BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:
Evaluation of Biomarkers for Alzheimer Disease

Policy #: 200
Latest Review Date: October 2021
Category: Laboratory

BACKGROUND:
Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11)*

POLICY:

Blue Advantage will treat **measurement of cerebrospinal fluid biomarkers of Alzheimer disease, including but not limited to tau protein, amyloid beta peptides, or neural thread proteins** as a **non-covered benefit** and as **investigational** for including, but not limited to, the following situations:

- 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

Blue Advantage will treat **measurement of urinary biomarkers of Alzheimer disease, including but not limited to neural thread proteins** as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Biochemical changes associated with the pathophysiology of Alzheimer disease (AD) are being evaluated to aid in the diagnosis of AD. This includes the potential use of biomarkers, such as amyloid beta peptide 1-42 and total or phosphorylated tau protein, in cerebrospinal fluid (CSF) and urine. Additionally, the potential correlation between CSF biomarkers and positron emission tomography (PET) amyloid scans may assist in selecting appropriate patients for the initiation or discontinuation of amyloid beta plaque targeted therapy.

Alzheimer Disease

Alzheimer Disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between four and eight years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 12 million by 2050. Per the 2018 American Academy of Neurology practice guideline update on mild cognitive impairment (MCI), the prevalence of MCI was 6.7% for ages 60 to 64, 8.4% for ages 65 to 69, 10.1% for ages 70 to 74, 14.8% for ages 75 to 79, and 25.2% for ages 80 to

84. The cumulative dementia incidence was 14.9% in individuals with MCI >65 years of age followed for two years.

Pathophysiology
The pathologic hallmarks of AD are extracellular deposits of amyloid beta, referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. There are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and their contributions to the pathophysiology of AD is not well understood. Generally referred to as the "amyloid hypothesis", it is believed that aggregation of amyloid beta oligomers in the brain leads to amyloid plaques. Amyloid aggregation in addition to accumulation of tau pathology and neurodegeneration are thought to be the main drivers of the disease process. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.

The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before symptoms arise. The National Institute on Aging-Alzheimer's Association (NIA-AA) has created a "numeric clinical staging scheme" (see table below) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme is primarily used in the research setting and reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia.

Table. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum

Stage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Severity	Pre-clinical	Pre-clinical	MCI due to Alzheimer disease	Mild Dementia	Moderate Dementia	Severe Dementia
Clinical Features	Performance within expected range on objective cognitive tests. No evidence of recent cognitive decline or new neurobehavioral symptoms.	Normal performance within expected range on objective cognitive tests. Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months). Mild neurobehavioral changes may coexist or may be the primary complaint rather than	Performance in the impaired/abnormal range on objective cognitive tests. Evidence of decline from baseline. Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life.	Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Clearly evident functional impact on daily life, affecting mainly instrumental activities. No longer fully independent/requires occasional assistance with daily life activities.	Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities.	Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible. Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

		cognitive. No functional impact on daily life activities.				

Adapted from Table 6, Jack et al (2018)

Applicable only to individuals in the Alzheimer continuum that fall into 1 of the 4 biomarker groups: 1) A+T+N+ 2) A+T-N- 3) A+T+N- 4) A+T-N+ where A: Aggregated Aβ or associated pathologic state (CSF Aβ42, or Aβ42/Aβ40 ratio or Amyloid PET), T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau or Tau PET) and N: Neurodegeneration or neuronal injury (anatomic MRI, FDG PET or CSF total tau)

For stages 1 to 6: Cognitive test performance may be compared to normative data of the investigators choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.

For stages 2 to 6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.

