Genetic Testing for Alzheimer's Disease

Policy # 00204
Original Effective Date: 05/17/2006
Current Effective Date: 12/14/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer Disease is addressed separately in medical policy 00381.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider targeted genetic testing for a known familial variant in the presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease (AD) in an asymptomatic individual to determine future risk of disease to be **eligible for coverage**** when the following criteria are met:

Patient Selection Criteria
Coverage eligibility will be considered when ALL of the following criteria are met:

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

Based on review of available data, the Company may consider genetic testing for variants in presenilin genes (*PSEN*) or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant early-onset Alzheimer disease (AD) in an asymptomatic individual to determine future risk of disease to be **eligible for coverage**** when the following criteria are met:

Genetic Testing for Alzheimer's Disease

Policy # 00204
Original Effective Date: 05/17/2006
Current Effective Date: 12/14/2020

Patient Selection Criteria
Coverage eligibility will be considered when ALL of the following criteria are met:

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

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for the risk assessment of Alzheimer disease (AD) in asymptomatic individuals in all other situations to be **investigational.***

Genetic testing includes, but is not limited to, testing for the apolipoprotein E ε4 allele (*APOE*) or triggering receptor expressed on myeloid cells 2 (*TREM2.)*

Policy Guidelines

Genetic testing for Alzheimer disease (AD) may be offered along with analysis of cerebral spinal fluid (CSF) levels of the tau protein and amyloid-β peptide 1-42. 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 Alzheimer disease 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.

Genetic Testing for Alzheimer's Disease

Policy # 00204
Original Effective Date: 05/17/2006
Current Effective Date: 12/14/2020

A family history of autosomal dominant Alzheimer disease AD is suggested by 3 affected members in 2 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.

Genetics Nomenclature Update
The Human Genome Variation Society nomenclature is used to report information on variants found in deoxyribonucleic acid (DNA) and serves as an international standard in deoxyribonucleic acid (DNA) diagnostics. It is being implemented for genetic testing medical evidence review 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. 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 Variants 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 Classification

Variant Classification	Definition
Pathogenic	Disease-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 effects 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 for 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.

Background/Overview

Alzheimer Disease

Alzheimer disease (AD) is commonly associated with a family history; 40% of patients with Alzheimer disease AD have a least 1 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 (ie, 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 3 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 E (APOE) epsilon 4 allele 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 3 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 ε4 (≈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 a 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 (eg, 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 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 epsilon 4 allele, although it occurs less frequently.

Diagnosis

The diagnosis of AD is divided into 3 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 2 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:
        - Amnestic presentation
        - Nonamnestic 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
- Exclusion of other disorders
    - Cognitive decline not explained by delirium or major psychiatric disorder
    - No evidence of other active neurologic diseases, 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 (eg, 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 is a precursor of AD in many instances. Mild cognitive impairment may be diagnosed when there is a change in cognition, but insufficient impairment for the diagnosis of dementia. Features of mild cognitive impairment are evidence of impairment in one or more cognitive domains and preservation of independence in functional abilities. In some patients, mild cognitive impairment may be a predementia phase of AD. Patients with mild cognitive impairment may undergo ancillary testing (eg, 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 amyloid precursor protein, as well as positron emission tomography amyloid imaging. Positron emission tomography amyloid imaging is considered in medical policy 00381.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 must be licensed by the Clinical Laboratory Improvement Amendments (CLIA) for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

Alzheimer disease (AD) is the most common cause of dementia in elderly patients. For late-onset AD, there is a component of risk that runs in families, suggesting the contribution of genetic factors. Early-onset AD is much less common but can occur in nonelderly individuals. Early-onset AD has a stronger component of family risk, with clustering in families, thus suggesting an inherited genetic disease-causing variant.

For individuals who are asymptomatic and at risk for developing late-onset AD who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. The relevant outcomes are test accuracy and validity, change in disease status, health status measures, and quality of life. Many genes, including apolipoprotein E

(*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 of effective methods to prevent the onset of AD or to target AD treatments based on genetic characteristics limits the clinical benefit for genetic testing. The evidence is insufficient to determine the effects of the technology on health outcomes.

