

2.04.13 Genetic Testing for Alzheimer Disease	
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Section: 2.0 Medicine	Page: Page 1 of 20

Policy Statement

Targeted genetic testing for a known familial variant in the presenilin (*PSEN1*, *PSEN2*) genes or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant early-onset Alzheimer disease (AD) may be considered **medically necessary** in an asymptomatic or minimally symptomatic individual to determine future risk of disease when the individual has a close relative (i.e., first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease.

Genetic testing for variants in presenilin (*PSEN1*, *PSEN2*) genes or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant early-onset Alzheimer disease may be considered **medically necessary** in an asymptomatic or minimally symptomatic individual to determine future risk of disease when the individual has a family history of dementia consistent with autosomal dominant Alzheimer disease for whom the genetic status of the affected family members is unavailable.

Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered **investigational** in all other situations. Genetic testing includes but is not limited to, testing for the apolipoprotein E (*APOE*) epsilon 4 ($\epsilon 4$) allele or triggering receptor expressed on myeloid cells 2 (*TREM2*).

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Testing Strategy

The 2011 guidelines from the American College of Medical Genetics and Genomics (ACMG) 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.

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 (HGVS) 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 (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 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.

Coding

Effective January 1, 2021, the following CPT code has been **revised**: The following CPT coding is used to report *APOE*, *PSEN*, and *APP* testing:

- **81401:** Molecular Pathology Procedure Level 2 (includes *APOE* [*apolipoprotein E*] [e.g., hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease], common variants [e.g., *2, *3, *4])
- **81405:** Molecular Pathology Procedure Level 6 (includes *PSEN1* [*presenilin 1*] [e.g., Alzheimer disease], full gene sequence)
- **81406:** Molecular Pathology Procedure Level 7 (includes: *APP* [amyloid beta {A4} precursor protein] [e.g., Alzheimer disease], full gene sequence and *PSEN2* [*presenilin 2* {Alzheimer disease 4}] [e.g., Alzheimer disease], full gene sequence)

There following is a HCPCS code specific to *APOE* ε4 allele testing:

- **S3852:** DNA analysis for *APOE* epsilon 4 allele for susceptibility to Alzheimer's disease

Description

Alzheimer disease (AD) is the most common cause of dementia in elderly patients. For late-onset Alzheimer disease (AD), there is a component of risk that runs in families, suggesting the contribution of genetic factors. Early-onset Alzheimer disease (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.

Related Policies

- Beta-Amyloid Imaging With Positron Emission Tomography for Alzheimer Disease
- Evaluation of Biomarkers for Alzheimer Disease

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (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.

Rationale

Background

Alzheimer Disease

Alzheimer disease (AD) 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.¹

Genetic Variants

Individuals with early-onset familial AD (i.e., before age 65 years but as early as 30 years) form a small subset of AD patients. 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- ϵ 2, 3, and 4-with the ϵ 3 allele being the most common. Individuals carry 2 *APOE* alleles. The presence of at least one, ϵ 4 allele is associated with a 1.2- to 3-fold increased risk of AD, depending on the ethnic group. Among those homozygous for ϵ 4 (>2% of the population), the risk of AD is higher than for those heterozygous for ϵ 4. Mean age of onset of AD is about age 68 years for ϵ 4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no ϵ 4 alleles. About half of patients with sporadic AD carry a ϵ 4 allele. However, not all patients with the allele develop AD. The ϵ 4 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.² There is evidence of possible interactions between ϵ 4 alleles, other risk factors for AD (e.g., risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, diabetes),³ 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.^{4,5} 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* ϵ 4 allele, although it occurs less frequently.

Diagnosis

The diagnosis of AD is divided into 3 categories: possible, probable, and definite AD.⁶ 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.⁷ 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.⁶ 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 comporment
- 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.⁶ This may consist of an atypical onset (e.g., sudden onset) or atypical progression. A diagnosis of possible AD is also made when there is another potentially causative systemic or neurologic disorder that is not thought to be the primary etiology of dementia.