For stages 3 to 6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.
CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

Biomarkers
Several potential biomarkers of AD are associated with AD pathophysiology (e.g., amyloid beta plaques, neurofibrillary tangles). Altered 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, an amyloid beta peptide such as 1-42 (Aβ42), and the synaptic protein, neurogranin. Other potential CSF, urinary, and blood 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. Amyloid beta-42 is a subtype of amyloid beta peptide produced from the metabolism of the amyloid precursor protein. Amyloid beta-42 is the key peptide deposited in amyloid plaques characteristic of AD. Low levels of amyloid beta-42 in the CSF have been associated with AD, perhaps because amyloid beta-42 is deposited in amyloid plaques instead of remaining in the fluid. Investigators have suggested the tau/amyloid beta-42 ratio may be a more accurate diagnostic marker than either alone. Neurogranin is a dendritic protein and CSF measurement may serve as a biomarker for dendritic instability and synaptic degeneration. Elevated CSF neurogranin may predict prodromal AD in MCI and has been confirmed in AD dementia and prodromal AD in several studies.

A variety of kits are commercially available to measure amyloid beta-42 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.

More recently, research has focused on blood as a new matrix for AD biomarkers that have already been validated in the CSF. As blood is more accessible than CSF, blood sampling would be preferable to CSF when taking samples to measure AD biomarkers, both for clinical diagnosis or screening. However, developing blood AD biomarkers has proven complex. While the CSF is continuous with the brain extracellular fluid, with a free exchange of molecules from the brain to the CSF, only a fraction of brain proteins enter the bloodstream. Examples of blood biomarkers that are currently under examination for use in AD include amyloid beta, tau protein, and neurofilament light. In a recent retrospective multicohort diagnostic performance study, both plasma tau phosphorylated at threonine 217 (p-tau217) and at threonine 181 (p-tau181) had excellent diagnostic performance for differentiating patients with AD syndromes from other neurodegenerative disorders. At this time, although a growing area of research, blood AD biomarkers are not addressed in this review.

KEY POINTS:
The most recent literature review was updated through September 11, 2021.

Summary of Evidence
For individuals who have MCI or AD who receive 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 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 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 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.

Practice Guidelines and Position Statements
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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:

"Meets criteria for dementia described ... and in addition, have the following characteristics:

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

- 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:

- 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
- 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 CSF AB-42, positive positron emission tomography (PET) amyloid imaging, or elevated CSF tau, and decreased 18-F fluorodeoxyglucose uptake on PET in the temporo-parietal cortex with accompanying atrophy by magnetic resonance imaging (MRI) in relevant structures. Detection of the "pathophysiological process" is further divided according to 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 AD 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." 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 three circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician."

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

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. The recommended algorithm for cognitive assessment was based on "current validated tools and commonly used rule-out assessments." Guideline authors noted that use of biomarkers (e.g., 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 (2018) published appropriate use criteria for lumbar puncture and CSF testing for AD. The table below 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.

Table. 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 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
Individuals who are apolipoprotein E (APOE) Ɛ4 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.

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 care-givers. 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.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in the table below.

Table. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05020106	Study on the Diagnostic Cut-off Value for Core Biomarkers in Cerebrospinal Fluid and Blood of Alzheimer's Disease	3200	Sep 2022 (recruiting)
NCT03136679	Discovery of Novel Biomarkers That Will Lead to the Early Detection of Alzheimer's Disease	220	Dec 2022 (recruiting)
NCT02612376	Rocky Mountain Alzheimer's Disease Center at the University of Colorado School of Medicine (RMADC at UCSOM) Longitudinal Biomarker and Clinical Phenotyping Study	800	Jan 2024 (recruiting)
NCT03860857	MRI and PET Biomarkers for Cognitive Decline in Older Adults	200	Dec 2024 (recruiting)
NCT04575337	Study on Body Fluid, Gene and Neuroimaging Biomarkers for Early Diagnosis of Alzheimer's Disease	6000	Jun 2025 (recruiting)

Unpublished			
NCT01642420	Quantitative Electroencephalography, Cerebrospinal Fluid Biomarkers, Linear CT Analyses, and Timed Up and GO Dual Task as Diagnostic Tools in Dementia and Their Ability to Predict Disease Progression	115	Feb 2017 (status unknown; updated 09/2012)

NCT: national clinical trial.

