Medical Policy

PARAMOUNT

HMO AND PPO
ELITE (MEDICARE ADVANTAGE)
MARKETPLACE

Genetic and Biomarker Testing for Alzheimer Disease

Policy Number: PG0441
Last Review: 09/01/2024

GUIDELINES:

- **This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder terms, conditions, exclusions, and limitations contract. It does not constitute a contract or guarantee regarding coverage or reimbursement/payment. Self-Insured group specific policy will supersede this general policy when group supplementary plan document or individual plan decision directs otherwise.**
- **Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards.**
- **This medical policy is solely for guiding medical necessity and explaining correct procedure reporting used to assist in making coverage decisions and administering benefits.**

SCOPE:
X Professional
X Facility

DESCRIPTION:
Alzheimer disease (AD) is a neurodegenerative disease defined by a gradual decline in memory, cognitive functions, gross atrophy of the brain, and an accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles. AD usually occurs in adulthood and is marked by a decline in cognitive functions such as remembering, reasoning, and planning.

Approximately 75% of Alzheimer disease is non-familial and about 25% of Alzheimer disease is familial. Familial Alzheimer disease (FAD) is typically defined by having 3 or more affected individuals with Alzheimer disease in a family. While most cases of FAD are late-onset (diagnosed at age 60-65 or later), less than 2% of Alzheimer disease cases are related to Early-Onset Familial Alzheimer Disease (EOFAD). 60-80% of EOFAD cases can be attributed to a gene mutation in *APP, PSEN1*, or *PSEN2*, and are inherited in an autosomal dominant manner, while the remaining genetic causes are unknown.

If a gene mutation in *APP, PSEN1*, or *PSEN2*, is identified in an affected family member, it can allow for predictive genetic testing (testing for asymptomatic at-risk individuals) for family members. Formal genetic counseling should be performed prior to such testing and recommendations for genetic counseling exist in the "Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors."

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

There are inadequate data regarding the role of biochemical testing in asymptomatic individuals or how test results may alter the medical management, treatment, or clinical outcomes in individuals with AD. With regard to symptomatic individuals, there is inadequate data to suggest that the addition of biochemical markers improves the clinical diagnosis of AD. There is inadequate data to suggest that the use of the tests would change clinical management in terms of either altering the diagnostic work up or therapy, or informing appropriateness for

therapy.

Neurofilament Light (NF-L) is 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. CSF NF-L concentrations are associated with cognitive deterioration and brain atrophy over time in AD and mild cognitive impairment (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, 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.

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 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 this time, peer-reviewed studies assessing the analytical validity of this test were limited. 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.

POLICY:

Paramount Commercial Insurance Plans and Elite (Medicare Advantage) Plans

- **Genetic testing for a known familial variant in the presenilin (PSEN1, PSEN2) genes or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease (AD) may be considered medically necessary when the coverage criteria below are met.**
- **Biomarker testing, cerebrospinal fluid, plasma, serum and/or urinary, for Alzheimer disease is considered experimental/investigational and therefore non-covered**

COVERAGE CRITERIA:

Paramount Commercial Insurance Plans and Elite (Medicare Advantage) Plans

Genetic Testing- PSEN1, PSEN2, or APP Known Familial Mutation Testing

1. Genetic counseling for familial Alzheimer disease genetic testing MEETS COVERAGE CRITERIA and is required for coverage of familial Alzheimer disease genetic testing.
2. Genetic testing for APP, PSEN1 and PSEN2 genes associated with familial Alzheimer disease (i.e., autosomal-dominant, early-onset dementia not attributable to other factors) only MEETS COVERAGE CRITERIA when;
    a. There is no previous genetic testing that would detect the familial mutation; AND
    b. The results of the testing will inform reproductive decision making; AND
    c. The individual is in one of the following situations:
        i. Individuals with a family history of autosomal dominant dementia with one or more instances of early-onset AD, OR
        ii. Individuals with a first-degree or second-degree biological relative with a known mutation in the PSEN1, PSEN2, or APP genes (Note: test for known familial mutation), OR
        iii. Symptomatic individuals with suspected early-onset AD when there is an unknown family history (adoption)

Genetic testing for confirming a diagnosis of Alzheimer’s disease or determining the risk assessment of developing AD when family planning is not an issue is considered experimental /investigational.