Mild cognitive impairment 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.⁸ 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 prodementia phase of AD. Patients with mild cognitive impairment may undergo ancillary testing (e.g., neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings.⁶ Other diagnostic tests for AD include cerebrospinal fluid levels of tau protein or amyloid precursor protein, as well as positron emission tomography amyloid imaging. The cerebrospinal fluid tests are considered separately in Blue Shield of California Medical Policy: Evaluation of Biomarkers for Alzheimer Disease. Positron emission tomography amyloid imaging is considered in Blue Shield of California Medical Policy: Beta-Amyloid Imaging with Positron Emission Tomography for Alzheimer Disease.

Literature Review

The review was informed by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (1999).⁹

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms are better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful.

Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Genetic Testing for Late-Onset Alzheimer Disease

Clinical Context and Test Purpose

The purpose of genetic testing in patients who are asymptomatic and at risk for developing late-onset Alzheimer disease (AD) is potentially to inform management decisions such as early treatment or behavioral changes. Asymptomatic patients at risk of late-onset AD are not generally treated with medical therapy but may choose to make behavioral changes associated with reduced risk of AD.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals who are asymptomatic and at risk for developing late-onset AD?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is adults who are asymptomatic and at risk for developing late-onset AD due to a family history of AD or dementia.

Interventions

The test being considered is genetic testing. It can be performed on a number of candidate genes, individually or collectively. Lists of genes associated with AD and testing laboratories in the U.S. are provided on the Genetic Testing Registry website of the National Center for Biotechnology Information.¹⁰

Genetic testing for variants associated with late-onset AD is complex. Referral for genetic counseling is important for the explanation of the genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators

The following practice is currently being used: standard clinical management without genetic testing.

Outcomes

The general outcomes of interest are a change in disease status, health status measures, and quality of life. Specific outcomes in each of these categories are listed in Table 1.

The potential beneficial outcomes of primary interest would be change in disease status if changes in management or behavior in asymptomatic patients at risk of late-onset AD are initiated that prevent or slow the progression of cognitive decline. Improvement in health status measures is also important.

Potential harmful outcomes are those resulting from a true- or false-positive test result. Patients might suffer from psychological harm or anxiety after receiving positive test results.

Table 1. Outcomes of Interest for Individuals With Symptomatic Late-Onset Alzheimer Disease

Outcomes	Details
Change in disease status	Incidence or time to Alzheimer disease onset; changes in cognitive test scores
Health status measures	Activities of daily living or functional scales such as the 36-Item Short-Form Health Survey, Alzheimer Disease Cooperative Study Activities of Daily Living scale, or Disability Assessment for Dementia
Quality of life	EuroQoL EQ-5D; measures of anxiety or depression

Trials of genetic testing in this population have been sparse and generally included short-term outcomes of distress and anxiety measured within a year. Trials of prevention strategies in AD

typically span many years to a decade to detect differences in conversion to AD in asymptomatic, at-risk individuals.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for AD, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Diagnostic tests detect the presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or an adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or predicting a response to therapy.

Review of Evidence

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Many studies have examined the association between the apolipoprotein E (*APOE*) epsilon 4 allele and AD. The Rotterdam and Framingham studies are examples of large observational studies demonstrating the association. The Rotterdam Study was a prospective cohort study in the city of Rotterdam, the Netherlands, with main objectives of investigating risk factors of cardiovascular, neurologic, ophthalmologic, and endocrine diseases in the elderly.¹¹ In a sample of 6852 participants, carriers of a single $\epsilon 4$ allele had a relative risk of developing AD approximately double that of $\epsilon 3/\epsilon 3$ carriers. Carriers of the two, $\epsilon 4$ alleles had a relative risk of developing dementia approximately 8 times that of $\epsilon 3/\epsilon 3$ carriers. The Framingham Heart Study was a longitudinal cohort study initiated in 1948 in Framingham, Massachusetts, to identify common risk factors for cardiovascular disease.¹² In 1030 participants, the relative risk for developing AD was 3.7 (95% confidence interval [CI], 1.9 to 7.5) for carriers of a single $\epsilon 4$ allele and 30.1 (95% CI, 10.7 to 84.4) for carriers with two $\epsilon 4$ alleles compared with those without a $\epsilon 4$ allele. The association between the *APOE* epsilon 4 allele and AD is significant; however, *APOE* genotyping does not have high specificity or sensitivity and is of little value in the predictive testing of asymptomatic individuals.¹³

