Anthem ✚

<div align="right">

Medical Policy

</div>

Subject: Testing for Biochemical Markers for Alzheimer's Disease
Document #: LAB.00046
Status: Revised

Publish Date: 04/01/2024
Last Review Date: 11/09/2023

Description/Scope

This document addresses the use of testing for biochemical markers (for example, tau protein, long form amyloid beta, and neural thread protein) as a diagnostic or screening technique for Alzheimer's disease.

Notes:

- This document does not address imaging tests, including MRI and PET. For criteria related to MRI and PET, refer to applicable guidelines used by the plan.

Position Statement

Medically Necessary:

Measurement of long form amyloid beta (also referred to as Aβ, Aβ1-42, Beta-amyloid [1-42], and Abeta42) in the cerebrospinal fluid is considered **medically necessary** in individuals for whom treatment with amyloid beta targeting therapy (for example, lecanemab-irmb [Leqembi™]) is being considered.

Investigational and Not Medically Necessary:

Measurements of biochemical markers (including but not limited to tau protein, long form amyloid beta, neural thread protein) is considered **investigational and not medically necessary** as a diagnostic technique for individuals with symptoms suggestive of Alzheimer's disease when the criteria above have not been met.

Measurements of biochemical markers as a screening technique in asymptomatic individuals with or without a family history of Alzheimer's disease is considered **investigational and not medically necessary.**

Rationale

Diagnosis of Alzheimer's disease (AD)

AD is an age-related disease caused by unrelenting neurodegeneration and brain atrophy. Behaviorally, AD is characterized by progressive memory loss and cognitive decline. Pathologically, AD is characterized by local accumulations of amyloid β (Aβ) peptide and neurofibrillary tangles (NFTs) comprised of tau protein in the brain. At present, a definitive diagnosis of AD requires postmortem verification of Aβ deposits (plaques) and NFTs in the brain. In current clinical practice, a diagnosis of AD is based on clinical presentations, a detailed clinical history, cognitive screening tools and clinical diagnostic criteria (for example, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] guidelines and the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-IV]). However, the diagnostic accuracy of these AD criteria is not perfect. Diagnosis of AD is often a diagnosis of exclusion and is challenging for both physicians and patients.

Based on the 2011 guidelines from the National Institute on Aging (NIAA) and the Alzheimer's Association (AA), the diagnosis of AD is a clinical diagnosis, focusing on the exclusion of other causes of senile dementia. Ancillary imaging studies such as computed tomography [CT], magnetic resonance imaging [MRI], single-photon emission CT [SPECT], or positron emission tomography [PET]) and laboratory tests may be used to aid in the diagnosis. These tests help rule out other possible causes for dementia (for example, cerebrovascular disease, cobalamin [vitamin B12] deficiency, syphilis, and thyroid disease). According to the NIA-AA, the core clinical criteria for AD dementia will continue to be the foundation of the diagnosis in clinical practice, however, "further studies are needed to prioritize biomarkers and to determine their value and validity in practice and research settings" (McKahn, 2011).

In 2018, the National Institute on Aging and Alzheimer's Association (NIA-AA) published an updated biological definition of AD that focuses on the underlying pathological activities of the disease, which can be identified either in living individuals (via biomarkers) or during autopsy. The NIA-AA framework proposes using three groups of biomarkers (Aβdeposition, pathologic tau, and neurodegeneration) that can be measured by obtaining spinal fluid and/or special radiological imaging tests. The new definition is intended for research purposes only (to identify and stage research participants) and is meant to provide a flexible framework amenable to new (yet to be discovered) biomarker tests. The definition is not intended to be used in routine clinical care, and further investigation is required to establish the role and utility of biomarkers (Jack, 2018).

Biomarkers for AD

Fluid biomarkers (found in the cerebrospinal fluid [CSF] or blood) have the potential to be easily implemented in clinical trials, and several biomarkers linked to different pathophysiological mechanisms can be analyzed in a single sample. Furthermore, fluid biomarkers may provide a window for identifying some biomarkers that cannot be detected via brain imaging.

Several CSF biomarkers, including but not limited to Aβ42, tau protein (T-tau) and neurofilament light chain (NF-L) are detectable in the blood and have been investigated as a means to screen for and diagnose AD. However, a major challenge in measuring these blood-based proteins is that their concentrations are lower in serum or plasma than in CSF. Currently, these tests are not considered standard of care in the evaluation of individuals with mild cognitive impairment (MCI) in the clinical setting (Petersen, 2018).

