Genetic Testing for Alzheimer’s Disease

Policy # 00204
Original Effective Date: 05/17/2006
Current Effective Date: 01/09/2023

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) (See Policy Guidelines) 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:
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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 (APOE) epsilon 4 allele or triggering receptor expressed on myeloid cells 2 (TREM2).

Based on review of available data, the Company considers genetic testing to guide initiation or management of a U.S. Food and Drug Administration-approved amyloid-beta targeting therapy (eg, aducanumab) to be investigational.* Genetic testing includes but is not limited to, testing for the APOE epsilon 4 allele.

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 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
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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 2 generations. Testing for genes associated with early-onset autosomal dominant AD is appropriate for symptomatic individuals with early-onset Alzheimer disease in the setting of a family history of dementia, the setting of an unknown family history (eg, adoption), or for guiding testing of unaffected family members making reproductive decisions. In individuals at risk of early-onset, autosomal dominant AD, ideally, an affected family member should be tested first to identify the familial variant. Additionally, targeted testing of the parents of a proband with early-onset autosomal dominant AD and a confirmed genetic variant to identify mode of transmission (germline versus de novo) may be considered appropriate in some families, such as families with unaffected parents and no affected closely related family members. 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 DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (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.
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**Table PG1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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 is commonly associated with a family history; 40% of patients with AD have at 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. Alzheimer disease 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 ε4 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 amyloid-beta 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 1 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 1 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.

**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 CLIA for high-complexity testing.

In November 2017, the 23andMe Personal Genome Service (PGS) Test with Genetic Health Risk Report for Late-onset Alzheimer Disease was granted a de novo classification by the U.S. Food and Drug Administration (class II with general and special controls, FDA product code: PTA). This is a direct-to-consumer test that has been evaluated by the FDA for accuracy, reliability, and consumer comprehension. This test reports whether an individual has variants associated with late-onset AD by detecting the presence of the APOE ε4 (rs429353) gene variant.

In June 2021, aducanumab (Aduhelm; Biogen) was approved by the FDA for treatment of AD. This indication was approved under accelerated approval based on reduction in amyloid-beta plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

In July 2021, FDA amended the approved label to emphasize the disease stages studied in the clinical trials. The amended label states, "Treatment with aducanumab should be initiated in..."
patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied."

The FDA, under the accelerated approval regulations (21 CFR 601.41), requires that Biogen conduct a randomized, controlled trial to evaluate the efficacy of aducanumab-avwa compared to an appropriate control for the treatment of AD. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The expected date of trial completion is August 2029 with final report submission to the FDA by February 2030.

**Rationale/Source**
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Alzheimer disease 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 non-elderly individuals. Early-onset AD has a stronger component of family risk, with clustering in families, thus suggesting an inherited genetic disease-causing variant.

**Summary of Evidence**
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. 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 of effective methods to prevent the onset of
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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.
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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 2 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 ARIA following treatment with the amyloid-beta targeting therapy aducanumab was 23% higher for ARIA-edema in APOE ε4 carriers compared to non-carriers, requiring dose modifications in 45% of carriers exposed to a full 10 mg/kg dose. Carriers and non-carriers had similar rates of radiographic severity and symptomatic status. While the APOE status of patients may identify those at higher risk for ARIA, the clinical benefit of aducanumab has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information
Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Medical Genetics and Genomics et al
The American College of Medical Genetics and Genomics (ACMG) 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 joint practice guidelines:
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• “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.
  o Symptomatic patients: Genetic counseling for symptomatic patients should be performed in the presence of the individual’s legal guardian or family member.
  o 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:
  o The lifetime risk of AD in the general population is approximately 10-12% in a 75-80 year lifespan.
  o The effect(s) of ethnicity on risk is still unclear.
  o 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 presenilin [PSEN]1/2 or amyloid-beta precursor protein [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 (reaffirmed 2004), the American Academy of Neurology made the following guideline recommendations for the diagnosis of dementia:
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- 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.

National Institute for Health and Care Excellence
In 2018, the National Institute for Health and Care Excellence (NICE) published guidelines on the assessment, management, and support of people living with dementia. The guidelines state that APOE genotyping should not be used to diagnose Alzheimer's disease.

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 ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
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</tr>
<tr>
<td>NCT00064870</td>
<td>National Cell Repository for Alzheimer's Disease (NCRAD)</td>
<td>3000</td>
<td>Jul 2026 (recruiting)</td>
</tr>
<tr>
<td>NCT01998841</td>
<td>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</td>
<td>252</td>
<td>Dec 2022 (ongoing)</td>
</tr>
</tbody>
</table>

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<th>Completion Date</th>
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</thead>
<tbody>
<tr>
<td>NCT01760005[^a]</td>
<td>Crenezumab in the Treatment of Autosomal-Dominant Alzheimer’s Disease</td>
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<tr>
<td>NCT03876314</td>
<td>The Effect of Physical Activity on Cognition Relative to APOE Genotype (PAAD-2)</td>
<td>240</td>
<td>Mar 2023 (recruiting)</td>
</tr>
<tr>
<td>NCT03634007[^a]</td>
<td>A 52-Week, Multicenter, Phase 1 Open-label Study to Evaluate the Safety of LX1001 in Participants With APOE4 Homozygote Alzheimer’s Disease</td>
<td>15</td>
<td>Sep 2024 (recruiting)</td>
</tr>
<tr>
<td>NCT05400330[^a]</td>
<td>Long-Term Follow-Up to Evaluate the Safety of LX1001 in Participants With APOE4 Homozygote Alzheimer's Disease</td>
<td>15</td>
<td>Dec 2027 (not yet recruiting)</td>
</tr>
<tr>
<td>NCT04241068[^a]</td>
<td>Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (Aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205 (EMBARK)</td>
<td>1696</td>
<td>Feb 2025 (ongoing)</td>
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<tr>
<td>NCT00869817</td>
<td>Dominantly Inherited Alzheimer Network (DIAN)</td>
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<tr>
<td>NCT04680013</td>
<td>Genetic Studies in Familial Dementia</td>
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<td>NCT03657732</td>
<td>A Multi-center Longitudinal Cohort Study of Familial Alzheimer's Disease in China (CFAN)</td>
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<td>NCT02564692</td>
<td>Alzheimer's Prevention Registry GeneMatch Program</td>
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<td>NCT03977584(^a)</td>
<td>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</td>
<td>150</td>
<td>Apr 2022</td>
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Unpublished

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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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NCT: national clinical trial.

\(^a\) Denotes industry-sponsored or cosponsored trial.

References

Genetic Testing for Alzheimer’s Disease

Policy # 00204
Original Effective Date: 05/17/2006
Current Effective Date: 01/09/2023


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Policy History

Original Effective Date: 05/17/2006
Current Effective Date: 01/09/2023

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
11/03/2011 Medical Policy Committee review

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Policy # 00204
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11/01/2012 Medical Policy Committee review
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.
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
11/08/2018 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
11/04/2021 Medical Policy Committee review
11/10/2021 Medical Policy Implementation Committee approval. No change to coverage.
12/02/2021 Medical Policy Committee review

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Policy # 00204
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12/20/2021 Coding update
03/25/2022 Coding update
12/01/2022 Medical Policy Committee review
12/14/2022 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 12/2023

Coding

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

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<th>Code Type</th>
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<td>CPT</td>
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<td>HCPCS</td>
<td>S3852</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
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</table>

*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 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;
Genetic Testing for Alzheimer’s Disease

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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.