Associations between late-onset AD and more than 20 non-*APOE* genes have been suggested. Examples of large studies and meta-analyses on these non-*APOE* genes are discussed below.

Naj et al (2014) published a genome-wide association study of multiple genetic loci in late-onset AD.¹⁴ Genetic data from 9,162 white participants with AD, from the Alzheimer Disease Genetics Consortium, were assessed for variants at 10 loci significantly associated with risk of late-onset AD. The analysis confirmed the association between *APOE* and early-onset and found significant associations for the *CR1*, *BIN1*, and *PICALM* genes. *APOE* contributed 3.7% of the variation in age of onset, and the other 9 loci combined contributed 2.2% of the variation. Each additional copy of the *APOE* epsilon 4 allele reduced the age of onset by 2.45 years.

Lambert et al (2013) published a large meta-analysis of a genome-wide association study of susceptibility loci for late-onset AD in 17,008 AD cases and 37,154 controls of European ancestry.¹⁵ Nineteen loci had genome-wide significance in addition to the *APOE* locus. The researchers confirmed several genes already reported to be associated with AD (*ABCA7*, *BIN1*, *CD33*, *CLU*, *CR1*, *CD2AP*, *EPHA1*, *MS4A6A-MS4A4E*, *PICALM*). New loci located included *HLA-DRB5-HLA-DRB1*, *PTK2B*, *SORL1*, and *SLC24A4-RIN3*.

Jonsson et al (2013) evaluated 3,550 subjects with AD and found a genome-wide association for only 1 marker, the T allele of rs75932628 (excluding the *APOE* locus and the *APP11* A673T variant).⁴ The frequency of rs75932628 (triggering receptor expressed on myeloid cells 2 [*TREM2*]) was then tested in a general population of 110,050 Icelanders of all ages and found to confer a risk of developing AD of 0.63% (odds ratio [OR], 2.26; 95% CI, 1.71 to 2.98; $p=1.13 \times 10^{-8}$). In the control population of 8,888 patients 85 years of age or older without a diagnosis of AD, the *TREM2* frequency was 0.46% (OR=2.92; 95% CI, 2.09 to 4.09; $p=3.42 \times 10^{-10}$). In 1236 cognitively intact controls age 85 or older, the frequency of *TREM2* decreased to 0.31% (OR=4.66; 95% CI, 2.38 to 9.14; $p=7.39 \times 10^{-6}$). The decrease in *TREM2* frequency in cognitively intact elderly patients supports findings associating *TREM2* with increasing risk of AD. Guerriero et al (2013) also found a strong association between the *TREM2* R47H variant and AD ($p=0.001$).⁵ Using 3 imputed data sets of a genome-wide association study, the meta-analysis found a significant association between the variant and AD ($p=0.002$). The authors further reported direct genotyping of R47H in 1994 AD patients and 4062 controls, which detected a highly significant association between the variant and AD (OR=5.05; 95% CI, 2.77 to 9.16; $p=9.0 \times 10^{-9}$).