Amyloid Beta (Aβ) Peptide

Aβ accumulation in the brain is proposed to be an early toxic event in the pathogenesis of Alzheimer's disease, which is the most common form of dementia associated with plaques and tangles in the brain. Currently, it is unclear what the physiological and pathological forms of Aβ are and by what mechanism Aβ causes dementia

Aβ in CSF

Researchers are investigating the use of CSF biomarkers to predict the conversion from MCI to dementia and to diagnose Alzheimer's disease. The most explored CSF biomarkers include tau protein or phosphorylated tau protein and Aß42 peptide, which may be represented by a low ratio of Aß42 to Aß40 levels, or a low ratio of Aß42 to tau levels or elevated levels of tau or tau protein phosphorylated at threonine 181.

Schmand and colleagues (2010) reported the results of a meta-analysis that sought to determine if biomarkers can detect preclinical AD prior to the onset of behavioral (for example, memory) symptoms. The researchers included relevant longitudinal studies of CSF and MRI biomarkers published between January 2003 and November 2008. Study participants were not demented at baseline, but some declined to MCI or to AD. A total of 21 MRI studies and 14 CSF studies were included in the analysis. The effect sizes of Aß42, total tau (t-tau), and phosphorylated tau (p-tau) ranged from 0.91 to 1.11. The effect size of medial temporal lobe (MTL) atrophy was 0.75. Memory performance had an effect size of 1.06. Memory impairment and MTL atrophy tended to increase when measured closer to the time of diagnosis, whereas effect sizes of CSF biomarkers tended to increase when measured longer before the diagnosis. The researchers concluded that memory impairment is a more accurate predictor of early AD than atrophy of MTL on MRI, whereas CSF abnormalities and memory impairment are about equally predictive. Therefore, the MRI and CSF biomarkers are not very sensitive to preclinical AD. While CSF markers have shown promise, additional studies with long follow-up periods in elderly participants who are normal at baseline are needed to evaluate this promise.

Roe and colleagues (2013) investigated whether Aβ42, tau, phosphorylated tau at threonine 181 (ptau181), tau/Aβ42, and ptau181/Aβ42 predict future decline in non-cognitive outcomes among individuals who were cognitively normal at baseline. Longitudinal data from 430 participants who donated CSF within 1 year of a clinical assessment indicating normal cognition and were 50 years of age or older were analyzed. Mixed linear models were used to assess whether baseline biomarker values predicted future decline in function (instrumental activities of daily living), weight, behavior, and mood. Clinical Dementia Rating Sum of Boxes (CDR-SB) and Mini-Mental State Examination (MMSE) scores were also assessed. Abnormal levels of each biomarker were related to greater impairment with time in behavior (p<0.035) and mood (p<0.012) symptoms, and increased difficulties with independent activities of daily living (p<0.012). However, biomarker levels were not linked to a change in weight with time (p>0.115). Abnormal biomarker values also forecasted more rapidly changing MMSE (p<0.041) and CDR-SB (p<0.001) scores compared with normal values. The investigators concluded that CSF biomarkers among cognitively normal individuals correlate with future decline in some, but not all, non-cognitive AD symptoms studied. The authors acknowledged that additional work is needed to determine the extent to which these findings generalize to other samples. The investigators also noted that future research should explore whether the ratio of tau/Aβ42 and ptau181/Aβ42 are better predictors of decline in non-cognitive outcomes compared with individual molecular marker alone.

Rivero-Santana and colleagues (2017) conducted a systematic review of studies analyzing the diagnostic performance of CSF Aβ42, t-tau, and p-tau in the discrimination between AD and frontotemporal lobar degeneration (FTLD) dementias. A Hierarchical Summary Receiver Operating Characteristic (HSROC) model was applied, which circumvents methodological problems of meta-analyses based on summary points of sensitivity and specificity values. They also examined relevant confounders of CSF biomarkers' diagnostic performance such as age, disease duration, and global cognitive impairment. The p-tau/Aβ42 ratio demonstrated the best diagnostic performance. No statistically significant effects of the confounders were detected. Nonetheless, the investigators found the p-tau/Aβ42 ratio may be especially indicated for younger subjects; p-tau may be preferable for less cognitively impaired individuals (high MMSE scores) and the t-tau/Aβ42 ratio for more cognitively impaired individuals (low MMSE scores). The researchers concluded that p-tau/Aβ42 ratio has potential for being implemented in the clinical routine for the differential diagnosis between AD and FTLD. The authors also recommended that future studies report information on confounders such as age, disease duration, and cognitive impairment.

