FEP 2.04.14 Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease

Description
Biochemical changes associated with the pathophysiology of Alzheimer disease (AD) are being evaluated to aid in the diagnosis of AD. Some common biomarkers studied are amyloid-b peptide 1-42 and total or phosphorylated tau protein in cerebrospinal fluid.

OBJECTIVE
The objective of this evidence review is to examine whether testing cerebrospinal fluid and urinary biomarkers improves the net health outcome in individuals with mild cognitive impairment or Alzheimer disease.

POLICY STATEMENT
Measurement of cerebrospinal fluid biomarkers of Alzheimer disease, including but not limited to tau protein, amyloid-β peptides, or neural thread proteins, is considered investigational.

Measurement of urinary biomarkers of Alzheimer disease is considered investigational, including but not limited to neural thread proteins.

BENEFIT APPLICATION
Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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

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. AlzheimAlert™ and AdMark® CSF analysis are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests...
FEP 2.04.14 Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease

must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence
For individuals who have AD or mild cognitive impairment who receive cerebrospinal fluid biomarker testing for AD, the evidence includes systematic reviews, meta-analyses, and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and resource utilization. The technical reliability of cerebrospinal fluid biomarker measurement in AD is limited by variability between laboratories and assay methods. 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 mild cognitive impairment to AD, limited evidence has suggested that testing may define increased risk. Whether an earlier diagnosis leads to improved health outcomes through delay of AD onset due to medical therapy or other interventions or improved quality of life is unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have AD or mild cognitive impairment who receive urinary biomarker testing for AD, the evidence includes a systematic review and observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and resource utilization. Limited data are available on the technical reliability of urinary biomarker measurement in AD. 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 delay of AD onset or improved quality of life is unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Institute of Neurological and Communicative Disorders et al

1984 Diagnostic Criteria

In 1984, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer Disease and Related Disorders Association (ADRDA) developed clinical criteria for the diagnosis of Alzheimer disease (AD). Although research to date continues to use the NINCDS-ADRDA’s AD classification, in 2011, the National Institute on Aging and the Alzheimer’s Association revised the diagnostic criteria for dementia due to AD.

In the 1984 guidelines, the diagnostic categories were defined as summarized in Table 1.
Table 1. The 1984 Diagnostic Categories for Alzheimer Disease

<table>
<thead>
<tr>
<th>Diagnostic Categories for AD</th>
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<tbody>
<tr>
<td><strong>Possible</strong></td>
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<tr>
<td>Clinical diagnosis of possible AD:</td>
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<tr>
<td>A. May be made on the basis of the dementia syndrome in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, the presentation, or the clinical course.</td>
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<tr>
<td>B. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.</td>
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<tr>
<td>C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.</td>
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<tr>
<td><strong>Probable</strong></td>
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<tr>
<td>Criteria for the clinical diagnosis of probable AD included:</td>
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<tr>
<td>A. Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests;</td>
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<tr>
<td>B. Deficits in 2 or more areas of cognition;</td>
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<tr>
<td>C. Progressive worsening of memory and other cognitive functions;</td>
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<tr>
<td>D. No disturbance of consciousness;</td>
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<tr>
<td>E. Onset between ages 40 and 90 years, most often after the age of 65 years; and</td>
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<tr>
<td>F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.</td>
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<tr>
<td>Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include</td>
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<tr>
<td>A. Plateaus in the course of progression of the illness;</td>
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<td>B. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sexual disorders, weight loss, and catastrophic verbal, emotional, or physical outbursts;</td>
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<td>C. Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder; and</td>
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<tr>
<td>D. Seizures in advanced disease CT normal for age.</td>
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<tr>
<td>Features that make the diagnosis of probable AD uncertain or unlikely include:</td>
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<tr>
<td>A. Sudden apoplectic onset;</td>
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<tr>
<td>B. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and</td>
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<tr>
<td>C. Seizures or gait disturbances at the onset or very early in the course of the illness.</td>
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<tr>
<td><strong>Definite</strong></td>
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<tr>
<td>Criteria for diagnosis of definite AD are:</td>
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<tr>
<td>A. Clinical criteria for probable Alzheimer disease; AND</td>
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<tr>
<td>B. Histopathologic evidence obtained from a biopsy or autopsy.</td>
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</table>

AD: Alzheimer Disease; CT: computed tomography.