Genetic testing for Alzheimer's disease is experimental/investigational and therefore considered not medically necessary in all other situations, may not be an all-inclusive listing:

- Testing to confirm a diagnosis of Alzheimer's disease (any type)
- Testing for familial Alzheimer's disease in children

- Testing for late-onset Alzheimer's disease (age > 65 years)
- Testing for other purposes than reproductive decision making
- Testing of APOE gene and/or any other genes not listed above
- Testing for purposes of Alzheimer's disease risk assessment
- Screening asymptomatic individuals
- Testing in all other situations not described above

Biomarker Testing

COVERAGE:

Measurement of cerebrospinal fluid biomarkers of Alzheimer disease or dementia (e.g., tau protein, amyloid beta peptides, α-synuclein, or neural thread proteins), when undertaken as a specified requirement for coverage of amyloid targeting antibodies for treatment of Alzheimer's disease.

NONCOVERGE:

Biomarker testing (for example, tau protein, AB-42, neural thread protein), via cerebrospinal fluid, plasma, serum and/or urinary, for Alzheimer disease is considered experimental/investigational and therefore non-covered because there is insufficient evidence in the peer-reviewed medical literature of the effectiveness of this testing, including, but may not be limited to;

- Aβ peptide testing (eg, SOBA-AD assay)
- CSF Aβ protein testing (eg, Lumipulse G [0358U])
- CSF or plasma biomarker testing for total tau or phospho-tau proteins
- CSF testing for alpha-Synuclein (eg, SYNTap biomarker test)
- Plasma Aβ protein testing (eg, PrecivityAD test and Quest AD-Detect [0346U])
- Plasma U-p53AZ (AZ 284) biomarker testing (eg, AlzoSure Predict test)
- Skin biopsy (eg, DISCERN test [0206U and 0207U])

Measurements of biochemical markers (including but not limited to tau protein, AB-42, neural thread protein) is considered experimental/investigational and not medically necessary as a diagnostic technique for individuals with symptoms suggestive of Alzheimer's disease.

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

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 is considered experimental/investigational and therefore considered not medically necessary.

The use of serum neurofilament light concentration measurements are considered experimental/investigational for the diagnosis and assessment of members with Alzheimer disease and related dementias because their clinical value remains unproven for this indication and therefore considered not medically necessary.

CODING/BILLING INFORMATION:

The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

CPT CODES	
81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) • *APOE (apolipoprotein E)* (e.g., hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (e.g., *2, *3, *4) [Not Covered if used to report any test indicated as not covered in the coverage criteria above.]