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. The statement discusses that screening tests are not intended to diagnose mild cognitive impairment or dementia, but a positive screening test result should prompt additional testing consisting of blood tests, radiology examinations, and/or medical and neuropsychologic evaluation.

KEY WORDS:
Biochemical marker, amyloid beta peptides, AB-42 Protein, Alzheimer's Disease, ADmark ProfileAD7C, Alzheimer's Disease, Beta-amyloid Protein, Neural thread Protein, Tau Protein, Alzheimer, Innotest, AlzheimAlert, MCI, mild cognitive impairment, AD, Alzheimer Disease

APPROVED BY GOVERNING BODIES:
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 is currently not intended to be used as a stand-alone diagnostic

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

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 (DISCERN™) (Effective 10/1/2020)
0207U	imaging of quantitative 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) (Use 0207U in conjunction with 0206U) (DISCERN™) (Effective 10/1/2020)
81099	Unlisted urinalysis procedure
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative; not otherwise specified
86849	Unlisted immunology procedure

REFERENCES:

1. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. Mar 2021; 17(3): 327-406.
2. 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 2011; 7(3):270-9.
3. Alexopoulos P, Thierjung N, Grimmer T, et al. Cerebrospinal Fluid BACE1 Activity and sAbetaPPbeta as Biomarker Candidates of Alzheimer's Disease. Dement Geriatr Cogn Disord. 2018; 45(3-4):152-161.
4. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf. Accessed September 1, 2021
5. Bian H, Van Swieten JC, et al. CSF biomarkers in frontotemporal lobar degeneration with known pathology. Neurology, May 2008; 70(19 Pt 2): 1827-1835.
6. Blasko I, Lederer W, Oberbauer H, et al. Measurement of thirteen biological markers in CSF of patients with Alzheimer's disease and other dementias. Dement Geratr Cogn Disord 2006; 21(1): 9-15.
7. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. J Intern Med. Dec 2018; 284(6): 643-663.

8. 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.
9. Bouwman FH, Schoonenboom SN, van der Flier WM, et al. CSF biomarkers and medial temporal lobe atrophy predict dementia in mild cognitive impairment. Neurobiol Aging 2007; 28(7): 1070-1074.
10. Chertkow H. Diagnosis and treatment of dementia: Introduction. CMAJ, January 29, 2008; 178(3): 316-321.
11. 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.
12. 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 September 7, 2021.
13. 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.
14. 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.
15. de Jong D, Jansen RW, et al. Cerebrospinal fluid amyloid beta42/phosphorylated tau ratio discriminates between Alzheimer's disease and vascular dementia. J Gerontol A Biol Sci Med Sci, July 2006; 61(7): 755-758.
16. De Meyer G, Shapiro F, Vanderstichele H et al. Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. Arch Neurol 2010; 67(8):949-56.
17. Dementia: assessment, management and support for people living with dementia and their carers. National Institute for Health and Care Excellence. Published June 20, 2018.https://www.nice.org.uk/guidance/ng97. Accessed September 7, 2021.
18. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. Lancet Neurol, August 2007; 6(8): 734-746.
19. 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.
20. Engelborghs S, De Vreese K, et al. Diagnostic performance of a CSF-biomarker panel in autopsy-confirmed dementia. Neurobiol Aging, August 2008; 29(8): 1143-1159.
21. Ewers M, Buerger K, Teipel SJ, et al. Multicenter assessment of CSF-phosphorylated tau for the prediction of conversion of MCI. Neurology, December 2007; 69(24): 2205-2212.

