DRAFT Medical Coverage Policy | Evaluation of Cerebrospinal Fluid, Urine and Plasma Tests for Alzheimer's Disease

EFFECTIVE DATE: 01|01|2027
POLICY LAST REVIEWED: 09|02|2026

OVERVIEW

Biochemical changes associated with the pathophysiology of Alzheimer's disease (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 plasma. Additionally, the potential correlation between CSF and plasma biomarkers as well as 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.

The following test(s) are addressed in this policy:

- Lumipulse® G ß-Amyloid Ratio (1-42/1-40) (Fujirebio Diagnostics, Inc) – CPT code 0358U
- PrecivityAD® blood test (C2N Diagnostics, LLC.) – CPT code 0412U
- Neurofilament Light Chain (NfL) by (Washington University in St. Louis School of Medicine-Neuromuscular Laboratory) – CPT code 0443U
- Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics) – CPT code 0445U
- Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics Operations, Inc) – CPT code 0459U

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

The following CPT code(s)/test(s) follow the medical necessity criteria below for Medicare Advantage Plans and Commercial Products:

- 82233
- 82234
- 84393
- 84394
- Lumipulse® G ß-Amyloid Ratio (1-42/1-40) (Fujirebio Diagnostics, Inc) – CPT code 0358U
- Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics) – CPT code 0445U
- Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics Operations, Inc) – CPT code 0459U

The use of cerebrospinal fluid biomarker testing of amyloid beta proteins and tau proteins using tests that confirm amyloid pathology* may be considered medically necessary in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease when:

- Used as part of an evaluation for the initiation of amyloid beta targeting therapy, and
- Not used as an adjunct to clinical diagnosis, and
- Not as part of an evaluation for the continuation of amyloid beta targeting therapy

*Biomarkers included in FDA approved tests that have proven to confirm amyloid pathology (through establishing clinical equivalency to amyloid PET imaging) for selecting amyloid beta targeting therapy are as follows:

1. Aβ42:Aβ40 ratio (Lumipulse *G* Amyloid Ratio 1-42/1-40); or

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2. Aβ42:phosphorylated-tau181 (p-tau181) (Elecsys B-Amyloid 1-42 CSF II, Elecsys Phospho-Tau 181P) CSF); or
3. Aβ42:total-tau (Elecsys ß-Amyloid 1-42 CSF II, Elecsys Total-Tau CSF).

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products for the following CPT codes/tests:

- 82233
- 82234
- 84393
- 84394
- Lumipulse® G ß-Amyloid Ratio (1-42/1-40) (Fujirebio Diagnostics, Inc) – CPT code 0358U
- Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics) – CPT code 0445U
- Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics Operations, Inc) – CPT code 0459U

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The following CPT code(s)/test(s) may be considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above are met:

- 82233
- 82234
- 84393
- 84394
- Lumipulse® G ß-Amyloid Ratio (1-42/1-40) (Fujirebio Diagnostics, Inc) – CPT code 0358U
- Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics) – CPT code 0445U
- Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics Operations, Inc) – CPT code 0459U

CSF

Cerebrospinal fluid testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins as an adjunct to clinical diagnosis, or as part of an evaluation for the continuation of amyloid beta targeting therapy is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome in individuals with:

- mild cognitive impairment
- mild dementia due to Alzheimer disease

Cerebrospinal fluid testing of neural thread proteins 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 is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Cerebrospinal fluid testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, 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 is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Therefore, the following tests are not covered for Medicare Advantage Plans and not medically necessary for

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Commercial Products (See Coding section for details):

- Neurofilament Light Chain (NfL) by (Washington University in St. Louis School of Medicine-Neuromuscular Laboratory) – CPT code 0443U

PLASMA

Plasma testing for, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome in individuals with:

- mild cognitive impairment
- mild dementia due to Alzheimer disease

Plasma testing of amyloid beta peptides and tau protein using tests that confirm amyloid pathology, and of neural thread proteins 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 is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Therefore, the following tests are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products (See Coding section for details):

- PrecivityAD® blood test (C2N Diagnostics, LLC.) – CPT code 0412U

URINE

Measurement of urine analytes as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine the effect of the technology on health outcomes.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for not medically necessary/not covered services.

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BACKGROUND

Alzheimer's 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 4 and 8 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.[1] 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.[2] The cumulative dementia incidence was 14.9% in individuals with MCI >65 years of age followed for 2 years.

Data from the National Institute on Aging have shown that Black Americans are approximately 1.5 to 2 times more likely to develop AD and related dementias as compared to Whites.[3] Additionally, Black participants in AD research studies were 35% less likely to be diagnosed with AD and related dementias and were found to have more risk factors for the disease as well as greater cognitive impairment and symptom severity than White participants. Findings from 2 national surveys conducted by the Alzheimer's Association also found that people of color face discrimination when seeking health care for AD and related dementias with the highest level of discrimination in dementia health care reported by Black Americans (50%) followed by Native (42%), Asian (34%), and Hispanic (33%) Americans.[4] Non-Hispanic White Americans reported a discrimination rate of 9%.

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.5,6,

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.7, The National Institute on Aging-Alzheimer's Association (NIA-AA) has created a "numeric clinical staging scheme" (Table 1) 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.

Biomarkers

Several potential biomarkers of AD are associated with AD pathophysiology (eg, 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.[2] 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

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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. Results from initial studies show that these blood biomarkers may potentially assist in early and more precise diagnosis, prognosis, or monitoring of disease progression and treatment in AD. In 2019, the Geneva AD Biomarker Roadmap Initiative expert panel concluded that of the currently assessed blood biomarkers plasma pTau has shown analytical validity and initial evidence of clinical validity, whereas the maturity level for amyloid beta remains to be partially achieved.