81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) • *PSEN1 (presenilin 1)* (e.g., Alzheimer disease), full gene sequence [Not Covered if used to report any test indicated as not covered in the coverage criteria above.]
81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) • *APP (amyloid beta [A4] precursor protein) (e.g., Alzheimer disease), full gene sequence* • *PSEN2 (presenilin 2 [Alzheimer disease 4]) (e.g., Alzheimer disease), full gene sequence* [Not Covered if used to report any test indicated as not covered in the coverage criteria above.]
82172	Apolipoprotein, each [Not Covered if used to report any test indicated as not covered in the coverage criteria above.]
82542	Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen [Not Covered if used to report any test indicated as not covered in the coverage criteria above.]
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [Not Covered if used to report any test indicated as not covered in the coverage criteria above.] [Used to report testing for tau protein and amyloid-β peptides: an example of this testing is the ADmark® CSF Analysis, which tests for phosphorylated tau protein, total tau protein, and amyloid-ß peptide 1-42 peptide in cerebrospinal fluid (CSF).]
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 **[Not Covered]** [CPT code that represents DISCERN™ by NeuroDiagnostics. Per the manufacturer, the Discern skin biopsy test can differentiate Alzheimer disease from non-AD dementias. This service may have been previously billed with 86849- Unlisted immunology procedure. Fibroblasts are cultured from a skin biopsy and subjected to morphological aggregation examination which is then scored.]
0207U	Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure) **[Not Covered]** [Represents a child code to 0206U. Phosphorylation of ERK1 and ERK2 in skin biopsy fibroblasts is measured in response to bradykinin treatment using in situ immunofluorescence and quantitative imaging.]
0289U	Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score **[Not Covered]**
0346U	Beta amyloid, Aβ40 and Aβ42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma **[Not Covered]** [CPT code that represents Quest Ad-Detect™. Per the manufacturer, this test measures plasma levels of Amyloid Beta (Abeta) 42 and 40 and utilizes the ratio of the two to assess the patient's risk of developing Alzheimer's Disease. • 0346U: Beta amyloid, Aβ40 and Aβ42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma]
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 [**Not Covered]**
0361U	Neurofilament light chain, digital immunoassay, plasma, quantitative (Effective 1/1/2023) **[Not Covered]** [CPT code that represents Neurofilament Light Chain (NfL), by Mayo Clinic. Per the lab, this is a plasma-based assay that can determine if cognitive decline may be related to a neurodegenerative condition. It is a non-specific biomarker for several neurodegenerative conditions, including Alzheimer's disease, multiple sclerosis, and amyotrophic lateral sclerosis.]

0393U	Neurology (eg, Parkinson disease, dementia with Lewy bodies), cerebrospinal fluid (CSF), detection of misfolded α-synuclein protein by seed amplification assay, qualitative **[Not Covered]**
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 **[Not Covered]**
0459U	β-amyloid (Abeta42) and total tau (tTau), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology **[Not Covered]**

REVISION HISTORY EXPLANATION: ORIGINAL EFFECTIVE DATE: 08/23/2018

Date	Explanation & Changes
08/23/2018	• Genetic testing for Alzheimer disease (e.g., *APOE, APP, PSEN1, PSEN2*) is non-covered for all product lines • Policy created to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG)
12/28/2020	• Medical policy placed on the new Paramount Medical policy format
03/03/2023	• Medical Policy updated to reflect Medicaid coverage to Anthem as of 02/01/2023
04/01/2023	• Policy created to reflect most current clinical evidence • Changed Policy name from Genetic Testing for Alzheimer Disease to Genetic and Biomarker Testing for Alzheimer Disease • Added noncoverage for biomarker testing, cerebrospinal fluid, plasma, serum and/or urinary, for Alzheimer disease is considered experimental/investigational and therefore non-covered • Added procedure codes 82172, 82542, 83520, 0206U, 0207U, 0289U, 0346U, 0358U, and 0361U
09/01/2024	• Policy updated to reflect most current clinical evidence. • Added noncovered procedures 0393U, 0412U, 0459U • Removed procedure S3852

Paramount reserves the right to review and revise our policies periodically when necessary. When there is an update, we will publish the most current policy to https://www.paramounthealthcare.com/providers/medical-policies/policy-library

REFERENCES/RESOURCES

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs

NCDs https://www.cms.gov/medicare-coverage-database/searchresults.aspx?keyword=&keywordType=starts&areaId=s29&docType=NCD&contractOption=all

LCDs https://www.cms.gov/medicare-coverage-database/searchresults.aspx?keyword=&keywordType=starts&areaId=s29&docType=F,P&contractOption=all

American Medical Association, *Current Procedural Terminology (CPT®)* and associated publications and services https://www.ama-assn.org/amaone/cpt-current-procedural-terminology

Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/HCPCS-Quarterly-Update

U.S. Preventive Services Task Force, https://www.uspreventiveservicestaskforce.org/uspstf/

Hayes, Inc., Lansdale, PA: Author. Health Technology Assessments. https://www.hayesinc.com/

Industry Standard Review