November 17, 2017; references 9-12, 20, 23, 24, 26, 27, and 35 added. References to individual studies that were included in metanalyses were removed. Policy statements unchanged. Title changed to "Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease€ .
March 2019	Replace policy	Policy updated with literature review through October 18, 2018; references 26, 28-30, and 34 added. Policy statements unchanged.
March 2020	Replace policy	Policy updated with literature review through October 14, 2019; references added. Policy statements unchanged.
December 2020	Replace policy	Policy updated with literature review through October 21, 2020; references added. Edits made to the second policy statement; intent of policy statements unchanged. Title changed to "Evaluation of Biomarkers for Alzheimer Disease" to accommodate 2 PLA codes effective 10/1/2020.
December 2021	Replace policy	Policy updated with literature review through September 11, 2021; references added. 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.
December 2022	Replace policy	Policy updated with literature review through August 24, 2022; references added. Additional PICO and evidence review added for use of blood biomarker testing in patients with mild cognitive impairment or dementia due to Alzheimer disease. The policy statement was revised to further clarify that this indication is considered investigational.