

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR ALZHEIMER DISEASE
POLICY NUMBER	MP 2.050

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:	RETIRED 7/1/2026

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I. POLICY

Targeted genetic testing for a known familial variant in the presenilin (*PSEN*) genes or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant early-onset Alzheimer disease may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when the following criteria are met:

- The individual has a close relative (i.e., first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease; **and**
- Results of testing will inform reproductive decision-making.

Genetic testing for variants in presenilin (*PSEN*) genes or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant early-onset Alzheimer disease may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when the following criteria are met:

- The individual has a family history of dementia consistent with autosomal dominant Alzheimer disease for whom the genetic status of the affected family members is unavailable; **and**
- Results of testing will inform reproductive decision-making.

Genetic testing for the apolipoprotein E (*APOE*) gene to guide initiation or management of a U.S. Food and Drug Administration-approved amyloid-beta targeting therapy is considered **medically necessary** in individuals with mild cognitive impairment or mild dementia associated with Alzheimer disease.

Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered **investigational** in all other situations, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure. Genetic testing includes but is not limited to, testing for the apolipoprotein E epsilon 4 (*APOE* ε4) allele or triggering receptor expressed on myeloid cells 2 (*TREM2*).

Cross-Reference:

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MP 2.391 Evaluation of Biomarkers for Alzheimer Disease

POLICY GUIDELINES:

Genetic testing for Alzheimer disease (AD) may be offered along with analysis of cerebral spinal fluid levels of the tau protein and amyloid-beta peptide 1-42 (see evidence review 2.04.14). This group of tests may be collectively referred to as the ADmark™ Profile, offered by Athena Diagnostics.

Testing Strategy

The 2011 guidelines from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors recommended that genetic testing for early-onset, autosomal dominant AD should only occur in the context of genetic counseling with support by someone expert in the area. In asymptomatic patients, a testing protocol based on the 1994 International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea guidelines has been recommended. Consultation of the Alzheimer Disease & Frontotemporal Dementia Mutation Database has also been recommended before disclosure of genetic test results.

A family history of autosomal dominant AD is suggested by 3 affected members in two generations. In individuals at risk of early-onset, autosomal dominant AD, ideally, an affected family member should be tested first to identify the familial variant. If no affected family member is available for testing and an asymptomatic individual remains interested in testing to inform reproductive decision making, then in-depth sequencing of the 3 genes (*APP*, *PSEN1*, *PSEN2*) associated with autosomal dominant AD may be indicated.

Treatment with Amyloid-beta Plaque Targeting Therapy

The lecanemab (LEQEMBI®) and donanemab (KISUNLA™) product labels include a boxed warning regarding the risk of amyloid-related imaging abnormalities (ARIA). The warning states that providers should discuss the potential risk of serious adverse events associated with ARIA with individuals considering treatment. The warning also states that patients who are *APOE* ε4 homozygotes have a higher incidence of ARIA and testing for *APOE* ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical policy updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes.

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Table PG2 shows the recommended standard terminology- “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”- to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variant Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence.
	Variant	Change in the DNA sequence.
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives.

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classifications

Variant Classification	Definition
Pathogenic	Disease-associated causing change in the DNA sequence.
Likely pathogenic	Likely disease-causing change in the DNA sequence.
Variant of uncertain significance	Change in DNA sequence with uncertain effect on disease.
Likely benign	Likely benign change in the DNA sequence.
Benign	Benign change in the DNA sequence.

ACMG: American College of Medical Genetics and Genomics; AMP: Association of Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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 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>

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III. DESCRIPTION/BACKGROUND

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Genetic Testing for Diagnosis of Alzheimer Disease

Alzheimer disease (AD) is commonly associated with a family history; 40% of patients with AD have at least one other afflicted first-degree relative. Numerous genes have been associated with late-onset AD, while variants in chromosomes 1, 14, and 21 have been associated with early-onset familial AD.

Genetic Variants

Individuals with early-onset familial AD (i.e., before age 65 years but as early as 30 years) form a small subset of AD patients. AD within families of these patients may show an autosomal dominant pattern of inheritance. Pathogenic variants in three genes have been identified in affected families: the amyloid-beta precursor protein (*APP*) gene, presenilin 1 (*PSEN1*) gene, and presenilin 2 (*PSEN2*) gene. *APP* and *PSEN1* variants have 100% penetrance absent death from other causes, while *PSEN2* has 95% penetrance. Variants within these genes have been associated with AD; variants in *PSEN1* appear to be the most common. While only 3% to 5% of all patients with AD have early-onset disease, pathogenic variants have been identified in 70% or more of these patients. Identifiable genetic variants are, therefore, rare causes of AD.