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. The 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 presenilin 1 and 2 (*PSEN1* and *PSEN2*) and amyloid-beta precursor protein (*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, 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 a meaningful 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. The 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, 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 a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics et al

The American College of Medical Genetics and Genomics has listed genetic testing for apolipoprotein E (*APOE*) alleles as 1 of 5 recommendations in the Choosing Wisely initiative. The recommendation is "Don't order APOE genetic testing as a predictive test for Alzheimer disease." The stated rationale is that *APOE* is a susceptibility gene for late-onset AD, the most common cause of dementia: "The presence of an ε4 allele is neither necessary nor sufficient to cause AD. The relative risk conferred by the ε4 allele is confounded by the presence of other risk alleles, gender, environment and possibly ethnicity, and the APOE genotyping for AD risk prediction has limited clinical utility and poor predictive value."

In 2011, the ACMG, jointly with the National Society of Genetic Counselors issued the following practice guidelines:

- "Pediatric testing for AD should not occur. Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation.
- Genetic testing for AD should only occur in the context of genetic counseling (in person or through video conference) and support by someone with expertise in this area.
    - Symptomatic patients: Genetic counseling for symptomatic patients should be performed in the presence of the individual's legal guardian or family member.
    - Asymptomatic patients: A protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea Guidelines is recommended.
- DTC [direct-to-consumer] *APOE* testing is not advised.
- A ≥3-generation family history should be obtained, with specific attention to the age of onset of any neurologic and/or psychiatric symptoms, type of dementia and method of diagnosis, current ages, or ages at death (especially unaffected relatives), and causes of death. Medical records should be used to confirm AD diagnosis when feasible. The history of additional

relatives may prove useful, especially in small families or those with a preponderance of early death that may mask a history of dementia.

- A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with EOAD [early-onset AD] or LOAD [late-onset AD] and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance.
- Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression.
- The following potential genetic contributions to AD should be reviewed:
    - The lifetime risk of AD in the general population is approximately 10-12% in a 75-80 year lifespan.
    - The effect(s) of ethnicity on risk is still unclear.
    - Although some genes are known, there are very likely others (susceptibility, deterministic, and protective) whose presence and effects are currently unknown.

For families in which an autosomal dominant AD gene mutation is a possibility:

- Discuss the risk of inheriting a mutation from a parent affected with autosomal dominant AD is 50%. In the absence of identifying a mutation in apparent autosomal dominant families, risk to offspring could be as high as 50% but may be less.
- Testing for genes associated with early onset autosomal dominant AD should be offered in the following situations:
    - A symptomatic individual with EOAD in the setting of a family history of dementia or the setting of an unknown family history (e.g., adoption).
    - Autosomal dominant family history of dementia with one or more cases of EOAD.
    - A relative with a mutation consistent with EOAD (currently *PSEN1/2* or *APP*).

The Alzheimer Disease & Frontotemporal Dementia Mutation Database should be consulted before disclosure of genetic test results, and specific genotypes should not be used to predict the phenotype in diagnostic or predictive testing….

- Discuss the likelihood of identifying a mutation in *PSEN1*, *PSEN2*, or *APP*, noting that current experience indicates that this likelihood decreases with lower proportions of affected family members and/or older ages of onset.
- Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains interested in testing despite

counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), he/she should be counseled according to the recommended protocol. If the affected relative, or their next of kin, is uninterested in pursuing testing, the option of DNA banking should be discussed."

In 2019, ACMG reaffirmed its position in the original document. However, an addendum was issued clarifying 2 points:

- Use of the phrase "pathogenic variant" should be adopted rather than the word "mutation" in discussing pathogenic variants related to autosomal dominant EOAD
- Because the original document no longer meets the criteria for an evidence-based practice guideline by either the ACMG or National Society of Genetic Counselors, both societies have since reclassified it as a Practice Resource

American Academy of Neurology

In 2001, the American Academy of Neurology made the following guideline recommendations:

- Routine use of *APOE* genotyping in patients with suspected AD is not recommended at this time.
- There are no other genetic markers recommended for routine use in the diagnosis of AD.

While an update was expected in February 2018, as of February 2019, none has been issued.

European Federation of Neurological Sciences

In 2010, the European Federation of Neurological Sciences (2010) made the following recommendations for genetic testing (level of evidence not reported):

- "Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia."
- "Testing of patients with familial dementia and of unaffected at-risk-relatives should be accompanied by neurogenetic counseling and undertaken only after full consent and by specialist centers. Pre-symptomatic testing may be performed in at-risk members of family-carrying mutation. It is recommended that the Huntington's disease protocol is followed for pre-symptomatic testing."
- "Routine Apo E genotyping is not recommended."

