# FEP 2.04.14 Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease

**Effective Date:** April 15, 2018

**Related Policies:**
2.04.13 Genetic Testing for Familial Alzheimer Disease
6.01.55 Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer Disease

## 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-□ peptide 1-42 and total or phosphorylated tau protein in cerebrospinal fluid.

### 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 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.

### 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.

### POLICY GUIDELINES

#### GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### BENEFIT APPLICATION

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

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

## 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).[40] 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.[15]

In the 1984 guidelines, the diagnostic categories were defined as summarized in Table 1.

**Table 1. The 1984 Diagnostic Categories for Alzheimer Disease**

| Diagnostic Categories for AD |
|---|
| **Possible** |
| Clinical diagnosis of possible AD:<br>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.<br>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.<br>C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause. |
| **Probable** |

| **Diagnostic Categories for AD** |
|---|
| Criteria for the clinical diagnosis of probable AD included:<br>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;<br>B. Deficits in 2 or more areas of cognition;<br>C. Progressive worsening of memory and other cognitive functions;<br>D. No disturbance of consciousness;<br>E. Onset between ages 40 and 90 years, most often after the age of 65 years; and<br>F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition. |
| Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include<br>A. Plateaus in the course of progression of the illness;<br>B. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sexual disorders, weight loss, and catastrophic verbal, emotional, or physical outbursts;<br>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<br>D. Seizures in advanced disease CT normal for age. |
| Features that make the diagnosis of probable AD uncertain or unlikely include:<br>A. Sudden apoplectic onset;<br>B. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and<br>C. Seizures or gait disturbances at the onset or very early in the course of the illness. |
| **Definite** |
| Criteria for diagnosis of definite AD are:<br>A. Clinical criteria for probable Alzheimer disease; AND<br>B. Histopathologic evidence obtained from a biopsy or autopsy. |

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[15]:

"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."[18] 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.[41]

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.[42] 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.[43] 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 posttesting 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 diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* May 2011;7(3):270-279. PMID 21514249
2. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement.* Jan 2012;8(1):1-13. PMID 22265587
3. Galasko D, Clark C, Chang L, et al. Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. *Neurology.* Mar 1997;48(3):632-635. PMID 9065538
4. Motter R, Vigo-Pelfrey C, Kholodenko D, et al. Reduction of beta-amyloid peptide42 in the cerebrospinal fluid of patients with Alzheimer's disease. *Ann Neurol.* Oct 1995;38(4):643-648. PMID 7574461
5. Zhang J, Peng M, Jia J. Plasma amyloid-beta oligomers and soluble tumor necrosis factor receptors as potential biomarkers of AD. *Curr Alzheimer Res.* May 2014;11(4):325-331. PMID 24635842
6. Maddalena A, Papassotiropoulos A, Muller-Tillmanns B, et al. Biochemical diagnosis of Alzheimer disease by measuring the cerebrospinal fluid ratio of phosphorylated tau protein to beta-amyloid peptide42. *Arch Neurol.* Sep 2003;60(9):1202-1206. PMID 12975284
7. Dumurgier J, Vercruysse O, Paquet C, et al. Intersite variability of CSF Alzheimer's disease biomarkers in clinical setting. *Alzheimers Dement.* Jul 2013;9(4):406-413. PMID 23141384
8. Mattsson N, Andreasson U, Persson S, et al. The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. *Alzheimers Dement.* Jul 2011;7(4):386-395 e386. PMID 21784349
9. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Qualification of the analytical and clinical performance of CSF biomarker analyses in ADNI. *Acta Neuropathol.* May 2011;121(5):597-609. PMID 21311900
10. Lewczuk P, Beck G, Ganslandt O, et al. International quality control survey of neurochemical dementia diagnostics. *Neurosci Lett.* Nov 27 2006;409(1):1-4. PMID 17045397
11. Verwey NA, van der Flier WM, Blennow K, et al. A worldwide multicentre comparison of assays for cerebrospinal fluid biomarkers in Alzheimer's disease. *Ann Clin Biochem.* May 2009;46(Pt 3):235-240. PMID 19342441
12. Monge-Argilés JA, Munoz-Ruiz C, Sanchez-Paya J, et al. Comparison of two analytical platforms for CSF biomarkers of Alzheimer's disease. *Biomed Res Int.* 2014;2014:765130. PMID 24971348
13. Rosa MI, Perucchi J, Medeiros LR, et al. Accuracy of cerebrospinal fluid Abeta(1-42) for Alzheimer's disease diagnosis: a systematic review and meta-analysis. *J Alzheimers Dis.* Jan 2014;40(2):443-454. PMID 24448789
14. Ferreira D, Perestelo-Perez L, Westman E, et al. Meta-review of CSF core biomarkers in Alzheimer's disease: the state-of-the-art after the new revised diagnostic criteria. *Front Aging Neurosci.* Apr 2014;6:47. PMID 24715863
15. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* May 2011;7(3):263-269. PMID 21514250