Testing for the apolipoprotein ε4 allele (*APOE*E4*) among patients with late-onset AD and for *APP*, *PSEN1*, or *PSEN2* pathogenic variants in the rare patient with early-onset AD has been investigated as an aid in diagnosis of patients presenting with symptoms suggestive of AD, or as a technique for risk assessment in asymptomatic patients with a family history of AD. Pathogenic variants in *PSEN1* and *PSEN2* are specific for AD; *APP* variants are also found in cerebral hemorrhagic amyloidosis of the Dutch type, a disease in which dementia and brain amyloid plaques are uncommon.

The *APOE* lipoprotein is a carrier of cholesterol produced in the liver and brain glial cells. The *APOE* gene has three alleles—ε2, 3, and 4—with the ε3 allele being the most common. Individuals carry 2 *APOE* alleles. The presence of at least one ε4 allele is associated with a 1.2- to 3-fold increased risk of AD, depending on the ethnic group. Among those homozygous for epsilon 4 (≈2% of the population), the risk of AD is higher than for those heterozygous for ε4. Mean age of onset of AD is about age 68 years for ε4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no ε4 alleles. About half of patients with sporadic AD carry an ε4 allele. However, not all patients with the allele develop AD. The ε4 allele represents a risk factor for AD rather than a disease-associated variant. In the absence of *APOE* testing, first-degree relatives of an individual with sporadic or familial AD are estimated to have a 2- to 4-fold greater risk of developing AD than the general population. There is evidence of possible interactions between ε4 alleles, other risk factors for AD (e.g., risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, diabetes), and a higher risk of developing AD. However, it is not clear that all risk factors have been taken into account in such studies, including the presence of variants in other genes that may increase the risk of AD.

Studies have also identified rs75932628-T, a rare functional substitution for R47H on the triggering receptor expressed on myeloid cells 2 (*TREM2*), as a heterozygous risk variant for

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late-onset AD. On chromosome 6p21.1, at position 47 (R47H), the T allele of rs75932628 encodes a histidine substitute for arginine in the gene that encodes *TREM2*.

TREM2 is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. *TREM2* may serve a protective role in the brain by suppressing inflammation and clearing it of cell debris, amyloids, and toxic products. A decrease in the function of *TREM2* would allow inflammation in the brain to increase and may be a factor in the development of AD. The effect size of the *TREM2* variant confers a risk of AD that is similar to the *APOE*E4* allele, although it occurs less frequently.

Diagnosis

The diagnosis of AD is divided into three categories: possible, probable, and definite AD. A diagnosis of definite AD requires postmortem confirmation of AD pathology, documenting the presence of extracellular β -amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. As a result, a diagnosis of definite AD cannot be made during life, and the diagnosis of probable or possible AD is made on clinical grounds. Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. Criteria for diagnosis of probable AD have been developed by the National Institute on Aging and the Alzheimer's Association. These criteria require evidence of a specific pattern of cognitive impairment, a typical clinical course, and exclusion of other potential etiologies, as follows:

- Cognitive impairment
 - Cognitive impairment established by history from the patient and a knowledgeable informant, plus objective assessment by bedside mental status examination or neuropsychological testing.
 - Cognitive impairment involving a minimum of two of the following domains:
 - Impaired ability to acquire and remember new information.
 - Impaired reasoning and handling of complex tasks, poor judgment.
 - Impaired visuospatial abilities.
 - Impaired language functions.
 - Changes in personality, behavior, or comportment.
 - Initial and most prominent cognitive deficits are one of the following:
 - Amnesic presentation.
 - Non-amnesic presentations, either a language presentation with prominent word-finding deficits; a visuospatial presentation with visual cognitive defects; or a dysexecutive presentation with prominent impairment of reasoning, judgment, and/or problem-solving.
- Clinical course
 - Insidious onset.
 - Clear-cut history of worsening over time.
 - Interference with the ability to function at work or usual activities.
 - Decline from previous level of functioning and performing.

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- Exclusion of other disorders
 - Cognitive decline not explained by delirium or major psychiatric disorder.
 - No evidence of other active neurologic disease, including substantial cerebrovascular disease or dementia with Lewy bodies.
 - Lack of prominent features of variant frontotemporal dementia or primary progressive aphasia.
 - No medication used with substantial effects on cognition.

A diagnosis of possible AD dementia is made when the patient meets most of the AD criteria but has an atypical course or an etiologically mixed presentation. This may consist of an atypical onset (e.g., sudden onset) or atypical progression. A diagnosis of possible AD is also made when there is another potentially causative systemic or neurologic disorder that is not thought to be the primary etiology of dementia.

Mild cognitive impairment (MCI) is a precursor of AD in many instances. MCI may be diagnosed when there is a change in cognition, but insufficient impairment for the diagnosis of dementia. Features of MCI are evidence of impairment in one or more cognitive domains and preservation of independence in functional abilities. In some patients, MCI may be a prodementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings. Other diagnostic tests for AD include cerebrospinal fluid levels of tau protein or APP, as well as positron emission tomography amyloid imaging.

