MEDICAL POLICY

POLICY TITLE	**EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE**
POLICY NUMBER	**MP 2.391**

CLINICAL BENEFIT	☒ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**7/1/2025**

I. POLICY

Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild cognitive impairment is considered **investigational**.

Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild dementia due to Alzheimer disease is considered **investigational**.

Cerebrospinal fluid biomarker testing of amyloid beta peptides and tau protein 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 considered **medically necessary** (see Policy Guidelines).

Cerebrospinal fluid biomarker 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 considered **investigational**.

Cerebrospinal fluid biomarker 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 considered **investigational**.

Measurement of urinary and blood biomarkers as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational.**

POLICY GUIDELINES

The labels for FDA-approved, amyloid beta targeting therapies, LEQEMBI® (lecanemab) and Kisunla™ (donanemab) state that the presence of amyloid beta pathology should be confirmed prior to initiating treatment. In the pivotal randomized controlled trial for lecanemab (Clarity AD), the protocol states that the eligibility criteria related to amyloid beta pathology required "confirmed amyloid pathology indicated by either 1) positive amyloid load confirmed by amyloid PET assessment, or 2) CSF assessment of t-tau / Aβ[1-42].'"

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: Refer to the FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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Alzheimer Disease

Alzheimer 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. 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. 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. 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. 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.

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. 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.

Table 1 National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum

Stage	Severity	Clinical Features
Stage 1	Pre-Clinical	• Performance within an expected range on objective cognitive tests. • No evidence of recent cognitive decline or new neurobehavioral symptoms.
Stage 2	Pre-Clinical	• Normal performance within the expected range on objective cognitive tests. • Transitional cognitive decline (change from individual baseline within the past 1 to 3 years, and persistent for at least 6 months). • Mild neurobehavioral changes may coexist or maybe the primary complaint rather than cognitive. • No functional impact on daily life activities.

Stage 3	MCI due to Alzheimer	• Performance in the impaired/abnormal range on objective cognitive tests. • Evidence of decline from baseline. • Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life.
Stage 4	Mild Dementia	• Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. • Clearly evident functional impact on daily life, affecting mainly instrumental activities. • No longer fully independent/requires occasional assistance with daily life activities.
Stage 5	Moderate Dementia	• Progressive cognitive impairment or neurobehavioral changes. • Extensive functional impact on daily life with impairment in basic activities. • No longer independent and requires frequent assistance with daily life activities.
Stage 6	Severe Dementia	• Progressive cognitive impairment or neurobehavioral changes. • Clinical interview may not be possible. • Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

Biomarkers

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. 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.

Several potential biomarkers of AD are associated with AD pathophysiology (e.g., 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. 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 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. In a recent retrospective multicohort diagnostic performance study, both plasma tau phosphorylated at threonine 217 (p-tau217) and at threonine 181 (p-tau181) had excellent diagnostic performance for differentiating patients with AD syndromes from other neurodegenerative disorders. At this time, although a growing area of research, blood AD biomarkers are not addressed in this review.

Regulatory Status

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. AlzheimAlert™ and AdMark® CSF analysis are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory

Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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Summary of Evidence: Cerebrospinal Fluid and Urinary Biomarkers

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 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-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.

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.

V. DEFINITIONS/BACKGROUND

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ALLELE refers to one of two or more different genes containing specific inheritable characteristics that occupy corresponding positions (loci) on paired chromosomes.

AUTOSOMAL DOMINANT INHERITANCE refers to a pattern of inheritance in which the transmission of a dominant allele on an autosome causes a trait to be expressed.

BIOCHEMICAL MARKER refers to any biochemical compound such as an antigen, antibody, abnormal enzyme, or hormone that is sufficiently altered in a disease to serve as an aid in diagnosing or in predicting susceptibility to disease.

GENE is the basic unit of heredity, made of DNA, the code for a specific protein.

LIPOPROTEIN refers to conjugated chemicals in the bloodstream consisting of simple proteins bound to fat. Cholesterol, phospholipids, and triglycerides are all fatty components of lipoproteins.

NEUROFIBRIL refers to any of the many tiny fibrils that extend in every direction of the nerve cell body. They extend into the axon and dendrites of the cell.

NEURON refers to a nerve cell, the structural and functional unit of the nervous system.

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement. The codes need to be in numerical order.

Investigational and therefore, not covered:

Procedure Codes							
0206U	0207U	0393U	0412U	0479U	0503U	0551U	0568U
81099	83520	86849					

Covered when medically necessary:

Procedure Codes							
0358U	0445U	0459U	82233	82234	84393	84394	

ICD-10-CM Diagnosis Code	Description
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management
Z82.0	Family history of epilepsy and other diseases of the nervous system

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 2.391	**01/03/2025 Major Review.** New policy.
	06/10/2025 Administrative Update. Added code 0568U eff 07/01/2025
	06/12/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.

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