of Tennessee

Policy

Reimbursement Policy

Biochemical Markers of Alzheimer Disease and Dementia

POLICY DESCRIPTION | INDICATIONS AND/OR LIMITATIONS OF COVERAGE | APPLICABLE STATE AND FEDERAL REGULATIONS | APPLICABLE CPT/HCPCS PROCEDURE CODES | EVIDENCE-BASED SCIENTIFIC REFERENCES |

I. Policy Description

Alzheimer disease (AD) is a neurodegenerative disease defined by a gradual decline in memory, cognitive functions, gross atrophy of the brain, and accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles (Karch et al., 2014).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in "Applicable State and Federal Regulations" section of this policy document.

1) For individuals with Alzheimer disease or mild cognitive impairment, measurement of amyloid beta peptides in cerebrospinal fluid **MEETS COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

2) Measurement of cerebrospinal fluid biomarkers of Alzheimer disease or dementia not mentioned above (e.g., tau protein, α-synuclein, or neural thread proteins) **DOES NOT MEET COVERAGE CRITERIA**.

3) Measurement of plasma and/or serum biomarkers of Alzheimer disease or dementia (e.g., tau protein, amyloid beta peptides, neural thread proteins, ApoE, and ApoE4) **DOES NOT MEET COVERAGE CRITERIA**.

4) Measurement of urinary biomarkers of Alzheimer disease or dementia (e.g., neural thread proteins, amyloid beta peptides, and urinary extracellular vesicle analysis) **DOES NOT MEET COVERAGE CRITERIA**.

5) The use of multianalyte assays, algorithmic analysis, and/or any other tests not mentioned above for the prognosis, diagnosis, and/or management of Alzheimer disease or dementia **DOES NOT MEET COVERAGE CRITERIA**.

III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

On February 15, 2018, the FDA released a statement concerning the advancement of the development of novel treatments for neurological conditions, including Alzheimer disease. FDA Commissioner Scott Gottlieb, M.D., states, "Symptoms and progression of neurological diseases can also vary significantly across patients, and even within patients, and across organ systems. Some diseases, like Alzheimer's, may progress invisibly for years. Once clinical symptoms become apparent, significant function may already be lost. These issues can make drug development more challenging for companies and are deeply frustrating for patients and caregivers living with these serious and life-threatening conditions. The FDA recognizes the urgent need for new medical treatments for many serious conditions including neurological disorders such as muscular dystrophies, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), migraine and epilepsy. This requires us to become more nimble, collaborative and patient-focused. As part of our ongoing efforts to expand access to safe and effective treatment options across all disease areas and promote innovation, the FDA is modernizing multiple aspects of our drug regulatory programs – including how we communicate scientific and regulatory guidance for drug development" (Gottlieb, 2018). Concurrently, the FDA released a guidance for industry concerning AD for public comment for 90 days. Within the guidance, the FDA states, "FDA supports and endorses the use of diagnostic criteria that are based on a contemporary understanding of the pathophysiology and evaluation of AD… Important findings applicable to the categorization of AD along its continuum of progression include the presence of pathophysiological changes as measured by biomarkers, the presence or absence of detectable abnormalities on sensitive neuropsychological measures, and the presence or absence of functional impairment manifested as meaningful daily life impact the present with subjective complaints or reliable observer reports" (FDA, 2024). The final draft of the guidance should be released in the future after the public comment period has concluded.

In 2022, the FDA permitted marketing for the Fujirebio Diagnostics Lumipulse® G β-Amyloid Ratio (1-42/1-40) test, which is administrated under a CMS laboratory certification process. It is intended to measure the ratio of beta-amyloid 1-42 and beta-amyloid 1-40 concentrations in CSF,

which can help predict the likelihood of amyloid plaque formation in potential AD. This assay received the "Breakthrough Device Designation" from the FDA in May 2022 (FDA, 2022).

Roche Diagnostics received 501(k) clearance from the FDA for their Elecsys® beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys® Phospho-Tau (181P) CSF (pTau181) assays in 2022 for adults 55 years and older who are evaluated for the disease to generate a pTau181/Abeta42 ratio value. In June 2023, Roche Diagnostics also received 501(k) clearance from the FDA for the Elecsys® beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys® Total-Tau CSF assays (tTau) in the same population through the tTau/Abeta42 ratio, and will be available in Q4 2023 (Roche, 2023).

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

IV. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
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 Proprietary test: DISCERN™ Lab/Manufacturer: NeuroDiagnostics
0207U	Quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure) Proprietary test: DISCERN™ Lab/Manufacturer: NeuroDiagnostics
0289U	Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score Proprietary test: MindX Blood Test™ - Memory/Alzheimer's Lab/Manufacturer: MindX Sciences™ Laboratory/MindX Sciences™ Inc
0346U	Beta amyloid, Aβ40 and Aβ42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma Proprietary test: QUEST AD-Detect™, Beta-Amyloid 42/40 Ratio, Plasma

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	Lab/Manufacturer: Quest Diagnostics
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 Proprietary test: Lumipulse® G β-Amyloid Ratio (1-42/1-40) Test Lab/Manufacturer: Fujirebio Diagnostics, Inc
0393U	Neurology (eg, Parkinson disease, dementia with Lewy bodies), cerebrospinal fluid (CSF), detection of misfolded α-synuclein protein by seed amplification assay, qualitative Proprietary test: SYNTap® Biomarker Test Lab/Manufacturer: Amprion Clinical Laboratory
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 Proprietary test: PrecivityAD® blood test Lab/Manufacturer: C2N Diagnostics LLC
0443U	Neurofilament light chain (nfl), ultra-sensitive immunoassay, serum or cerebrospinal fluid Proprietary test: Neurofilament Light Chain (NfL) Lab/Manufacturer: Neuromuscular Clinical Laboratory at Washington University in St. Louis School of Medicine, Neuromuscular Clinical Laboratory at Washington University in St. Louis School of Medicine
0445U	B-amyloid (abeta42) and phospho tau (181p) (ptau181), electrochemiluminescent immunoassay (eclia), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology Proprietary test: Elecsys® PhosphoTau (181P) CSF (pTau181) and βAmyloid (1-42) CSF II (Abeta 42) Ratio Lab/Manufacturer: Roche Diagnostics Operations, Inc (US owner/operator)
0459U	β-amyloid (Abeta42) and total tau (tTau), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology Proprietary test: Elecsys® Total Tau CSF (tTau) and βAmyloid (1-42) CSF II (Abeta 42) Ratio Lab/Manufacturer: Roche Diagnostics Operations, Inc (US owner/operator)
0479U	Tau, phosphorylated, pTau217 Proprietary test: ALZpath pTau217 Lab/Manufacturer: Neurocode USA, Inc, Quanterix/ALZpath
0503U	Neurology (Alzheimer disease), beta amyloid (Aβ40, Aβ42, Aβ42/40 ratio) and tau-protein (ptau217, np-tau217, ptau217/nptau217 ratio), blood,

	immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS), algorithm score reported as likelihood of positive or negative for amyloid plaques Proprietary test: PrecivityAD2™ Lab/Manufacturer: C2N Diagnostics, LLC

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Evidence-based Scientific References

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