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.[8] 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 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 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

REFERENCES:

1. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. Mar 2021; 17(3): 327-406. PMID 33756057
2. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology.Jan 16 2018; 90(3): 126-135. PMID 29282327
3. National Institutes on Aging. Data shows racial disparities in Alzheimer's disease diagnosis between Black and white research study participants. December 16, 2021. https://www.nia.nih.gov/news/data-shows-racial-disparities-alzheimers-disease-diagnosis-between-black-and-white-research. Accessed August 24, 2022.
4. Centers for Disease Control and Prevention. Barriers to equity in Alzheimer's and dementia care. June 2, 2021.https://www.cdc.gov/aging/publications/features/barriers-to-equity-in-alzheimers-dementia-care/index.html. Accessed August24, 2022.
5. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf. Accessed August 22, 2022.
6. Roberts RO, Aakre JA, Kremers WK, et al. Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting. JAMA Neurol. Aug 01 2018; 75(8): 970-979. PMID 29710225
7. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimers Dement. Jul 2019; 15(7): 888-898. PMID 31164314
8. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. Apr 2018; 14(4): 535-562. PMID 29653606
9. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. J Intern Med. Dec2018; 284(6): 643-663. PMID 30051512
10. 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): 632-5. PMID 9065538
11. 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): 643-8. PMID 7574461
NA
12. 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): 1202-6. PMID12975284
13. 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): 406-13. PMID 23141384
14. 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.e6. PMID 21784349

15. Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. Lancet Neurol. Jan 2022; 21(1): 66-77. PMID 34838239
16. Ashton NJ, Leuzy A, Karikari TK, et al. The validation status of blood biomarkers of amyloid and phospho-tau assessed with the5-phase development framework for AD biomarkers. Eur J Nucl Med Mol Imaging. Jul 2021; 48(7): 2140-2156. PMID 33677733
17. Rosa MI, Perucchi J, Medeiros LR, et al. Accuracy of cerebrospinal fluid A(1-42) for Alzheimer's disease diagnosis: a systematic review and meta-analysis. J Alzheimers Dis. 2014; 40(2): 443-54. PMID 24448789
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): 627-45. 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. 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. 2014; 6: 47. PMID 24715863
21. Fink HA, Linskens EJ, Silverman PC, et al. Accuracy of Biomarker Testing for Neuropathologically Defined Alzheimer Disease in Older Adults With Dementia. Ann Intern Med. May 19 2020; 172(10): 669-677. PMID 32340038
22. 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. 2014; 42(1): 169-82. PMID 24840572
23. 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
24. 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
25. 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 102014; (6): CD008782. PMID 24913723
26. 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 04 2008; 148(5): 379-97. PMID 18316756
27. 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 06 2005; 331(7512): 321-7. PMID 16081444
28. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. Apr 19 2006; (2):CD003154. PMID 16625572
29. 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): 251-83. PMID 24605808
30. Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the In DDEx study. Lancet Neurol. Jun 2007; 6(6): 501-12. PMID 17509485
31. 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): 2024-35. PMID 18322263
32. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N EnglJ Med. Jun 09 2005; 352(23): 2379-88. PMID 15829527
33. 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. 2014; 40(1): 153-9. PMID 24346218
34. Thijssen EH, La Joie R, Wolf A, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. Nat Med. Mar 2020; 26(3): 387-397. PMID 32123386

35. Janelidze S, Mattsson N, Palmqvist S, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nat Med. Mar 2020; 26(3): 379-386. PMID 32123385
36. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA. Aug 25 2020; 324(8): 772-781. PMID 32722745
37. Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 257-62. PMID 21514247
38. 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 a Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 270-9. PMID 21514249
39. 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): 263-9. PMID 21514250
40. Janelidze S, Pannee J, Mikulskis A, et al. Concordance Between Different Amyloid Immunoassays and Visual Amyloid Positron Emission Tomographic Assessment. JAMA Neurol. Dec 01 2017; 74(12): 1492-1501. PMID 29114726
41. Hansson O, Lehmann S, Otto M, et al. Advantages and disadvantages of the use of the CSF Amyloid (A) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther. Apr 22 2019; 11(1): 34. PMID 31010420
42. Chetelat G, Arbizu J, Barthel H, et al. Amyloid-PET and 18 F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. Lancet Neurol. Nov 2020; 19(11): 951-962. PMID 33098804
43. Palmqvist S, Zetterberg H, Mattsson N, et al. Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. Neurology. Oct 06 2015; 85(14): 1240-9. PMID 26354982
44. Lewczuk P, Matzen A, Blennow K, et al. Cerebrospinal Fluid A42/40 Corresponds Better than A42 to Amyloid PET inAlzheimer's Disease. J Alzheimers Dis. 2017; 55(2): 813-822. PMID 27792012
45. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. JAMA. Apr 02 2019;321(13): 1286-1294. PMID 30938796
46. 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
47. 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):141-50. PMID 23265826
48. Shaw LM, Arias J, Blennow K, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosisof Alzheimer's disease. Alzheimers Dement. Nov 2018; 14(11): 1505-1521. PMID 30316776
49. Hansson O, Batrla R, Brix B, et al. The Alzheimer's Association international guidelines for handling of cerebrospinal fluid for routine clinical measurements of amyloid and tau. Alzheimers Dement. Sep 2021; 17(9): 1575-1582. PMID 33788410
50. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. Alzheimers Dement. Jul 31 2022. PMID 35908251
51. Dementia: assessment, management and support for people living with dementia and their careers. National Institute for Health and Care Excellence. Published June 20, 2018. https://www.nice.org.uk/guidance/ng97. Accessed August 22, 2022.
52. Cognitive impairment in older adults: screening. U.S. Preventative Task Force. Published February 25, 2020.https://uspreventiveservicestaskforce.org/uspstf/recommendation/cognitive-impairment-in-older-adults-screening. Accessed August 22, 2022.

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