Canadian Consensus Conference on Diagnosis and Treatment of Dementia

Fourth Canadian Consensus Conference
In 2012, the Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia updated guidelines from the Third Consensus Conference, referenced next. Previous recommendations were endorsed if there were no changes in the literature.

A summary of consensus recommendations from the Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia was published by Gauthier et al (2012). It was noted that: "Despite a large number of important advances, the Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia concluded that fundamental changes in dementia diagnosis and management have not yet arrived." The Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia summary recommended:

"All patients with early onset dementia should be referred to a memory clinic, preferably one with access to genetic counselling and testing when appropriate."

Recommendations regarding PET amyloid imaging included: "Testing and longitudinal follow-up of asymptomatic individuals or patients with subjective cognitive impairments not meeting mild cognitive impairment criteria, or at-risk individuals (eg, gene mutation carriers, family history of AD, APOE epsilon 4) should be restricted to research."

Third Canadian Consensus
The Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia recommended the following:

- "Predictive genetic testing for asymptomatic 'at-risk' individuals with an apparent autosomal dominant inheritance and a family-specific mutation that has been identified
  - With appropriate pre- and post-testing counseling, predictive genetic testing can be offered to 'at-risk' individuals (Grade B, Level 2). Examples:
    - First-degree relatives of an affected individual with the mutation (eg, children and siblings);

  - First cousins of an affected individual if the common ancestors (parents who were siblings) died before the average age of onset of dementia in the family;
  - Nieces and nephews of affected individuals whose parent (sibling of the affected individual) died well before the average age of onset of dementia in the family;
  - Predictive genetic testing in minors is not generally offered in Canada, but occasionally may be considered on a case-by-case basis by the relevant medical ethics committee(s);
  - Individuals who are not 'at risk' for the inherited disease do not require testing.
- In young persons (60 years or younger) presenting with an early onset dementia, it is sometimes worthwhile to test for the most common mutations based on the 'best estimate' diagnosis (eg, in early-onset AD, one might test for the most common mutations in PS1, APP). (Grade B, Level 2) If a mutation is identified, it would have direct implications for offspring of the individual (if a de novo mutation is assumed). Conversely, it would also be important to test other family members such as parents and siblings for possible non-penetrance of a mutation.
- Genetic screening with APOE genotype in asymptomatic individuals in the general population is not recommended because of the low specificity and sensitivity. (Grade E, Level 2)
- Genetic testing with APOE genotype is not recommended for the purpose of diagnosing AD because the positive and negative predictive values are low. (Grade E, Level 2)"