The effects of *APOE* and ancestry on AD risk in diverse populations continue to be elucidated.¹⁶

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

There are no RCTs comparing outcomes of asymptomatic adults at risk for developing late-onset AD managed with and without genetic testing for AD.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study as reported by Chao et al (2008) was designed to examine the consequences of AD risk assessment by *APOE* genotype.¹⁷ Of 289 eligible participants, 162 were randomized (mean age, 52.8 years; 73% female) to risk assessment based on *APOE* testing plus family history ($n=111$) or family history alone ($n=51$). During a 1-year follow-up, those undergoing *APOE* testing with a high-risk genotype were more likely than low-risk or untested individuals to take more vitamins (40% vs. 24% and 30%), change diet (20% vs. 11% and 7%), or change exercise behaviors (8% vs. 4% and 5%), all respectively. There is insufficient evidence to conclude that these short-term behavioral changes would alter clinical outcomes. Green et al (2009) examined anxiety, depression, and test-related distress at 6 weeks, 6 months, and 1 year in the 162 participants randomized in REVEAL.¹⁸ However, there were no significant differences between the group that received the results of *APOE* testing and the group that did not, in changes in anxiety or depression overall, or the subgroup of participants with the *APOE* epsilon 4 allele. However, the $\epsilon 4$ negative participants had significantly lower test-related distress than $\epsilon 4$ positive participants ($p=0.01$).

Christensen et al (2016) examined disclosing associations between *APOE* genotype and AD risk alone versus AD and coronary artery disease (CAD) risk in an equivalence trial from the REVEAL group.¹⁹ Two hundred ninety participants were randomized to AD risk disclosure alone or AD plus CAD risk disclosure. The 257 participants who received their genetic information were included in the analyses. Mean anxiety, depression, and test-related distress scores were below cutoffs for mood disorders at all time points in both disclosure groups and were similar to baseline levels. At the 12-month follow-up, both anxiety (measured by the Beck Anxiety Index) and depression (measured by the Center for Epidemiologic Studies Depression Scale) fell within the equivalence margin indicating no difference between disclosure groups. Among participants with a $\epsilon 4$ allele, distress (measured by Impact of Event Scale) was lower at 12 months in AD plus CAD group than in the AD-only group (difference, -4.8; 95% CI, -8.6 to -1.0; $p=0.031$). AD plus CAD participants also reported more health behavior changes than AD-alone participants, regardless of *APOE* genotype.

There is a lack of interventions that can delay or mitigate late-onset AD. There is no evidence that early intervention for asymptomatic disease-associated variant carriers can delay or mitigate future diseases. There are many actions patients can take following knowledge of a disease-associated variant. Changes in lifestyle factors (e.g., diet, exercise) and/or incorporation of “brain training” exercises can be made, but there is no evidence that these interventions impact clinical disease.

Section Summary: Genetic Testing for Late-Onset Alzheimer Disease

The *APOE* epsilon 4 allele is strongly associated with the incidence of and age at onset of AD; many other genes have shown statistical associations with AD incidence and onset, thus demonstrating some degree of clinical validity. However, the clinical sensitivity and specificity of the *APOE* epsilon 4 allele is poor,²⁰ and there is a lack of evidence on the clinical sensitivity and specificity of other genes.

Literature searches did not identify any studies that address how the use of the *APOE* or other AD-associated genetic variants might be incorporated into clinical practice. It is also unclear how changes in the management of asymptomatic patients with these genes would improve outcomes. The REVEAL studies found short-term changes in behaviors following disclosure of *APOE* genetic testing results in high-risk adults with little increase in anxiety or depression overall, although with a possible increase in distress among $\epsilon 4$ allele carriers. It is unclear whether these changes in behaviors would improve clinical outcomes or whether there are long-term effects on psychological outcomes among $\epsilon 4$ carriers. Therefore, the clinical utility has not been demonstrated for these tests.