16. van Harten AC, Kester MI, Visser PJ, et al. Tau and p-tau as CSF biomarkers in dementia: a meta-analysis. *Clin Chem Lab Med.* Mar 2011;49(3):353-366. PMID 21342021
17. Cure S, Abrams K, Belger M, et al. Systematic literature review and meta-analysis of diagnostic test accuracy in Alzheimer's disease and other dementia using autopsy as standard of truth. *J Alzheimers Dis.* May 19 2014;42(1):169-182. PMID 24840572
18. Bloudek LM, Spackman DE, Blankenburg M, et al. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. *J Alzheimers Dis.* 2011;26(4):627-645. PMID 21694448
19. Formichi P, Battisti C, Radi E, et al. Cerebrospinal fluid tau, A beta, and phosphorylated tau protein for the diagnosis of Alzheimer's disease. *J Cell Physiol.* Jul 2006;208(1):39-46. PMID 16447254
20. Howell JC, Watts KD, Parker MW, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. *Alzheimers Res Ther.* Nov 02 2017;9(1):88. PMID 29096697
21. de Jong D, Jansen RW, Kremer BP, et al. Cerebrospinal fluid amyloid beta42/phosphorylated tau ratio discriminates between Alzheimer's disease and vascular dementia. *J Gerontol A Biol Sci Med Sci.* Jul 2006;61(7):755-758. PMID 16870640
22. Le Bastard N, Van Buggenhout M, De Leenheir E, et al. LOW specificity limits the use of the cerebrospinal fluid AB1-42/P-TAU181P ratio to discriminate Alzheimer's disease from vascular dementia. *J Gerontol A Biol Sci Med Sci.* Aug 2007;62(8):923-924; author reply 924-925. PMID 17702886
23. Park SA, Chae WS, Kim HJ, et al. Cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease in South Korea. *Alzheimer Dis Assoc Disord.* Jan-Mar 2017;31(1):13-18. PMID 28030437
24. Sauvee M, DidierLaurent G, Latarche C, et al. Additional use of Abeta(4)(2)/Abeta(4)(0) ratio with cerebrospinal fluid biomarkers P-tau and Abeta(4)(2) increases the level of evidence of Alzheimer's disease pathophysiological process in routine practice. *J Alzheimers Dis.* Mar 2014;41(2):377-386. PMID 24614902
25. Janelidze S, Zetterberg H, Mattsson N, et al. CSF Abeta42/Abeta40 and Abeta42/Abeta38 ratios: better diagnostic markers of Alzheimer disease. *Ann Clin Transl Neurol.* Mar 2016;3(3):154-165. PMID 27042676
26. Kahle PJ, Jakowec M, Teipel SJ, et al. Combined assessment of tau and neuronal thread protein in Alzheimer's disease CSF. *Neurology.* Apr 11 2000;54(7):1498-1504. PMID 10751266
27. Ritchie C, Smailagic N, Noel-Storr AH, et al. Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* Jun 10 2014;6(6):CD008782. PMID 24913723
28. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol.* Jun 2016;15(7):673-684. PMID 27068280
29. Ritchie C, Smailagic N, Noel-Storr AH, et al. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* Mar 22 2017;3:Cd010803. PMID 28328043
30. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. *Ann Intern Med.* Mar 4 2008;148(5):379-397. PMID 18316756
31. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. *BMJ.* Aug 6 2005;331(7512):321-327. PMID 16081444
32. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev.* Apr 19 2006(2):CD003154. PMID 16625572
33. Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. *J Intern Med.* Mar 2014;275(3):251-283. PMID 24605808
34. Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. *Lancet Neurol.* Jun 2007;6(6):501-512. PMID 17509485
35. Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. *Neurology.* May 27 2008;70(22):2024-2035. PMID 18322263
36. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med.* Jun 9 2005;352(23):2379-2388. PMID 15829527
37. Levy S, McConville M, Lazaro GA, et al. Competitive ELISA studies of neural thread protein in urine in Alzheimer's disease. *J Clin Lab Anal.* Jan 2007;21(1):24-33. PMID 17245761
38. Zhang J, Zhang CH, Li RJ, et al. Accuracy of urinary AD7c-NTP for diagnosing Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis.* Dec 2014;40(1):153-159. PMID 24346218

39. Goodman I, Golden G, Flitman S, et al. A multi-center blinded prospective study of urine neural thread protein measurements in patients with suspected Alzheimer's disease. *J Am Med Dir Assoc.* Jan 2007;8(1):21-30. PMID 17210499
40. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* Jul 1984;34(7):939-944. PMID 6610841
41. Vanderstichele H, Bibl M, Engelborghs S, et al. Standardization of preanalytical aspects of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's Biomarkers Standardization Initiative. *Alzheimers Dement.* Jan 2012;8(1):65-73. PMID 22047631
42. Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. *Alzheimers Dement.* Mar 2013;9(2):141-150. PMID 23265826
43. Herukka SK, Simonsen AH, Andreasen N, et al. Recommendations for cerebrospinal fluid Alzheimer's disease biomarkers in the diagnostic evaluation of mild cognitive impairment. *Alzheimers Dement.* Mar 2017;13(3):285-295. PMID 28341066

## POLICY HISTORY

| Date | Action | Description |
|---|---|---|
| June 2012 | New Policy | |
| December 2013 | Update Policy | Policy updated with literature search; references 2, 3, 7, 12, 28, 31, 34-35, and 44 added; policy statements unchanged. |
| December 2014 | Update 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 | Update Policy | Policy updated with literature review through July 30, 2015; no references added. Policy statements unchanged. |
| March 2018 | Update 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 meta-analyses were removed. Policy statements unchanged. Title changed to “Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease”. |