In the Decision Summary section of the Centers for Medicare & Medicaid Services (CMS) National Coverage Analysis of Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (2022), the authors point out the following limitations of Aβ as a biomarker of Alzheimer's disease:

1. Amyloid is associated with normal physiologic processes. Normal functions of Aβ include disease prevention by protecting against oxidative stress and regulating cholesterol transport and anti-microbial activity. Additionally, Aβ protects the brain from infections, promotes recovery from injury and repairs leaks in the blood–brain barrier.
2. Amyloid plaques are seen in other diseases, such as cerebral amyloid angiopathy, dementia with Lewy bodies, Parkinson's disease, Huntington's disease, and inclusion body myositis.
3. Amyloid plaques can be identified in cognitively normal older adults. Autopsy studies demonstrate that approximately 1/3 of cognitively normal older individuals (20-65% depending on age) have amyloid accumulation at levels consistent with AD pathology (CMS, 2022).

In 2023, Nisenbaum published the results of a follow-up study of the EMERGE and ENGAGE clinical trials used in the FDA application for the anti-amyloid drug aducanumab. As noted below, those studies did not use measurement of CSF Aβ42, p-tau, or t-tau as clinical trial inclusion criteria or for subject selection purposes. The Nisenbaum study assessed the use of these biomarkers as an alternative to amyloid PET for confirmation of brain pathology using data from 350 subjects (EMERGE n=208, ENGAGE n=142) who had an evaluable baseline CSF screening value and baseline PET scan. A total of 308 subjects were identified as PET positive and 42 were identified as PET negative. Compared with the PET negative group, the mean CSF Aβ42 level was numerically lower in the PET positive group (484.4 pg/mL in the CSF group vs. 933.3 pg/mL in the PET negative group). The p-tau181 level was numerically higher (91.42 pg/mL in the PET positive group vs.40.09 pg/mL in the PET negative group). The t-tau level was numerically higher in the PET positive group (594.8 pg/mL in the PET positive group vs. 374.6 pg/mL in the PET positive group). In contrast, Aβ40 levels were similar between groups (10,973.9 pg/mL in the PET positive group vs.11,251.0 pg/mL in the PET negative group). The Aβ42/Aβ40 ratio was numerically lower in the PET positive group (0.048 in the PET positive group vs. 0.087 in the PET negative group). The p-tau181/Aβ42 and t-tau/Aβ42 ratios were numerically higher in the PET positive group (0.203 in the PET positive group vs. 0.050 in the PET negative group for and t-tau181/Aβ42; and 1.329 in the PET positive group vs. 0.433 in the PET negative group for t-tau/Aβ42). The area under the curve (AUC) for Aβ42, p-tau and t-tau were calculated by receiver operating characteristic curve (ROC curve), which indicated high accuracy for all three (AUCs ≥ 0.90; p<0.0001). In contrast, Aβ40 was found to have an unfavorable AUC and deemed not useful for the detection of the visual status of PET scans (AUC, 0.49; p=0.782). Finally, the combination of Aβ42 with Aβ40 demonstrated high diagnostic accuracy with PET visual assessment (AUCs, 0.90; p<0.0001). The sensitivity, specificity and overall percent agreement (OPA) was calculated using optimal cutoff values that maximize the Youden J index in the ROC analysis. The maximum Youden J index was observed at a cutoff of 664 pg/mL for Aβ42. For the Aβ42/Aβ40 ratio the best cut-off was 0.062. With these cutoffs, Aβ42 showed the highest diagnostic accuracy as a single biomarker with an OPA of 89.4%. Additionally, the sensitivity and specificity were improved when Aβ42 was combined with a second analyte (94.4% and 88.1% for Aβ42/Aβ40, 95.4% and 83.3% for p-tau181/Aβ42, and 92.3% and 81.6% fort-tau/Aβ42. The authors concluded that their data supported the use of CSF biomarkers as reliable alternatives to PET imaging for brain Aβ pathology confirmation.

Neural Thread Protein (NTP)

Neural thread protein is a protein that is associated with neurofibrillary tangles. Both CSF and urine levels of this protein have been

investigated as a potential biochemical marker of AD.

Zhang et al (2014) conducted a systematic review and meta-analysis of urinary AD-associated neural thread protein (NTP) for diagnosing AD in individuals with suspected AD. Nine studies met the inclusion criteria (n=841 individuals with probable or possible AD; 37 individuals with MCI, 992 with non-AD dementia or controls without dementia). The reference standard consisted of a clinical diagnosis in eight studies and not described in another. Varying cutoffs for positive diagnosis were used amongst included studies. Controls were both healthy volunteers and individuals with other dementias. For a probable AD, pooled sensitivity and specificity were 89% (95% confidence interval [CI], 86% to 92%) and 90% (95% CI, 88% to 92%), respectively. Pooled positive and negative likelihood ratios were 8.9 (95% CI, 7.1 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively. The authors concluded that urinary AD7c-NTP is both a sensitive and specific test for the diagnosis of probable AD. However, whether urinary AD7c-NTP can be used as an early marker is still uncertain.