Genetic Testing for Early-Onset Alzheimer Disease With and Without a Known Familial Variant Clinical Context and Test Purpose

The purpose of genetic testing in patients who are asymptomatic and at risk for developing early-onset AD is to inform management decisions such as initiation of AD therapy and to inform reproductive decision making. Asymptomatic patients at risk for early-onset AD are not generally treated with medical therapy.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals who are asymptomatic, at risk for developing early-onset AD, and have a known or unknown familial variant?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is adults who are asymptomatic and at risk for developing early-onset AD due to family history of early-onset AD, specifically those with autosomal dominant AD.

Interventions

Adults with a family history of early-onset AD caused by a known pathogenic amyloid-beta precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) variant would undergo targeted testing for the specific familial variant. In adults with a family history consistent with autosomal dominant AD but for whom the familial variant is unknown, genetic testing can be performed on the 3 genes (*APP*, *PSEN1*, *PSEN2*) individually or collectively. Multiple variants in these genes can cause early-onset AD, so sequencing the entire coding regions is necessary to comprehensively assess risk when the familial variant is unknown.

Asymptomatic patients are likely to be managed in primary care. Reproductive decision making is a complex psychological process. Referral for genetic counseling is important for the explanation of the genetic disease, heritability, genetic risk, test performance, and possible outcomes. The American College of Medical Genetics and Genomics and the National Society of Genetic Counselors guidelines have 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.² 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 also been recommended.²¹

Comparators

The following practice is currently being used: targeted familial variant testing for those with a known familial variant and genetic testing for those without a known familial variant.

Outcomes

The general outcomes of interest are a change in disease status, health status measures, quality of life, and changes in reproductive decision making.

The potential beneficial outcome of primary interest would be change in reproductive decision making. Changes in management in asymptomatic patients at risk of AD might be initiated with the intent to prevent or slow the progression of cognitive decline leading to changes in disease status. Improvement in health status measures is also important.

Potential harmful outcomes are those resulting from a true- or a false-positive test result. Patients might suffer from psychological harm or anxiety after receiving positive test results.

Outcomes of reproductive decision making are relevant during child-bearing years for asymptomatic adults at risk.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for AD, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Diagnostic tests detect the presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or an adverse response. The term predictive test is often used to refer to the

response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or predicting a response to therapy.

Review of Evidence

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In the scenario of targeted testing of individuals with a known familial pathogenic variant, due to nearly complete penetrance of pathogenic variants, an identified carrier will almost certainly develop the disease unless dying at an age preceding disease onset. Therefore, clinical validity is nearly certain.

In the scenario of genetic testing of individuals with a family history consistent with autosomal dominant early-onset AD but in whom a pathogenic variant has not been found, the testing yield is less certain. Genetic testing for *PSEN1* is estimated to detect disease-causing variants in 30% to 60% of individuals with familial early-onset AD,^{22,23} although estimates vary. A number of variants scattered throughout the *PSEN1* gene have been reported, requiring sequencing of the entire gene when the first affected member of a family with an autosomal dominant pattern of AD inheritance is tested. Variants in *APP* and *PSEN2* genes account for another 10% to 20% of cases.

Genetic yields may vary by population. Giau et al (2019) reported on 200 patients with clinically diagnosed early-onset AD from Thailand, Malaysia, the Philippines, and Korea who were genetically screened between 2009 and 2018.²⁴ Thirty-two (16%) patients carried pathogenic *APP* (8/32 [25%]), *PSEN1* (19/32 [59%]), or *PSEN2* (5/32 [16%]) variants. However, this analysis included possible and probable pathogenic variants in addition to those classified as definite. Overall, approximately 84% ($p=0.01$) of autosomal dominant pedigrees in the tested Asian population were genetically unexplained.