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. Lab tests listed in Tables 1 and 3 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

Summary of Evidence

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For individuals who are asymptomatic and at risk for developing late-onset Alzheimer disease (AD) who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, and quality of life. Many genes, including *APOE*, *CR1*, *BIN1*, *PICALM*, and *TREM2*, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing for indicating which individuals will progress to AD is low, and numerous other factors can affect progression. Overall, genetic testing has not been shown to add value to the diagnosis of AD made clinically. The current lack

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of effective methods to prevent the onset of AD limits the clinical benefit for genetic testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have a known familial variant who receive targeted genetic testing, the evidence includes studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision making, health status measures, and quality of life. Variants in the *PSEN1* and *PSEN2* and *APP* genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be nearly certain when a familial pathogenic variant has previously been identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, the clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have no known familial variant who receive genetic testing, the evidence includes studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision making, health status measures, and quality of life. Variants in the *PSEN1*, *PSEN2*, and *APP* genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be reasonably certain when a variant found in the database of pathogenic *PSEN1*, *PSEN2*, and *APP* variants are identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, the clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a clinical diagnosis of mild cognitive impairment or mild dementia associated with AD who are considering initiation or discontinuation of an FDA-approved amyloid-beta targeting therapy who receive genetic testing, the evidence includes randomized clinical trials. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related morbidity and mortality. The incidence of asymptomatic, symptomatic and serious amyloid-related imaging abnormalities (ARIA) following treatment with the amyloid-beta targeting therapies is significantly higher in *APOE* $\epsilon 4$ homozygotes compared to heterozygotes and noncarriers. The boxed warnings in the FDA labels for approved amyloid-beta targeting therapies states that testing for *APOE* $\epsilon 4$ status should be performed prior to initiation of treatment to inform the risk

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of developing ARIA. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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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.

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 policies 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.

Investigational; therefore, not covered for genetic testing for the diagnosis or risk assessment of Alzheimer disease:

Procedure Codes							
0289U							

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Medically Necessary and covered for genetic testing when criteria is met

Procedure Codes							
81401	81405	81406	S3852				

ICD-10-CM Diagnosis Codes	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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1. Bird TD. Genetic aspects of Alzheimer disease. *Genet Med.* Apr 2008; 10(4): 231-9. PMID 18414205
2. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling, and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med.* Jun 2011; 13(6): 597-605. PMID 21577118
3. Caselli RJ, Dueck AC, Locke DE, et al. Cerebrovascular risk factors and preclinical memory decline in healthy APOE 4 homozygotes. *Neurology.* Mar 22, 2011; 76(12): 1078-84. PMID 21325652
4. Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *N Engl J Med.* Jan 10, 2013; 368(2): 107-16. PMID 23150908
5. Guerreiro R, Wojtas A, Bras J, et al. TREM2 variants in Alzheimer's disease. *N Engl J Med.* Jan 10, 2013; 368(2): 117-27. PMID 23150934
6. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* May 2011; 7(3): 263-9. PMID 21514250
7. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement.* Jan 2012; 8(1): 1-13. PMID 22265587
8. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* May 2011; 7(3): 270-9. PMID 21514249
9. National Center for Biotechnology Information. GTR: Genetic Testing Registry. n.d.; Accessed March 25, 2022.