Neurofilament Light (NF-L)

Neurofilaments are intermediate filaments that serve as structural components of neuronal axons, in particular large, myelinated axons. NF-L has been studied in individuals with neuronal injury and neurodegenerative diseases because it is released into CSF and systemic circulation when neurons are damaged. Sjogren and colleagues (2000) reported that CSF NF-L levels are increased in subjects with frontotemporal dementia (FTD) and late onset AD compared with control subjects, and the increase in FTD subjects is higher than in late onset AD.

In a meta-analysis, Olsson and colleagues (2016) found that NF-L has a large effect size for differentiating individuals with AD from control subjects. Additionally, Zetterberg and colleagues (2016) demonstrated that higher CSF NF-L concentrations are associated with cognitive deterioration and brain atrophy over time in AD and MCI groups and concluded that CSF NF-L could be used as a marker for AD progression. However, elevated CSF levels of NF-L are also found in other neurodegenerative diseases, such normal-pressure hydrocephalus, multiple sclerosis, Parkinson's disease and amyotrophic lateral sclerosis. Therefore, CSF NF-L could be a representative marker of neurodegeneration, but not a precise marker for distinguishing AD from other neurological disorders.

Skin Fibroblast

Researchers are also exploring the use of skin fibroblast testing as a means to detect and differentiate AD from other dementias. The Discern™ Alzheimer's disease test (NeuroDiagnostics, Rockville, MD) examines skin fibroblast cells to identify and quantify three biomarkers (the phosphorylated Erk1 and Erk2, quantitatively measure skin fibroblast networks and protein kinase C€ levels), each of which is reported to independently identify and differentiate AD. At the time of this review, peer-reviewed studies assessing the analytical validity of this test were limited (Chirila, 2013; Chirila, 2014; Nelson, 2017). Large, randomized, controlled trials demonstrating this test is as accurate as autopsy results (the gold standard in the definitive diagnosis of AD) are needed in order to assess the clinical utility of the test.

Tau Protein

CSF t-tau and p-tau are frequently studied in neurodegenerative disorders. CSF t-tau levels can serve as a neuronal injury marker and are elevated in many neurodegenerative diseases, such as Creutzfeldt-Jakob disease, AD, and FTD, whereas CSF p-tau 181 or p-tau 231 (tau phosphorylated at threonine 181 or threonine 231) levels are elevated more specifically in AD than in other neurodegenerative diseases. Like CSF Aβ42, t-tau and p-tau tests are difficult to use in healthy people at the preclinical stage because of the limitation of obtaining CSF samples.

Mattsson and colleagues (2016) investigated if plasma tau is altered in AD and whether it is related to alterations in cognition, CSF biomarkers of AD pathology (Aβ and tau), brain metabolism and brain atrophy. This was a study of plasma tau in prospectively followed subjects with AD (n=179), subjects with MCI (n=195), and cognitive healthy controls (n=189) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and cross-sectionally studied subjects with AD (n=61), MCI (n=212), and subjective cognitive decline (n=174) and controls (n=274) from the Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER) study at Lund University, Sweden. A total of 1284 participants were evaluated. Tested associations were between plasma tau and diagnosis, CSF biomarkers, MRI measures, 18fluorodeoxyglucose-PET, and cognition. The researchers reported that higher plasma tau was associated with AD dementia, higher CSF tau, and lower CSF Aβ42, but the correlations were weak and differed between ADNI and BioFINDER. The longitudinal analysis in ADNI demonstrated significant associations between plasma tau and worse cognition, more atrophy, and more hypo-metabolism during follow-up. The researchers concluded that plasma tau partly reflected AD pathology, but the overlap between normal aging and AD was large, especially in subjects without dementia. They also concluded that despite group-level differences, these results did not support plasma tau as an AD biomarker in individual people.

The authors noted that while this was the largest published study on plasma tau, there were some drawbacks. For example: some ADNI participants had plasma tau below the lower limit of quantification of the assay. Although these measurements were uncertain, they were included because excluding them would have biased the data toward higher plasma tau. Also, the researchers utilized only one plasma tau assay, but it is possible that other assays capture tau fragments that are less sensitive to peripheral degradation and more likely to reflect AD pathology.

Olsson and colleagues (2020) reported the results of a systematic review and meta-analysis for 15 biomarkers in both CSF and blood to assess which of these were most altered in Alzheimer's disease. Of the eligible studies, 151 provided data on T-tau in CSF. These studies consisted of 164 cohorts with AD and 153 control cohorts representing a total of 11,341 AD subjects and 7086 controls. The authors found that increased levels of CSF t-tau and p-tau were strongly associated with AD and MCI subjects that developed AD.