Clinical and phenotypic expressivity is variable, i.e., the presence of *PSEN1*, *PSEN2*, or *APP* variants is not useful in predicting the age of onset (although the age of onset is usually similar in affected family members), severity, type of symptoms, or rate of progression in asymptomatic individuals.²⁵

A study by Cochran et al (2019) confirmed a high diagnostic yield in early-onset or atypical dementia. Fifty percent (16/32) of patients tested harbored 1 or more genetic variants capable of explaining symptoms, including variants in *APP*. Nine of 32 patients (28%) had a variant defined as pathogenic or likely pathogenic whereas 6 had 1 or more variants with moderate penetrance. The authors noted this supports a potential oligogenic model for early-onset dementia.²⁶

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

There are no RCTs comparing outcomes of asymptomatic adults at risk for developing early-onset AD managed with and without genetic testing for AD.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The potential clinical utility of testing is the early identification of asymptomatic patients who are at risk for developing early-onset AD. Genetic testing will in most cases lead to better risk stratification, distinguishing patients who will develop the disease from those who will not. If the early identification of patients at risk leads to interventions to delay or mitigate clinical disease, then the clinical utility would be established. Identification of asymptomatic, young adult carriers could impact reproductive planning. And clinical utility may be demonstrated if testing leads to informed reproductive planning that improves outcomes. Alternatively, the clinical utility could be demonstrated if knowledge of variant status leads to beneficial changes in psychological outcomes.

A systematic review, reported by Rahman et al (2012), which assessed the psychological and behavioral impact of genetic testing for AD, found few studies on the impact of testing for early-onset familial AD. The existing studies generally have small sample sizes and retrospective designs, and the research was conducted in different countries, which may limit the generalizability of the findings.²⁷

There is no evidence that early intervention for asymptomatic pathogenic variant carriers can delay or mitigate future diseases. There are many actions patients may take following knowledge of a pathogenic variant: changes in lifestyle factors (e.g., diet, exercise) and incorporation of “brain training” exercises; but there is no evidence that these interventions impact clinical disease.

When a known pathogenic variant is identified in a prospective parent, with reasonable certainty, the disease will develop and there is a 50% risk of an affected offspring. For purposes of informing family planning, when a pathogenic variant is detected in a prospective parent, the prospective parent can choose to refrain from having children or choose medically assisted reproduction during which preimplantation testing would allow a choice to avoid an affecting offspring. Identification of a pathogenic variant by genetic testing is more accurate than the alternative of obtaining a family history alone. Therefore, testing in the reproductive setting can improve health outcomes.

Section Summary: Genetic Testing for Early-Onset Alzheimer Disease

The clinical validity for autosomal dominant, early-onset AD will be nearly certain when a pathogenic variant has previously been identified in a family pedigree or the variant database.

For those from families with early-onset, familial AD, when a pathogenic familial variant is known or when the family pedigree is consistent with autosomal dominant AD but the affected family members have not been tested to determine the familial variant, 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. There are currently no known preventive measures or treatments that can mitigate the effect of AD. It is not clear how a change in the management of asymptomatic patients with these genes would improve outcomes. 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.

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 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 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 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, 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.²⁸ 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 Alzheimer

disease (AD), the most common cause of dementia: "The presence of an $\epsilon 4$ allele is neither necessary nor sufficient to cause AD. The relative risk conferred by the $\epsilon 4$ 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:²

- "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:²⁹

- 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:³⁰

- 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.³¹ The guidelines state that apolipoprotein E 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 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00064870	National Cell Repository for Alzheimer's Disease (NCRAD)	3,000	Jul 2021 (recruiting)
NCT01998841 ^a	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	252	Feb 2022 (ongoing)
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)
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	Jul 2022 (recruiting)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03634007	Gene Therapy for APOE4 Homozygote of Alzheimer's Disease	15	Jan 2023(recruiting)
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	40,000	Jan 20 38 (recruiting)
NCT02564692	Alzheimer's Prevention Registry GeneMatch Program	500,000	Dec 2030 (ongoing)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
 - Diagnosis
 - Family history
 - Genetic counseling notes
 - How test result will impact clinical decision making including but not limited to how it might affect reproductive decision making
 - Reason for performing test
 - Signs/symptoms/test results related to reason for genetic testing
- Lab results documenting both partners carrier status or genetic disorder
- Physician order for genetic test
- Name and description of genetic test
- CPT codes billed for the particular genetic test

