Genetic Testing for Alzheimer's Disease

Policy # 00204
Original Effective Date: 05/17/2006
Current Effective Date: 01/08/2024

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 for Asymptomatic Individuals
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.

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.

Treatment with Amyloid-beta Plaque Targeting Therapy
The lecanemab (LEQEMBI®)‡ product label includes 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 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.

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 is commonly associated with a family history; 40% of patients with 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. 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.

Treatment
Lecanemab has been evaluated in 2 double-blind RCTs (Study 201 and Study 301/Clarity AD) with samples sizes of 390 and 1795. Both trials reported an approximately 27% statistically significantly slower rate of decline in the full analysis population for the primary cognitive and functional outcome (ADCOMS for Study 201; CDR-SB for Study 301) for lecanemab versus placebo. In the phase 3 Study 301 (Clarity AD), subgroup analyses for the primary and secondary cognitive outcomes were performed by APOE status. Treatment comparisons favored lecanemab in all subgroups across the outcome measures except for the CDR-SB outcome in ApoE ε4 homozygous participants which favored placebo (n=132 vs 136 in placebo vs lecanemab). While results for ADAS-Cog 14 and ADCS-ADL-MCI did favor lecanemab in the APOE ε4 homozygous subgroup, the effect size was attenuated compared to APOE ε4 noncarriers and ε4 heterozygous.

In Study 201, ARIA was observed in about 12% (20/161) of individuals treated with lecanemab 10 mg/kg biweekly compared to 5% (13/245) in the placebo arm. The incidence of ARIA was higher in ApoE ε4 homozygotes than in heterozygotes and noncarriers among individuals treated with lecanemab. Of the 5 individuals treated with lecanemab who had symptomatic ARIA, 4 were ApoE ε4 homozygotes, 2 of whom experienced severe symptoms.

In Study 301 (Clarity AD), ARIA was observed in 21% (191/898) of individuals treated with lecanemab compared to 9% (84/897) of individuals on placebo. ARIA incidence was higher in ApoE ε4 homozygotes (45% on lecanemab vs 22% on placebo) compared to heterozygotes (19% on lecanemab vs 9% on placebo) and noncarriers (13% on lecanemab vs 4% on placebo). Rates of symptomatic ARIA were 9.2% for homozygotes, 1.7% for heterozygotes and 1.4% for noncarriers. Serious events of ARIA were reported in 3% of ApoE ε4 homozygotes compared to 1% of heterozygotes and noncarriers.

Individuals who are ApoE ε4 homozygotes have a higher incidence of ARIA, symptomatic ARIA and recurrent ARIA. The boxed warning in the FDA label for lecanemab states that testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.

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

In January 2023, lecanemab (Leqembi; Eisai) was approved by the FDA for treatment of AD under accelerated approval based on the reduction in amyloid beta plaques observed in patients treated with lecanemab. On July 6, 2023, the FDA converted the accelerated approval of Leqembi to traditional approval for the treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of disease. The label includes a boxed warning for amyloid related imaging abnormalities (ARIA), in general, and emphasizing that ApoE ε4 homozygotes have a higher incidence of ARIA.

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 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.

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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 ARIA following treatment with the amyloid-beta targeting therapy lecanemab was at least 2 to 3 times higher in APOE ε4 homozygotes compared to heterozygotes and noncarriers. The boxed warning in the FDA label for lecanemab states that testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing amyloid-related imaging abnormalities (ARIA). 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:

- "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 (eg, 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:

- 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.

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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.

Medicare National Coverage Analysis (NCA) Decision Memo on Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease notes that "Monoclonal antibodies directed against amyloid that are approved by FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS approved prospective comparative studies. Study data for CMS approved prospective comparative studies may be collected in a registry." NCA lists the protocol and the analysis plan for the CMS-approved studies. It is also noted that "Monoclonal antibodies directed against amyloid indicated for the treatment of AD are covered when furnished according to the FDA approved indication in National Institute of Health (NIH)-supported trials. Monoclonal antibodies directed against amyloid for the treatment of AD provided outside of a FDA approved randomized controlled trial (RCT), CMS approved studies, or studies supported by the NIH, are nationally non-covered.