Building upon the premise that blood total-tau originates primarily from peripheral, non-brain sources, Gonzalez-Ortiz and colleagues (2022) investigated if an anti-tau antibody that selectively binds brain-derived tau (BD-tau) and avoids the peripherally expressed 'big tau' isoform could be used as a biomarker to identify AD-type neurodegeneration. The researchers validated their assay in five cohorts that included a total of 609 patient samples. The researchers' observations included the following:

1. Blood-based BD-tau demonstrated equivalent diagnostic performance to both CSF total-tau and CSF brain-derived tau in distinguishing biomarker-positive Alzheimer's disease participants from biomarker-negative controls.
2. Plasma-based BD-tau accurately differentiated autopsy-confirmed Alzheimer's disease from other neurodegenerative diseases with an area under the receiver operating curve (AUC) of 86.4%, while plasma neurofilament light was not significantly increased (AUC 54.3%).
3. Serum BD-tau distinguished Alzheimer's from other neurodegenerative disorders -- including frontotemporal lobar degeneration and atypical parkinsonian disorders -- with AUCs up to 99.6%.
4. Plasma/serum BD-tau correlated with neurofilament light only in Alzheimer's disease, but not in the other neurodegenerative diseases.

Researchers plan to conduct large-scale clinical validation of blood brain-derived-tau in a wide range of cohorts including individuals with diverse racial and ethnic backgrounds. Studies will incorporate older adults with no biological evidence of Alzheimer's disease as

well as those at different stages of the disease. The authors also acknowledge that more research is needed to address the characteristics of this biomarker, longitudinal changes across the Alzheimer's disease continuum in both sporadic and familial Alzheimer's disease. Additionally, research is needed to verify the generalizability of the biomarker in diverse, multi-ethnic cohorts from a variety of populations.

For additional information, please see the discussion Nisenbaum (2023) above.

Targeted Therapy

On June 7, 2021, the United States Food and Drug Administration (FDA) granted accelerated approval of the anti-amyloid drug aducanumab based on results of EMERGE and ENGAGE clinical trials. The two trials of 18-month duration were conducted in participants with MCI due to AD or mild AD, mean age of 70 years. The ENGAGE trial demonstrated no benefit while the high-dose EMERGE trial initially also exhibited no benefit but with longer follow-up demonstrated a significant decrease in amyloid plaque on PET scans. The inclusion criteria for both of these trials required participants to have a positive amyloid PET scan and to consent to apolipoprotein E (ApoE) genotyping, as part of trial entry. Researchers conducted biomarker substudies in subgroups of participants in each trial to assess the effects of Aduhelm on brain amyloid pathology as well as CSF Aβ and tau levels; however, biomarker evaluations did not constitute defined endpoints in either of the trials and only included 30% and 35% of the participants in EMERGE and ENGAGE, respectively. Furthermore, use of CSF Aβ and tau levels were not used as clinical trial inclusion criteria, or for patient selection purposes. Because the cognitive deterioration associated with MCI and mild AD dementia often occurs over the span of years, the 78-week follow up duration period of EMERGE and ENGAGE complicates the ability to draw conclusions regarding the effectiveness of Aduhelm for treating early AD.

In April 2022, CMS announced a National Coverage Determination (NCD) that provides coverage for FDA-approved monoclonal antibodies directed against amyloid for the treatment of AD when furnished in accordance with Section B (Coverage Criteria) (CMS, 2022).

On January 6, 2023 the FDA granted accelerated approval of another anti-amyloid drug, lecanemab-irmb (Leqembi), for the treatment of individuals diagnosed with Alzheimer's disease with mild cognitive impairment or mild dementia stage of disease. Full approval was granted on July 6, 2023 based on results of an 18-month long double-blind, placebo-controlled, parallel-group, dose-finding study of 856 subjects aged 50 to 90 years with Alzheimer's disease-related mild cognitive impairment or mild dementia stage of disease and confirmed presence of amyloid beta pathology (van Dyck, 2022). Inclusion criteria required amyloid positivity determined by either PET imaging or CSF measurement of Aβ42 peptide. Subjects receiving the treatment were reported to have a change of 0.45 points on an 18-point scale in the Clinical Dementia Rating–Sum of Boxes (CDR-SB) over 18 months. A sub study of amyloid burden on PET imaging involving 698 subjects found a significant decrease in mean amyloid level from baseline to 18 months (-55.48 centiloids in the lecanemab group vs. 3.64 centiloids in the placebo group, p<0.001).