22. Ewers M, Walsh C, Trojanowski JQ, et al. Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. Neurobiol Aging. Jul 2012; 33(7):1203-1214.
23. 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 2007; 6(6):501-12.
24. 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.
25. 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.
26. Formichi P, Battisti C, Radi E and Federico A. Cerebrospinal fluid tau, A beta, and phosphorylated tau protein for the diagnosis of Alzheimer's disease. J Cell Physiol, July 2006; 208(1): 39-46.
27. Gauthier S, Patterson C, Chertkow H, et al. Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4). Can Geriatr J. Dec 2012; 15(4):120-126.
28. Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, et al. Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. Arch Gen Psychiatry. Sep 2011; 68(9):961-969.
29. 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 2007; 8(1): 21-30.
30. 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. Mar 31 2021.
31. 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.
32. Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts.. Alzheimers Dement, 2018 Mar 3; 14(11).
33. Hansson O, Zetterberg H, Buchhave P, Londos E, et al. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: A follow-up study. Lancet Neurol, March 2006; 5(3): 228-234.
34. Herukka SK, Helisalmi S, Hallikainen M, et al. CSF Abeta42, Tau and phosphorylated Tau, APOE epsilon4 allele and MCI type in progressive MCI. Neurobiol Aging 2007; 28(4): 507-514.

35. 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.
36. Hort J, O'Brien JT, Gainotti G et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol 2010; 17(10):1236-48.
37. 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.
38. 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 2012; 8(1):1-13.
39. Ibach B, Binder H, Dragon M, et al. Cerebrospinal fluid tau and beta-amyloid in Alzheimer patients, disease controls and an age-matched random sample. Neurobiol Aging 2006; 27(9): 1202-1211.
40. IOM (Institute of Medicine). 2011. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press.
41. 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.
42. 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.
43. 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.
44. Jia JP, Meng R, Sun YX, et al. Cerebrospinal fluid tau, Abeta 1-42 and inflammatory cytokines in patients with Alzheimer’s disease and vascular dementia. Neurosci Lett 2005; 383(1-2): 12-16.
45. Landau SM, Harvey D, Madison CM et al. Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 2010; 75(3):230-8.
46. 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.
47. 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.
48. 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.
49. Lewczuk P, Matzen A, Blennow K, et al. Cerebrospinal Fluid A42/40 Corresponds Better than A42 to Amyloid PET in Alzheimer's Disease. J Alzheimers Dis. 2017; 55(2): 813-822.

50. Liu Y, He X, Li Y, et al. Cerebrospinal fluid CD4+ T lymphocyte-derived miRNA-let-7b can enhances the diagnostic performance of Alzheimer's disease biomarkers. Biochem Biophys Res Commun. Jan 1 2018; 495(1):1144-1150.
51. Locascio JJ, Fukumoto H, Yap L, et al. Plasma amyloid beta-protein and C-reactive protein in relation to the rate of progression of Alzheimer disease. Arch Neurol, June 2008; 65(6): 776-785.
52. Lowe VJ, Peller PJ, Weigand SD et al. Application of the National Institute on Aging-Alzheimer's Association AD criteria to ADNI. Neurology 2013; 80(23):2130-7.
53. Mattsson N, Andreasson U, Persson S et al. The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. Alzheimers Dement 2011; 7(4):386-95 e6.
54. Mattsson N, Zetterberg H, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA 2009; 302(4): 385-393.
55. McKhann GM, Knopman DS, Chertkow H et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement 2011; 7(3):263-9.
56. McShane R, Areosa Sastre A and Minakaran N. Memantine for dementia. Cochrane Database Syst Rev, April 2006; (2): CD003154.
57. Monge-Argiles 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.
58. 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.
59. 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.
60. Parnetti L, Lanari A, Silverstrelli G, et al. Diagnosing prodromal Alzheimer's disease: Role of CSF biochemical markers. Mech Ageing Dev 2006; 127(2): 129-132.
61. 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.
62. Pencina MJ, D'Agostino Sr RB, D'Agostino Jr RB and Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Stat Med, January 2008; 27(2): 157-172; discussion 207-12.
63. 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.
64. 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.