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 (LDTs) must be certified by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests. Several AD biomarker tests are available as LDTs.

The FDA has cleared the following AD biomarker tests for marketing via the De Novo and 510(k) pathways:

- Lumipulse *G* Amyloid Ratio (1-42/1-40)
- Elecsys B-Amyloid (1-42) CSF II, Elecsys Phospho-Tau (181P) CSF
- Elecsys ß-Amyloid (1-42) CSF II, Elecsys Total-Tau CSF

For individuals who have mild cognitive impairment (MCI) or dementia who receive cerebrospinal fluid (CSF) biomarker testing for Alzheimer disease (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 quality of life (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 dementia 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 dementia who receive blood biomarker testing for AD, the evidence includes a systematic review and cohort studies. Relevant outcomes include test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and QOL. Clinical validity studies have primarily focused on the biomarker, plasma pTau, and have shown that this biomarker may be beneficial in screening for and diagnosing AD. 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 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. Further research is required to determine whether the use of CSF biomarkers alone in conjunction with amyloid beta PET scans is 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.

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 who receive plasma biomarker testing, the evidence includes multisite longitudinal studies, and an analysis of mixed cohort studies, including FDA decision summary documents. These studies assess the correlation between CSF and plasma biomarkers as well as positron emission tomography (PET) amyloid scans and the clinical utility of amyloid PET, CSF, and plasma biomarkers in cognitively impaired individuals who are being evaluated for treatment with anti-amyloid therapies. Relevant outcomes include test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. Overall, the diagnostic accuracy of plasma biomarkers versus CSF biomarkers and amyloid PET scans to identify MCI-AD was found to be similar. CSF biomarkers have been used as an alternative to PET amyloid scans to establish eligibility regarding the presence of amyloid beta pathology in randomized controlled trials that showed the efficacy of anti-amyloid therapies, which in turn demonstrates that the CSF biomarkers can identify individuals who may benefit from therapy. Plasma biomarkers have established clinical equivalency to amyloid PET and CSF biomarkers in their ability to characterize amyloid beta pathology under research conditions using bio-banked samples. However, limited evidence has been generated regarding the utility of these tests when used in clinical laboratory setting or real-world settings with the findings of these studies suggesting varying test performance metrics. In order for plasma biomarkers to substitute or replace CSF biomarkers or amyloid PET scans for selecting targeted treatment with anti-amyloid therapy, prospective data demonstrating that plasma biomarkers are non-inferior to CSF biomarkers or amyloid PET scans within a clinical or real-word setting are needed, thus a chain of evidence cannot be constructed to demonstrate clinical utility that plasma biomarkers can identify individuals who may benefit from therapy. 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 randomized controlled trials, multisite longitudinal studies, and an analysis of a mixed cohort. These studies assess both the correlation between CSF biomarkers and positron emission tomography (PET) amyloid scans and the clinical utility of amyloid PET or CSF biomarkers in cognitively impaired patients who are being evaluated for treatment with anti-amyloid therapies. 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. CSF biomarkers have been used as an alternative to PET amyloid scans to establish eligibility regarding the presence of amyloid beta pathology in randomized controlled trials that showed the efficacy of anti-amyloid therapies, which in turn demonstrates that the CSF biomarkers can identify patients who may benefit from therapy. The FDA-

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approved labels for lecanemab and donanemab state that the presence of amyloid beta pathology should be confirmed prior to initiating treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code(s)/test(s) may be considered medically necessary for Medicare Advantage Plans and Commercial Products when the above criteria are met:

82233 Beta-amyloid; 1-40 (Abeta 40)
82234 Beta-amyloid; 1-42 (Abeta 42)
84393 Tau, phosphorylated (eg, pTau 181, pTau 217), each
84394 Tau, total (tTau)

This code can be used for Lumipulse® G ß-Amyloid Ratio (1-42/1-40) test
0358U Neurology (mild cognitive impairment), analysis of B-amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative

This code can be used for Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio test
0445U βamyloid (Abeta42) and Phospho Tau (181P) (pTau181), electrochemiluminescence immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology

This code can be used for Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio test
0459U βamyloid (Abeta42) and Phospho Tau (181P) (pTau181), electrochemiluminescence immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology

The following CPT code(s), when filed with one of the ICD-10 Diagnosis Code(s)* listed below, are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

This code can be used for Neurofilament Light Chain (NfL) test (Washington University in St. Louis School of Medicine-Neuromuscular Laboratory)
0443U Neurofilament light chain (NfL), ultra-sensitive immunoassay, serum or cerebrospinal fluid

Not all testing addressed in this policy has been assigned specific CPT codes. Therefore, the following CPT codes may be used. Testing using these CPT codes is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products when filed with one of the ICD-10 Diagnosis Code(s)* listed below:
The following CPT code may be used to test urine:
81099 Unlisted Urinalysis Procedure

The following CPT code(s) may be used to report testing for tau protein and amyloid-β peptides:
83520 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

The following CPT code may be used to test cerebrospinal fluid:
86849 Unlisted Immunology Procedure

***ICD-10 Diagnosis Code(s)**
F03.90-F03.91
G30.0-G30.9
G31.1
G31.84
R41.81

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The following CPT code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

This code can be used for PrecivityAD® blood test

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

RELATED POLICIES

Biomarker Testing Mandate
Unlisted Procedures

PUBLISHED

Provider Update, November 2026
Provider Update, September 2025
Provider Update, January 2025
Provider Update, February 2024
Provider Update, January/November 2023

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