Recommendations from Authoritative Organizations

In a collaborative position statement, the joint committee of the American Academy of Neurology, American Neurological Association, and Child Neurology Society stated that biomarker testing in asymptomatic individuals is recommended only in a research setting, in part due to the potential harms and the absence of interventions that can favorably alter the natural history of the disease. For symptomatic individuals, the author indicated that "CSF and PET biomarkers of amyloid and tau aggregation are now also being used to diagnose symptomatic patients with atypical presentations of dementia" (Chiong, 2021).

Summary

At this time, there are inadequate data regarding the role of biochemical testing in *asymptomatic* individuals or whether test results might alter the medical management, treatment, or clinical outcomes in individuals with AD. With regard to *symptomatic* individuals, testing for the presence of Aβ in CSF (PET imaging) is required for the selection of appropriate candidates for treatment with amyloid beta targeting therapy (for example, lecanemab-irmb [Leqembi™]).

Testing for other biochemical markers has not been demonstrated to improve the accuracy of a clinical diagnosis of AD. The majority of available studies focus on those with probable AD, for whom the clinical diagnosis has a sensitivity of 85%. Additionally, there are inadequate data to suggest that the use of biomarker tests (other than Aβ in CSF) is likely to impact clinical management in terms of either altering the diagnostic work up or therapy, or informing appropriateness for therapy, in a manner that improves net health outcomes.

Background/Overview

AD is a progressive and ultimately fatal dementia that can be familial or idiopathic (no family history). The majority of AD is late-onset, but there is also a less common early-onset form of AD, which appears before the age of 65 and is associated with a rapid decline, cognitive and behavioral changes, and severe neurochemical and neuropathological changes.

Biomarkers are biological changes that can be quantified to indicate the absence or presence a disease or the risk of developing a disease. Biomarkers may be used to help researchers and medical practitioners diagnose diseases and health conditions, identify health risks in an individual, monitor responses to treatment, and see how an individual's disease or health condition changes over time. Researchers continue to explore the use of biomarkers as an accurate and conclusive means to diagnose and screen for AD.

Definitions

Alzheimer's disease: A progressive neurological condition, including dementia, which primarily affects memory.

Amyloid-beta 42 (Aβ42): A protein that accumulates abnormally in the brains of individuals with AD; the major component of amyloid plaques in the brain.

Biomarker: A naturally occurring, measurable substance in an organism whose presence is indicative of a normal physiological state, pathological processes, or pharmacologic responses to therapy; Objective medical signs that are used to measure the presence or progress of disease, or the effects of treatment.

Frontotemporal dementia: A broad term for a group of brain disorders that primarily affect the frontal and temporal lobes of the brain.

Neurofilament light chain (NFL) protein, A biomarker associated with neurodegeneration, neuronal damage.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [when specified as testing for long form amyloid beta, also referred to as Aβ, Aβ1-42, Beta-amyloid (1-42), and Abeta42, in CSF specimen]
84999	Unlisted chemistry procedure [when specified as testing for long form amyloid beta, also referred to as Aβ, Aβ1-42, Beta-amyloid (1-42), and Abeta42, in CSF specimen]
0358U	Neurology (mild cognitive impairment), analysis of β-amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative
	Lumipulse® G βAmyloid Ratio (1-42/1-40) Test, Fujirebio Diagnostics, Inc, Fujirebio Diagnostics, Inc

ICD-10 Diagnosis

G30.0-G30.9	Alzheimer's disease

When services are Investigational and Not Medically Necessary:

For the procedure and diagnosis codes listed above when criteria are not met.

When services are Investigational and Not Medically Necessary:

For the following procedure and diagnosis codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [when specified as tau protein, or amyloid beta peptide testing other than long form Aβ, Aβ1-42, Beta-amyloid (1-42), and Abeta42 in CSF specimen]
84999	Unlisted chemistry procedure [when specified as tau protein, amyloid beta peptide testing other than long form Aβ, Aβ1-42, Beta-amyloid (1-42), and Abeta42 in CSF specimen, or neural thread protein biochemical testing]

ICD-10 Diagnosis

F03.90-F03.94	Unspecified dementia, unspecified severity
F03.A0-F03.C4	Unspecified dementia, mild/moderate/severe
G30.0-G30.9	Alzheimer's disease
G31.1	Senile degeneration of brain, not elsewhere classified
R41.0	Disorientation, unspecified
R41.3	Other amnesia (memory loss NOS)
R41.81	Age-related cognitive decline

When services are also Investigational and Not Medically Necessary:

CPT

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™, NeuroDiagnostics, 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
	DISCERN™, NeuroDiagnostics, NeuroDiagnostics
0346U	Beta amyloid, Aβ40 and Aβ42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma
	QUEST AD-Detect™, Beta-Amyloid 42/40 Ratio, Plasma, Quest Diagnostics
0361U	Neurofilament light chain, digital immunoassay, plasma, quantitative
	Neurofilament Light Chain (NfL), Mayo Clinic, Mayo Clinic
0412U	Beta amyloid, Aβ42/40 ratio, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and qualitative ApoE isoform-specific proteotyping, plasma combined with age, algorithm reported as presence or absence of brain amyloid pathology
	PrecivityAD® blood test, C2N Diagnostics LLC, C2N Diagnostics LLC
0445U	β-amyloid (Abeta42) and phospho tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
	Elecsys® PhosphoTau (181P) CSF (pTau181) and βAmyloid (1-42) CSF II (Abeta 42) Ratio, Roche Diagnostics Operations, Inc (US owner/operator)

ICD-10 Diagnosis

	All diagnoses

References

Peer Reviewed Publications:

1. Andreasen N, Blennow K. CSF biomarkers for mild cognitive impairment and early Alzheimer's disease. Clinical Neurol Neurosurg. 2005; 107:165-173.
2. Bian H, Van Swieten JC, Leight S, et al. CSF biomarkers in frontotemporal lobar degeneration with known pathology. Neurology. 2008; 70(19 Pt 2):1827-1835.
3. Chirila FV, Khan TK, Alkon DL. Fibroblast aggregation rate converges with validated peripheral biomarkers for Alzheimer's disease. J Alzheimers Dis. 2014; 42(4):1279-1294.
4. Chirila FV, Khan TK, Alkon DL. Spatiotemporal complexity of fibroblast networks screens for Alzheimer's disease. J

Alzheimers Dis. 2013; 33(1):165-176.

5. Du Y, Dodel R, Hampel H, et al. Reduced levels of amyloid beta-peptide antibody in Alzheimer disease. Neurol. 2001; 57(5):801-805.
6. Galasko D, Clark C, Chang L, et al. Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. Neurology. 1997; 48(3):632-635.
7. Gonzalez-Ortiz F, Turton M, Kac PR, et al. Brain-derived tau: a novel blood-based biomarker for Alzheimer's disease-type neurodegeneration. Brain. 2023;146(3):1152-1165.
8. Hansson O, Lehmann S, Otto M, et al. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther. 2019; 11(1):34.
9. Jia JP, Meng R, Sun YX, et al. Cerebrospinal fluid tau, AB(1-42) and inflammatory cytokines in patients with Alzheimer's disease and vascular dementia. Neuroscience Letters. 2005; 383:12-16.
10. Josephs KA, Whitwell JL, Knopman DS, et al. Abnormal TDP-43 immunoreactivity in AD modifies clinicopathologic and radiologic phenotype. Neurology. 2008; 70(19 Pt 2):1850-1857.
11. Kapaki E, Liappas I. Paraskevas GP, et al. The diagnostic value of tau protein, beta-amyloid (1-42) and their ration for the discrimination of alcohol-related cognitive disorders from Alzheimer's disease in the early stages. Internat J Geriatric Psych. 2005; 20:722-729.
12. Lannfelt L, Blennow K, Zetterberg H, et al.; PBT2-201-EURO study group. Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol. 2008; 7(9):779-786.
13. Li D, Mielke MM. An Update on blood-based markers of Alzheimer's disease Using the SiMoA platform. Neurol Ther. 2019; 8(Suppl 2):73-82.
14. Matthews KA, Xu W, Gaglioti AH, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015-2060) in adults aged ≥65 years. Alzheimers Dement. 2019; 15(1):17-24.
15. Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA. 2009 22; 302(4):385-393.
16. Mattsson N, Zetterberg H, Janelidze S, et al. ADNI Investigators. Plasma tau in Alzheimer disease. Neurology. 2016; 87(17):1827-1835.
17. Nam E, Lee YB, Moon C, Chang KA. Serum tau proteins as potential biomarkers for the assessment of Alzheimer's disease progression. Int J Mol Sci. 2020; 21(14):5007.
18. Nelson TJ, Sun MK, Lim C, et al, Chirila FV, Alkon DL. Bryostatin effects on cognitive function and PKCε in Alzheimer's disease Phase IIa and expanded access trials. J Alzheimers Dis. 2017; 58(2):521-535.
19. Nisenbaum L, Martone R, Chen T, et al. CSF biomarker concordance with amyloid PET in Phase 3 studies of aducanumab. Alzheimers Dement. 2023; 19(8):3379-3388.
20. 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. 2016, 15(7);673-684.
21. 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. 2019; 321(13):1286-1294.
22. Rivero-Santana A, Ferreira D, Perestelo-Pérez L, et al. Cerebrospinal fluid biomarkers for the differential diagnosis between Alzheimer's disease and frontotemporal lobar degeneration: systematic review, HSROC analysis, and confounding factors. J Alzheimers Dis. 2017; 55(2):625-644.
23. Roe CM, Fagan AM, Grant EA, et al. CSF biomarkers of Alzheimer disease: "noncognitive" outcomes. Neurology. 2013; 81(23):2028-2031.
24. Schmand B, Huizenga HM, van Gool WA. Meta-analysis of CSF and MRI biomarkers for detecting preclinical Alzheimer's disease. Psychol Med. 2010; 40(1):135-145.
25. Sinha S. The role of beta-amyloid in Alzheimer's disease. Med Clin North Am. 2002; 86(3): 629-639.
26. Sjogren M, Rosengren L, Minthon L, et al. Cytoskeleton proteins in CSF distinguish frontotemporal dementia from AD. Neurology 2000, 54, 1960–1964.
27. Teunissen CE, de Vente J, Steinbusch HW, De Bruijn C. Biochemical markers related to Alzheimer's dementia in serum and cerebrospinal fluid. Neurobiol Aging. 2002; 23(4):485-508.
28. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's Disease (Clarity AD). NEJM. 2023; 388:9-21.
29. Zetterberg, H, Skillback, T, Mattsson, N, et al. Association of cerebrospinal fluid neurofilament light concentration with Alzheimer disease progression. JAMA Neurol. 2016; 73(1):60-67.
30. 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.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Psychological Association. Guidelines for the evaluation of dementia and age-related cognitive change. Am Psychol. 2012; 67(1):1-9. Available at: https://www.apa.org/practice/guidelines/guidelines-dementia-age-related-cognitive-change.pdf. Accessed on October 13, 2023.
2. Biogen. Aducanumab. (Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document. https://fda.report/media/143503/PCNS-20201106-CombinedFDABiogenBackgrounder_0.pdf. Accessed on October 13, 2023.
3. Centers for Medicare and Medicaid Services (CMS). National Coverage Analysis (NCA), Decision Memo. CAG-00460N. Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. April 7, 2022. Available at: https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=305. Accessed on October 13, 2023.
4. Chiong W, Tsou AY, Simmons Z, et al. Ethics, Law, and Humanities Committee (a joint committee of the American Academy of Neurology, American Neurological Association, and Child Neurology Society). Ethical considerations in dementia diagnosis and care: AAN Position Statement. Neurology. 2021; 97(2):80-89.
5. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol. 2021; 20(6):484-496.
6. 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 2017; 13(3):285-295.
7. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018; 14(4):535-562.
8. 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. 2011; 7(3):263-269.
9. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001; 56(9):1143-1153.
10. Petersen RC, 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. 2018; 90:126-135.

