Biochemical and Cellular Markers of Alzheimer's Disease

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IMPORTANT REMINDER

The Medicare Advantage Medical Policy manual is not intended to override the member Evidence of Coverage (EOC), which defines the insured's benefits, nor is it intended to dictate how providers are to practice medicine. Physicians and other health care providers are expected to exercise their medical judgment in providing the most appropriate care for the individual member, including care that may be both medically reasonable and necessary.

The Medicare Advantage medical policies are designed to provide guidance regarding the decision-making process for the coverage or non-coverage of services or procedures in accordance with the member EOC and Centers of Medicare and Medicaid Services (CMS) policies and manuals, along with general CMS rules and regulations. In the event of a conflict, applicable CMS policy or EOC language will take precedence over the Medicare Advantage Medical Policy. In the absence of a specific CMS coverage determination for a requested service, item or procedure, the health plan may apply CMS regulations, as well as their Medical Policy Manual or other applicable utilization management vendor criteria developed with an objective, evidence-based process using scientific evidence, current generally accepted standards of medical practice, and authoritative clinical practice guidelines.

Some services or items may appear to be medically indicated for an individual, but may be a direct exclusion of Medicare or the member's benefit plan. Medicare and member EOCs exclude from coverage, among other things, services or procedures considered to be investigational (experimental) or cosmetic, as well as services or items considered not medically reasonable and necessary under Title XVIII of the Social Security Act, §1862(a)(1)(A). In some cases, providers may bill members for these non-covered services or procedures. Providers are encouraged to inform members in advance when they may be financially responsible for the cost of non-covered or excluded services. Members, their appointed representative, or a treating provider can request coverage of a service or item by submitting a pre-service organization determination prior to services being rendered.

DESCRIPTION

The diagnosis of Alzheimer's disease (AD) has traditionally been a clinical diagnosis, focusing on the exclusion of other causes of dementia. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's and Related Disorders Association (ADRDA) published clinical criteria for the diagnosis of AD. Three categories were defined: possible, probable, and definite AD. Definite AD is typically identified only at autopsy. Since diagnosis by exclusion can be frustrating for physicians, patients and families, there has been considerable research interest in identifying an inclusive laboratory test for AD, particularly for use early in the course of disease. Select biochemical and cellular marker testing has been investigated to predict risk of Alzheimer's disease (AD).

MEDICARE ADVANTAGE POLICY CRITERIA

CMS Coverage Manuals*	None
National Coverage Determinations (NCDs)*	None
Noridian Healthcare Solutions (Noridian) Local Coverage Determinations (LCDs) and Articles (LCAs)*	None
Medical Policy Manual	*Medicare coverage guidance is not available for the testing of biochemical markers of Alzheimer's disease. Therefore, the health plan's medical policy is applicable.* Biochemical and Cellular Markers of Alzheimer's Disease, Laboratory, Policy No. 22 *(see "NOTE" below)*

NOTE: If a procedure or device lacks scientific evidence regarding safety and efficacy because it is investigational or experimental, the service is noncovered as not reasonable and necessary to treat illness or injury. (*Medicare IOM Pub. No. 100-04, Ch. 23, §30 A*). According to Title XVIII of the Social Security Act, §1862(a)(1)(A), only medically reasonable and necessary services are covered by Medicare. In the absence of a NCD, LCD, or other coverage guideline, CMS guidelines allow a Medicare Advantage Organization (MAO) to make coverage determinations, applying an ***objective, evidence-based process, based on authoritative evidence***. (*Medicare IOM Pub. No. 100-16, Ch. 4, §90.5*). The Medicare Advantage Medical Policy - Medicine Policy No. M-149 - provides further details regarding the plan's evidence-assessment process (see Cross References).

POLICY GUIDELINES

MEDICARE AND MEDICAL NECESSITY

To be eligible for Medicare coverage, Medicare requires diagnostic laboratory tests be ordered by the physician who is treating the beneficiary for a specific medical problem **and** who will use the test results in the management of that specific medical problem.[1,2] The clinical usefulness of biomarker testing is based on whether the test results will inform management changes that lead to improved outcomes, as compared with management of symptoms, clinical assessment, and standard laboratory evaluation. Validation of the clinical use of any diagnostic test focuses on analytic validity, diagnostic validity, and clinical utility. *Analytic validity* demonstrates technical feasibility as compared to a gold standard, including assessment of test reproducibility and precision. *Diagnostic utility* is evaluated by the ability of a test to accurately predict the clinical outcome in appropriate populations of patients. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a gold standard must be known. *Clinical utility* is established when the evidence demonstrates that the diagnostic information obtained from a test can be used to benefit patient management and improve health outcomes.