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10. Slioter AJ, Cruts M, Hofman A, et al. The impact of APOE on myocardial infarction, stroke, and dementia: the Rotterdam Study. *Neurology*. Apr 13, 2004; 62(7): 1196-8. PMID 15079025
11. Myers RH, Schaefer EJ, Wilson PW, et al. Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study. *Neurology*. Mar 1996; 46(3): 673-7. PMID 8618665
12. Bird TD. Alzheimer Disease Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 2015.
13. Naj AC, Jun G, Reitz C, et al. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. *JAMA Neurol*. Nov 2014; 71(11): 1394-404. PMID 25199842
14. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet*. Dec 2013; 45(12): 1452-8. PMID 24162737
15. Blue EE, Horimoto ARVR, Mukherjee S, et al. Local ancestry at APOE modifies Alzheimer's disease risk in Caribbean Hispanics. *Alzheimers Dement*. Dec 2019; 15(12): 1524-1532. PMID 31606368
16. Chao S, Roberts JS, Marteau TM, et al. Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. *Alzheimer Dis Assoc Disord*. Jan-Mar 2008; 22(1): 94-7. PMID 18317253
17. Green RC, Roberts JS, Cupples LA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. *N Engl J Med*. Jul 16, 2009; 361(3): 245-54. PMID 19605829
18. Christensen KD, Roberts JS, Whitehouse PJ, et al. Disclosing Pleiotropic Effects During Genetic Risk Assessment for Alzheimer Disease: A Randomized Trial. *Ann Intern Med*. Feb 02, 2016; 164(3): 155-63. PMID 26810768
19. Elias-Sonnenschein LS, Viechtbauer W, Ramakers IH, et al. Predictive value of APOE-4 allele for progression from MCI to AD-type dementia: a meta-analysis. *J Neurol Neurosurg Psychiatry*. Oct 2011; 82(10): 1149-56. PMID 21493755
20. International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. *J Med Genet*. Jul 1994; 31(7): 555-9. PMID 7966192
21. Kowalska A, Wender M, Florczak J, et al. Molecular genetics of Alzheimer's disease: presenilin 1 gene analysis in a cohort of patients from the Poznan region. *J Appl Genet*. 2003; 44(2): 231-4. PMID 12817569
22. Janssen JC, Beck JA, Campbell TA, et al. Early onset familial Alzheimer's disease: Mutation frequency in 31 families. *Neurology*. Jan 28, 2003; 60(2): 235-9. PMID 12552037
23. Giau VV, Bagyinszky E, Youn YC, et al. APP, PSEN1, and PSEN2 Mutations in Asian Patients with Early-Onset Alzheimer Disease. *Int J Mol Sci*. Sep 25, 2019; 20(19). PMID 31557888
24. Stoychev KR, Stoimenova-Popova M, Chumpalova P, et al. A Clinical Case of Patient Carrying Rare Pathological PSEN1 Gene Mutation (L424V) Demonstrates the Phenotypic Heterogeneity of Early Onset Familial AD. *Front Psychiatry*. 2019; 10: 857. PMID 31920735

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25. Cochran JN, McKinley EC, Cochran M, et al. Genome sequencing for early-onset or atypical dementia: high diagnostic yield and frequent observation of multiple contributory alleles. *Cold Spring Harb Mol Case Stud.* Dec 2019; 5(6). PMID 31836585
26. Rahman B, Meiser B, Sachdev P, et al. To know or not to know: an update of the literature on the psychological and behavioral impact of genetic testing for Alzheimer disease risk. *Genet Test Mol Biomarkers.* Aug 2012; 16(8): 935-42. PMID 22731638
27. American College of Medical Genetics and Genomics. *Choosing Wisely.* 2015
28. Goldman JS, Hahn SE, Catania JW, et al. ADDENDUM: Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med.* Oct 2019; 21(10): 2404. PMID 31217590
29. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* May 08, 2001; 56(9): 1143-53. PMID 11342678
30. National Institute for Health and Care Excellence (NICE). *Dementia: assessment, management and support for people living with dementia and their carers [NG97].* 2018
31. Goldman JS. Predictive Genetic Counseling for Neurodegenerative Diseases: Past, Present, and Future. *Cold Spring Harb Perspect Med.* 2020;10(7):a036525. Published 2020 Jul 1. doi:10.1101/cshperspect.a036525 PMID: 31548223
32. Summary Review for Leqembi (lecanemab) Application Number: 761269Orig1s000. Center for Drug Evaluation and Research.
33. Prescribing Label for LEQEMBI (lecanemab-irmb) injection, for intravenous use.
34. Press, D. Amyloid-targeted therapiest for the treatment of Alzheimer disease. In UpToDate Online. Updated Dec 03, 2024. Literature review through Nov. 2024
35. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis.* 2023;10(3):362-377. doi:10.14283/jpad.2023.30

IX. POLICY HISTORY

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MP 2.050	06/13/2023 Administrative Update. Added procedure code 0393U Effective 07/01/2023.
	10/01/2023 Administrative Update. Added procedure code 0412U. Effective 10/01/2023
	12/11/2023 Consensus Review. No change to policy statement, added code 0289U to INV. New references.
	03/15/2024 Administrative Update. New code 0445U, effective 04/01/2024
	06/11/2024 Administrative Update. New code 0459U, effective 07/01/2024.
	09/18/2024 Administrative Update. New codes 0479U, 0503U added effective 10/24/2024.
	12/23/2024 Minor Review. Biomarker testing removed from this policy and placed in MP 2.391. Codes 0206U, 0207U, 0358U, 0412U, 0445U, 0459U, 0479U, 0503U, 81099, 82233, 82234, 84393, 84394, 86849 removed.

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	Genetic testing for APOE medically necessary prior to initiating FDA approved medication. Code S3852 now MN when criteria is met.
	7/22/2025 Consensus Review. Policy statement unchanged
	09/23/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/09/2026 Retirement review. Services managed by EviCore.

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Health care benefit programs issued or administered by Capital Blue Cross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the Blue Cross BlueShield Association. Communications issued by Capital Blue Cross in its capacity as administrator of programs and provider relations for all companies.