11. U.S. Food and Drug Administration (FDA). Aducanumab (Aduhelm) Product label. Biogen; Rockville, MD: FDA. July 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s003lbl.pdf. Accessed on October 13, 2023.
12. U.S. Food and Drug Administration (FDA) Denovo Notification Database. Lumipulse G β-Amyloid Ratio (1-42/1-40) ™ Summary of Safety and Effectiveness. DEN200072. Rockville, MD: FDA. May 4, 2022. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm. Accessed on November 05, 2023.
13. U.S. Food and Drug Administration (FDA). Lecanemab-irmb (Leqembi™) Product label. Eisai; Nutley, NJ: FDA. January 6, 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s000lbl.pdf. Accessed on October 13, 2023.

Websites for Additional Information

1. National Institutes of Health (NIH) Biomarkers for dementia detection and research. Last reviewed January 21, 2022. Available at: https://www.nia.nih.gov/health/biomarkers-dementia-detection-and-research#CSF. Accessed on October 5, 2023.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	04/01/2024	Updated Coding section with 04/01/2024 CPT changes, added 0445U.
Revised	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Added MN criteria for measurement of amyloid beta. Revised INV/NMN statement. Updated Rationale, Coding, References, Websites for Additional Information and Index sections.
	09/27/2023	Updated Coding section with 10/01/2023 CPT changes; added 0412U.
Reviewed	02/16/2023	MPTAC review. Updated Description/Scope, Rationale, References, Websites for Additional Information sections.
	12/28/2022	Updated Coding section with 01/01/2023 CPT changes; add 0358U and 0361U.
	09/28/2022	Updated Coding section with 10/01/2022 CPT changes to add 0346U, and 10/01/2022 ICD-10-CM changes to add F03.94 and F03.A0-F03.C4.
New	02/17/2022	MPTAC review. Moved content related to biomarker testing for AD from GENE.00003 "Biochemical Markers for the Diagnosis and Screening of Alzheimer's Disease" to this document, including CPT codes 83520, 84999, 0206U and 0207U.