Medical Coverage Policy | Evaluation of Biomarkers for Alzheimer Disease

EFFECTIVE DATE: 01|01|2017
POLICY LAST UPDATED: 02|17|2020

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). 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

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

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

Commercial Products

Measurement of cerebrospinal fluid biomarkers of Alzheimer disease, including but not limited to tau protein, amyloid-β peptides, or neural thread proteins, is considered not medically necessary as whether 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.

Measurement of urinary biomarkers of Alzheimer disease is considered not medically necessary, including but not limited to neural thread proteins as whether 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.

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.[5,6] 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 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). AlzheimAlert™ and AdMark® CSF analysis are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

CODING

BlueCHiP for Medicare and Commercial

The following codes (effective 10/1/2020) are not covered for Medicare Advantage plans and not medically necessary for Commercial Products.

0206U Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease (eff 10/1/2020) (PLA code for the DiscernTM test from NeuroDiagnostics)

0207U Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure) (eff 10/1/2020) (PLA code for the DiscernTM test from NeuroDiagnostics)

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

For claims filed with date of service prior to 10/1/2020

There are no specific codes for these tests. Claims should be filed with code 81099 when performed in urine and the unlisted immunology code 86849 when performed in CSF.

RELATED POLICIES

None

PUBLISHED

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

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

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. 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. 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. 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
21. 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
22. Sauvee M, DidierLaurent G, Latarche C, et al. Additional use of abeta42/abeta40 ratio with cerebrospinal fluid biomarkers p-tau and abeta42 increases the level of evidence of Alzheimer's disease pathophysiological process in routine practice. J Alzheimers Dis. 2014;41(2):377-386. PMID 24614902
23. 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
24. 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
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. 2014;6:CD008782. PMID 24913723

26. 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
27. 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
28. 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
29. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. 2006(2):CD003154. PMID 16625572
30. 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
31. 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
32. 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
33. 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
34. 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. 2007;21(1):24-33. PMID 17245761
35. 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):153-159. PMID 24346218