Canadian Consensus Conference on Diagnosis and Treatment of Dementia used the following evidence ratings for the Third Canadian Consensus: grade (B) is fair evidence to support this maneuver; grade (E) is good evidence to recommend against this procedure; level 2 evidence is that obtained from (1) well-designed controlled trial without randomization or (2) well-designed cohort or case-control analytic studies, preferably from more than one center or (3) comparisons between times or places with or without intervention. Dramatic results in uncontrolled experiments are included in this category.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01760005	A Phase II/III Randomized, Double-Blind, Placebo-Controlled Multi-Center Study of 2 Potential Disease Modifying Therapies in Individuals at Risk for and With Dominantly Inherited Alzheimer's Disease	490	Mar 2021 (recruiting)
NCT00064870	National Cell Repository for Alzheimer's Disease (NCRAD)	3000	Jul 2021 (recruiting)
NCT03634007	Gene Therapy for APOE4 Homozygote of Alzheimer's Disease	15	Dec 2021 (recruiting)
NCT01998841[a]	A Double-Blind, Placebo-Controlled Parallel-Group Study in Preclinical PSEN1 E280A Mutation Carriers Randomized to	252	Feb 2022 (ongoing)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Crenezumab or Placebo, and in Non-Randomized, Placebo-Treated Non-Carriers From the Same Kindred, to Evaluate the Efficacy and Safety of Crenezumab in the Treatment of Autosomal-Dominant Alzheimer's Disease		
NCT03977584[a]	Tau PET Longitudinal Substudy Associated With: A Double-Blind, Placebo-Controlled Parallel-Group Study in Preclinical PSEN1 E280A Mutation Carriers Randomized to Crenezumab or Placebo, and in Non-randomized, Placebo-treated Non-carriers From the Same Kindred, to Evaluate the Efficacy and Safety of Crenezumab in the Treatment of Autosomal-Dominant Alzheimer's Disease	150	Feb 2022 (recruiting)
NCT00869817	Dominantly Inherited Alzheimer Network (DIAN)	700	Jul 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03657732	A Multi-center Longitudinal Cohort Study of Familial Alzheimer's Disease in China	10,000	Jan 2028 (recruiting)
NCT02564692	Alzheimer's Prevention Registry GeneMatch Program	500,000	Dec 2030 (ongoing)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genetic Testing for Alzheimer Disease", 2.04.13, 5:2020.
2. Bird TD. Genetic aspects of Alzheimer disease. Genet Med. Apr 2008;10(4):231-239. PMID 18414205
3. 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
4. Caselli RJ, Dueck AC, Locke DE, et al. Cerebrovascular risk factors and preclinical memory decline in healthy APOE epsilon4 homozygotes. Neurology. Mar 22 2011;76(12):1078-1084. PMID 21325652
5. 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):107-116. PMID 23150908
6. Guerreiro R, Wojtas A, Bras J, et al. TREM2 variants in Alzheimer's disease. N Engl J Med. Jan 10 2013;368(2):117-127. PMID 23150934
7. 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):263-269. PMID 21514250
8. 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
9. 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):270-279. PMID 21514249
10. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Genetic Testing for Alzheimer's Disease: APOE Epsilon 4 Allele. TEC Assessments. 1999;Volume 14:Tab 7.
11. National Center for Biotechnology Information. GTR: Genetic Testing Registry. n.d.; https://www.ncbi.nlm.nih.gov/gtr/.
12. Slooter 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):1196-1198. PMID 15079025
13. 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):673-677. PMID 8618665
14. Bird TD. Alzheimer Disease Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2015.
15. 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):1394-1404. PMID 25199842
16. 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):1452-1458. PMID 24162737
17. Blue EE, Horimoto ARVR, Mukherjee S, et al. Local ancestry at APOE modifies Alzheimer's disease risk in Caribbean Hispanics. Alzheimers Dement. 2019 Dec;15(12). PMID 31606368
18. 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):94-97. PMID 18317253
19. 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):245-254. PMID 19605829

20. 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):155-163. PMID 26810768
21. 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):555-559. PMID 7966192
22. 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):231-234. PMID 12817569
23. 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):235-239. PMID 12552037
24. 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. 2019 Sep;20(19). PMID 31557888
25. 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
26. 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. 2019 Dec;5(6). PMID 31836585
27. 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):935-942. PMID 22731638
28. American College of Medical Genetics and Genomics. Choosing Wisely. 2015; http://www.choosingwisely.org/societies/american-college-of-medical-genetics-and-genomics/.
29. 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. 2019 Oct;21(10). PMID 31217590
30. 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):1143-1153. PMID 11342678
31. Hort J, O'Brien JT, Gainotti G, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol. Oct 2010;17(10):1236-1248. PMID 20831773

32. Gauthier S, Patterson C, Chertkow H, et al. Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4). Can Geriatr J. Dec 2012;15(4):120-126. PMID 23259025
33. Patterson C, Feightner JW, Garcia A, et al. Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease. CMAJ. Feb 26 2008; 178(5): 548-56. PMID 18299540
34. Chertkow H. Introduction: the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, 2006. Alzheimers Dement. 2007 Oct;3(4). PMID 19595947

Policy History

Original Effective Date: 05/17/2006
Current Effective Date: 12/14/2020

05/03/2006	Medical Director review
06/21/2006	Medical Policy Committee approval
11/05/2008	Medical Director review
11/18/2008	Medical Policy Committee approval. No change to coverage eligibility.
11/04/2010	Medical Policy Committee review
11/16/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2013	Medical Policy Committee review
11/20/2013	Medical Policy Implementation Committee approval. TREM2 added to investigational policy statement.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2015	Coding Update
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

Genetic Testing for Alzheimer's Disease

Policy # 00204
Original Effective Date: 05/17/2006
Current Effective Date: 12/14/2020

10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. No change to coverage.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Policy and evidence reviewed separately for late-onset and early-onset Alzheimer disease. Policy statement changed to eligible for coverage for autosomal dominant early-onset AD for reproductive decision making.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Added "early onset" to coverage statement.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. No change to coverage.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 11/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT,

and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81401, 81405, 81406
HCPCS	S3852
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.