Post Service (in addition to the above, please include the following):

- Laboratory report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81401	Molecular pathology procedure, Level 2 (Code revision effective 1/1/2021)
	81405	Molecular pathology procedure, Level 6 (Code revision effective 1/1/2021)
	81406	Molecular pathology procedure, Level 7 (Code revision effective 1/1/2021)
HCPCS	S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/02/2010	New policy Policies combined: Apolipoprotein E Epsilon (apoE) 4 Allele and Alzheimers Disease: Role for Genetic Testing for Diagnosis and Risk Management Cerebrospinal Fluid and Urinary Assays of Neuronal (Neural) Thread Protein in the Diagnosis of Alzheimers Dementia

Effective Date	Action
04/19/2012	Added documentation required for clinical review
02/22/2013	Coding Update
02/27/2015	Policy title change from Alzheimer's Disease - Genetic and Biochemical Testing Policy revision without position change
09/01/2016	Policy title change from Genetic Testing for Familial Alzheimer's Disease Policy revision without position change
11/01/2017	Policy revision with position change
06/01/2018	Policy revision without position change
07/01/2019	Policy revision without position change
07/01/2020	Annual review. No change to policy statement. Literature review updated.
01/01/2021	Coding Update
06/01/2021	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. 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 covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p>Genetic Testing for Alzheimer Disease 2.04.13</p> <p>Policy Statement: Targeted genetic testing for a known familial variant in the presenilin (<i>PSEN1</i>, <i>PSEN2</i>) genes or amyloid-beta precursor protein (<i>APP</i>) gene associated with autosomal dominant early-onset Alzheimer disease (AD) may be considered medically necessary in an asymptomatic or minimally symptomatic individual to determine future risk of disease when the individual has a close relative (i.e., first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease.</p> <p>Genetic testing for variants in presenilin (<i>PSEN1</i>, <i>PSEN2</i>) genes or amyloid-beta precursor protein (<i>APP</i>) gene associated with autosomal dominant early-onset Alzheimer disease may be considered medically necessary in an asymptomatic or minimally symptomatic individual to determine future risk of disease when the individual has a family history of dementia consistent with autosomal dominant Alzheimer disease for whom the genetic status of the affected family members is unavailable.</p> <p>Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered investigational in all other situations. Genetic testing includes but is not limited to, testing for the apolipoprotein E (<i>APOE</i>) epsilon 4 ($\epsilon 4$) allele or triggering receptor expressed on myeloid cells 2 (<i>TREM2</i>).</p>	<p>Genetic Testing for Alzheimer Disease 2.04.13</p> <p>Policy Statement: Targeted genetic testing for a known familial variant in the presenilin (<i>PSEN1</i>, <i>PSEN2</i>) genes or amyloid-beta precursor protein (<i>APP</i>) gene associated with autosomal dominant early-onset Alzheimer disease (AD) may be considered medically necessary in an asymptomatic or minimally symptomatic individual to determine future risk of disease when the individual has a close relative (i.e., first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease.</p> <p>Genetic testing for variants in presenilin (<i>PSEN1</i>, <i>PSEN2</i>) genes or amyloid-beta precursor protein (<i>APP</i>) gene associated with autosomal dominant early-onset Alzheimer disease may be considered medically necessary in an asymptomatic or minimally symptomatic individual to determine future risk of disease when the individual has a family history of dementia consistent with autosomal dominant Alzheimer disease for whom the genetic status of the affected family members is unavailable.</p> <p>Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered investigational in all other situations. Genetic testing includes but is not limited to, testing for the apolipoprotein E (<i>APOE</i>) epsilon 4 ($\epsilon 4$) allele or triggering receptor expressed on myeloid cells 2 (<i>TREM2</i>).</p>