2011 Revised Diagnostic Criteria

In 2011, probable AD was defined by the National Institute on Aging and the Alzheimer’s Association workgroup using the following diagnostic criteria:\textsuperscript{15}: 

\textsuperscript{15} The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
“Meets criteria for dementia…and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
B. Clear-cut history of worsening of cognition by report or observation; and
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
   a. 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.
   b. 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.
D. The diagnosis of probable AD dementia should not be applied when there is evidence of:
   a. 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
   b. Core features of dementia with Lewy bodies other than dementia itself; or
   c. Prominent features of behavioral variant frontotemporal dementia; or
   d. Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or
   e. 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.”

All probable AD by NINCDS-ADRDA criteria are subsumed in the revised probable AD criteria. Revised criteria include a category of “Probable AD dementia with increased level of certainty” due to documented decline or having a causative AD genetic mutation. 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-β 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.

Note on the 2011 Revised Criteria and Biomarkers

The biomarkers considered in this evidence review include in a category among the 2011 revisions to AD diagnostic criteria, “probable AD dementia with evidence of the AD pathophysiological process.”15 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 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 3 circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician.15.

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.”16 In 2012, the Alzheimer’s Biomarkers Standardization Initiative published consensus recommendations for standardization of pre-analytical aspects (eg, fasting, tube types, centrifugation, storage time, temperature) of CSF biomarker testing.45.

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.47 The recommended algorithm for cognitive assessment was based on “current validated tools and commonly used rule-out assessments.” Guidelines noted that 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.”

EU Joint Program-Neurodegenerative Disease Research

In 2017, the EU Joint Program-Neurodegenerative Disease Research sponsored a meta-review with accompanying recommendations on the performance of CSF biomarkers of AD, compared with clinical measures or other biomarkers.48 Minimal data from the individual systematic reviews and meta-analyses were discussed; instead, using the GRADE method, the consensus group rated the studies based on their relevance to 6 predetermined clinical questions. Of these questions, two were key, assessing the efficacy of cerebrospinal fluid in (1) determining whether mild cognitive impairment is caused by AD, and (2) predicting the decay of cognitive ability and/or the onset of AD dementia; for all questions, CSF was compared with clinical factors and a number of known biomarkers. The absence of follow-up data made any conclusive answer to the first question impossible. For the second question, the consensus group strongly recommended CSF biomarkers over clinical measures alone; however, insufficient data precluded a strong recommendation of CSF over other biomarkers. The group offered additional recommendations regarding appropriate cutoff points for levels of Aβ42, and pre- and post-testing counseling to address the possible implications of biomarkers.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on
FEP 2.04.14 Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease

22. Le Bastard N, Van Buggenhout M, De Leenheer E, et al. LOW specificity limits the use of the cerebrospinal fluid AB1-42/P-TAU181P ratio to discriminate Alzheimer's disease from vascular
FEP 2.04.14 Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease

FEP 2.04.14 Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease


POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>June 2012</td>
<td>New Policy</td>
<td>Policy updated with literature search; references 2, 3, 7, 12, 28, 31, 34-35, and 44 added; policy statements unchanged.</td>
</tr>
<tr>
<td>December 2013</td>
<td>Update Policy</td>
<td>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.</td>
</tr>
<tr>
<td>December 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review through July 30, 2015; no references added. Policy statements unchanged.</td>
</tr>
<tr>
<td>March 2018</td>
<td>Update Policy</td>
<td>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 meta-analyses were removed. Policy statements unchanged. Title changed to &quot;Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease&quot;.</td>
</tr>
<tr>
<td>March 2019</td>
<td>Update Policy</td>
<td>Policy updated with literature review through October 18, 2018; references 26, 28-30, and 34 added. Policy statements unchanged.</td>
</tr>
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