65. 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.
66. Raschetti R, Albanese E, et al. Cholinesterase inhibitors in mild cognitive impairment: A systematic review of randomized trials. PLOS Medicine, November 2007, vol. 4, Issue 11, pp. 1818-1828.
67. Richard E, Schmand BA, Eikelenboom P et al. MRI and cerebrospinal fluid biomarkers for predicting progression to Alzheimer's disease in patients with mild cognitive impairment: a diagnostic accuracy study. BMJ Open 2013; 3(6).
68. Ringman JM, Younkin SG, et al. Biochemical markers in persons with preclinical familial Alzheimer disease. Neurology 2008; 71: 85-92.
69. 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. June 10, 2014.
70. 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.
71. 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.
72. 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.
73. Rosa-Neto P, Hsiung GY, Masellis M. Fluid biomarkers for diagnosing dementia: rationale and the Canadian Consensus on Diagnosis and Treatment of Dementia recommendations for Canadian physicians. Alzheimers Res Ther. Nov 25 2013;5(Suppl 1):S8
74. 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.
75. Schmand B, Eikelenboom P, van Gool WA. Value of diagnostic tests to predict conversion to Alzheimer's disease in young and old patients with amnestic mild cognitive impairment. J Alzheimers Dis 2012; 29(3):641-8.
76. Schmand B, Eikelenboom P, van Gool WA. Value of neuropsychological tests, neuroimaging, and biomarkers for diagnosing Alzheimer's disease in younger and older age cohorts. J Am Geriatr Soc 2011; 59(9):1705-10.
77. 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.

78. Schoonenboom NS, van der Flier WM, Blankenstein MA, et al. CSF and MRI markers independently contribute to the diagnosis of Alzheimer's disease. Neurobiol Aging 2008; 29(5): 669-675.
79. Shaw LM, Arias J, Blennow K, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. Alzheimers Dement, 2018 Oct 15; 14(11).
80. 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.
81. Sorbi S, Hort J, Erkinjuntti T, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. Eur J Neurol. Sep 2012; 19(9):1159-1179.
82. Thijssen EH, La Joie R, Strom A, et al. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. Lancet Neurol. Sep 2021; 20(9): 739-752.
83. Trombetta BA, Carlyle BC, Koenig AM, et al. The technical reliability and biotemporal stability of cerebrospinal fluid biomarkers for profiling multiple pathophysiologies in Alzheimer's disease. PLoS One. 2018; 13(3):e0193707.
84. 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.
85. 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.
86. 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.
87. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, et al. MRI and CSF biomarkers in normal, MCI, and AD subjects: Diagnostic discrimination and cognitive correlations. Neurology, July 2009; 73(4): 287-293.
88. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, et al. MRI and CSF biomarkers in normal, MCI and AD subjects: Predicting future clinical change. Neurology, July 2009; 73(4): 294-301.
89. 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.
90. Vickers Andrew J. Decision analysis for the evaluation of diagnostic tests, prediction models and molecular markers. Am Stat 2008; 6294): 314-320.
91. Vogelgsang J, Wedekind D, Bouter C, et al. Reproducibility of Alzheimer's Disease Cerebrospinal Fluid-Biomarker Measurements under Clinical Routine Conditions. J Alzheimers Dis. 2018; 62(1):203-212.

92. Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol, January 2007; 14(1): e1-26.
93. Wang H, Stewart T, Toledo JB, et al. A Longitudinal Study of Total and Phosphorylated alpha-Synuclein with Other Biomarkers in Cerebrospinal Fluid of Alzheimer's Disease and Mild Cognitive Impairment. J Alzheimers Dis. 2018; 61(4):1541-1553.
94. Winblad B, Gauthier S, Scinto L et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008; 70(22):2024-35.
95. Zhang J, Peng M, Jia J. Plasma amyloid-beta oligomers and soluble tumor necrosis factor receptors as potential biomarkers of AD. Curr Alzheimer Res. Mar 16 2014.
96. 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.

POLICY HISTORY:

Adopted for Blue Advantage, March 2005
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Medical Policy Group, August 2006
Medical Policy Group, August 2008
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Medical Policy Group, March 2013
Medical Policy Group, September 2013
Medical Policy Group, September 2014
Medical Policy Group, August 2015
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