The evidence for testing for AD-related CSF biomarkers for diagnosis in patients who have dementia or mild cognitive impairment consists of systematic reviews, meta-analyses and case series. However, most of the studies focus on select patient populations and define optimal

test cutoffs without validation, thereby limiting generalizability. Further, there is limited existing evidence examining incremental diagnostic accuracy of CSF biomarkers for AD diagnosis employing autopsy as a referent standard. The evidence does not demonstrate improvement over a clinical diagnosis, or whether diagnosis using CSF biomarkers would lead to improved net health outcomes. For predicting conversion from mild cognitive impairment (MCI) to AD, limited evidence suggests testing might define increased risk; however, further validation studies are needed. Whether earlier diagnosis leads to improved health outcomes through delay of AD onset or quality of life is also unknown.

At present, the diagnostic accuracy of neural thread protein for diagnosis of AD has not been established and studies of clinical utility not been identified. Additional research on both diagnostic and clinical validity of this biomarker is needed before conclusions can be made about the effectiveness of its use. With respect to skin cell (fibroblast) testing for Alzheimer's Disease, of the identified case studies, it is not clear how the measures in these studies compare to the DISCERN™ test that is commercially available. No studies evaluating the performance of this test were identified.

REGULATORY STATUS

The Lumipulse® G ß-Amyloid Ratio (1-42/1-40) Test (Fujirebio Diagnostics) and the Elecsys® CSF assays for P-tau181/Aβ42 andT-tau/Aβ42 (Roche) have received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA).

Many biomarker tests for AD do not have FDA approval or clearance, including:

- AlzheimAlert™ (Nymox Pharmaceutical Corp.)
- Innotest® assays for T-tau, P-tau, and Aβ42 (Fujirebio Diagnotics)
- AdMark® CSF analysis
- DISCERN™ (Neurodiagnostics) skin sample fibroblast testing
- AD-Detect (Quest Diagnostics)

These are laboratory-developed tests (LDTs). Clinical laboratories may develop and validate tests inhouse and market them as a laboratory service; LDTs must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

The issuance of a CPT/HCPCS code and/or FDA approval for a specific indication does not, in itself, make the procedure medically reasonable and necessary. The FDA determines safety and effectiveness of a device or drug but does not establish medical necessity. While Medicare may adopt FDA determinations regarding safety and effectiveness, Medicare or Medicare contractors evaluate whether or not the drug or device is reasonable and necessary for the Medicare population under §1862(a)(1)(A).

CROSS REFERENCES

Investigational (Experimental) Services, New and Emerging Medical Technologies and Procedures, and Other Non-Covered Services, Medicine, Policy No. M-149

REFERENCES

1. 42 CFR §410.32(a)

2. Medicare Benefit Policy Manual, Ch. 15 – Covered Medical and Other Health Services, §80.1 - Clinical Laboratory Services

CODING

Codes	Number	Description
CPT	81099	Unlisted urinalysis procedure
	82233	Beta-amyloid; 1-40
	82234	Beta-amyloid; 1-42
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative; not otherwise specified
	84393	Tau, phosphorylated
	84394	Tau, total
	86849	Unlisted immunology procedure
	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
	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)*
	~~0346U~~	~~Beta amyloid, Aβ40 and Aβ42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma~~ (Deleted 01/01/2025)
	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
	0412U	Beta amyloid, Aβ42/40 ratio, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and qualitative ApoE isoformspecific proteotyping, plasma combined with age, algorithm reported as presence or absence of brain amyloid pathology
	0445U	β-a Amyloid Beta (Abeta42) and phospho tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
	0459U	B-amyloid (Abeta42) and total tau (tTau), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
	0479U	Tau, phosphorylated, pTau217
	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
	0551U	Tau, phosphorylated, pTau217, by single-molecule array (ultrasensitive digital protein detection), using plasma

	0568U	Neurology (dementia), beta amyloid (AB40, AB42, AB42/40 ratio), tau-protein phosphorylated at residue (eg, pTau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP), by ultra-high sensitivity molecule array detection, plasma, algorithm reported as positive, intermediate, or negative for Alzheimer pathology
HCPCS	None	

***IMPORTANT NOTE:** Medicare Advantage medical policies use the most current Medicare references available at the time the policy was developed. Links to Medicare references will take viewers to external websites outside of the health plan's web control as these sites are not maintained by the health plan.*