CMS press release dated July 6, 2023, announced broader Medicare coverage for Leqembi (lecanemab) following the FDA traditional approval of the drug. Press release noted that "To receive Medicare coverage, people will need to: 1) be enrolled in Medicare, 2) be diagnosed with mild cognitive impairment or mild Alzheimer's disease dementia, with documented evidence of beta-amyloid plaque on the brain, and 3) have a physician who participates in a qualifying registry with an appropriate clinical team and follow-up care. Clinicians participating in the registry will only need to complete a short, easy-to-use data submission. Individuals with Medicare should speak to their physician about whether this drug is right for them.

Consistent with CMS' National Coverage Determination, Medicare is covering this drug when a physician and clinical team participates in the collection of evidence about how these drugs work in the real world, also known as a registry. Registries are common tools in clinical settings that have successfully gathered information on patient outcomes for decades. The CMS-facilitated registry is easy to use and adheres to robust privacy and security protections in accordance with applicable federal laws and regulations, including the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Researchers will have access to the information to conduct studies intended to further the knowledge of how these drugs can help people with Medicare by answering the research questions outlined in the National Coverage Determination.

Other registries may become available in the coming months and will be posted on CMS' website. Physicians can select the study that works the best for them from the list of studies that will be available at https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development.

Under the Medicare National Coverage Determination, if FDA grants traditional approval to other drugs in this class, Medicare will cover them using this same coverage framework."

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00064870	National Cell Repository for Alzheimer's Disease (NCRAD)	3000	Jul 2026 (recruiting)
NCT01998841[a]	A Double-Blind, Placebo-Controlled Parallel-Group Study in Preclinical PSEN1 E280A Mutation Carriers Randomized to Crenezumab	252	Dec 2022 (ongoing)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	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		
NCT01760005[a]	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 (DIAN-TU)	490	Jul 2022 (recruiting)
NCT03876314	The Effect of Physical Activity on Cognition Relative to APOE Genotype (PAAD-2)	240	Mar 2023 (recruiting)
NCT03634007[a]	A 52-Week, Multicenter, Phase 1 Open-label Study to Evaluate the Safety of LX1001 in Participants With APOE4 Homozygote Alzheimer's Disease	15	Sep 2024 (recruiting)
NCT05400330[a]	Long-Term Follow-Up to Evaluate the Safety of LX1001 in Participants With APOE4 Homozygote Alzheimer's Disease (LEADLTFU)	15	Dec 2027 (not yet recruiting)
NCT04241068[a]	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)	1696	Feb 2025 (ongoing)
NCT04770220[a]	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Efficacy,	300	Jul 2024 (recruiting)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Safety and Biomarker Effects of ALZ-801 in Subjects With Early Alzheimer's Disease and APOE4/4 Genotype		
NCT00869817	Dominantly Inherited Alzheimer Network (DIAN)	700	Jul 2024 (recruiting)
NCT04680013	Genetic Studies in Familial Dementia	20,000	Nov 2025 (recruiting)
NCT03657732	A Multi-center Longitudinal Cohort Study of Familial Alzheimer's Disease in China (CFAN)	40,000	Jan 2038 (recruiting)
NCT02564692	Alzheimer's Prevention Registry GeneMatch Program	500,000	Dec 2030 (recruiting)
Unpublished			
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	Apr 2022

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

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Policy History

Original Effective Date: 05/17/2006
Current Effective Date: 01/08/2024

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.
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.

Genetic Testing for Alzheimer's Disease

Policy # 00204
Original Effective Date: 05/17/2006
Current Effective Date: 01/08/2024

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
12/08/2021	Medical Policy Implementation Committee approval. Investigational policy statement added for initiation or management of amyloid-beta targeting therapy. Policy guidelines updated.
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.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. lecanemab (LEQEMBI®) product added to body of policy. Coverage eligibility unchanged. References and FDA updated.

Next Scheduled Review Date: 12/2024

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 2022 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.

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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 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.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.