2.04.13	Genetic Testing for Alzheimer Disease		
Original Policy Date:	April 2, 2010	**Effective Date:**	October 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 30

Policy Statement

I. Targeted genetic testing for a known familial variant in the presenilin (PSEN) genes or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when **all** of the following criteria are met:
   A. 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 (see Policy Guidelines)
   B. Results of testing will inform reproductive decision making

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

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

IV. 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 epsilon 4 (*APOE* ε4) 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

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

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in 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.

Coding

See the Codes table for details.

Description

Alzheimer disease (AD) is the most common cause of dementia in elderly patients. For late-onset AD, there is a component of risk that runs in families, suggesting the contribution of genetic factors. Early-onset AD is much less common but can occur in 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 Alzheimer disease (AD) who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, and quality of life. Many genes, including *APOE*, *CR1*, *BIN1*, *PICALM*, and *TREM2*, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing for indicating which individuals will progress to AD is low, and numerous other factors can affect progression. Overall, genetic testing has not been shown to add value to the diagnosis of AD made clinically. The current lack of effective methods to prevent the onset of AD limits the clinical benefit for genetic testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have no known familial variant who receive genetic testing, the evidence includes studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision making, health status measures, and quality of life.

Variants in the *PSEN1*, *PSEN2*, and *APP* genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be reasonably certain when a variant found in the database of pathogenic *PSEN1*, *PSEN2*, and *APP* variants are identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, the clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a clinical diagnosis of mild cognitive impairment or mild dementia associated with AD who are considering initiation or discontinuation of an FDA-approved amyloid-beta targeting therapy who receive genetic testing, the evidence includes randomized clinical trials. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related morbidity and mortality. The incidence of asymptomatic, symptomatic and serious amyloid-related imaging abnormalities (ARIA) following treatment with the amyloid-beta targeting therapiesis significantly higher in *APOE* ε4 homozygotes compared to heterozygotes and noncarriers. The boxed warnings in the FDA labels for approved amyloid-beta targeting therapies states that testing for *APOE* ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Clinical input was sought to help determine whether the use of genetic testing for those for individuals with early AD who are considering initiation or discontinuation of an FDA-approved amyloid-beta targeting therapy would provide a clinically meaningful improvement in net health outcome. In response to requests, clinical input was received from 3 respondents; 1 physician-level response identified through a specialty society; 2 physician-level responses (joint response) identified through an academic medical center.

For individuals with early AD who are considering initiation or discontinuation of an FDA-approved amyloid-beta targeting therapy who receive genetic testing, clinical input supports this use provides a clinically meaningful improvement in net health outcome with the criteria described.
Further details from clinical input are included in the Appendix.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services 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 law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

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.

In January 2023, lecanemab (Leqembi; Eisai) was approved by the FDA for the 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 AD 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.

In July 2024, donanemab (Kisunla, Eli Lilly) was approved by the FDA via a traditional approval for the treatment of AD 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

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 epsilon 4 (*APOE* ε4) 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.[2,] There is evidence of possible interactions between ε4 alleles and 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* ε4 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 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.[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 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.[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 predementia 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.

Literature Review

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 individuals 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 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.[9,]

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 epsilon 4 allele (*APOE* ε4) 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.[10,] In a sample of 6852 participants, carriers of a single ε4 allele had a relative risk of developing AD approximately double that of ε3/ε3 carriers. Carriers of the two, ε4 alleles had a relative risk of developing dementia approximately 8 times that of ε3/ε3 carriers. The Framingham Heart Study was a longitudinal cohort study initiated in 1948 in Framingham, Massachusetts, to identify common risk factors for cardiovascular disease.[11,] 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 ε4 allele and 30.1 (95% CI, 10.7 to 84.4) for carriers with two ε4 alleles compared with those without a ε4 allele. The association between the *APOE ε4* 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.[12,]

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.[13,] Genetic data from 9162 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* ε4 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.[14,] 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 3550 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=.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=.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 x10^{-9}). The effects of *APOE* and ancestry on AD risk in diverse populations continue to be elucidated.[15,]

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.[16,] 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.[17,] 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* ε4 allele. However, the ε4 negative participants had significantly lower test-related distress than ε4 positive participants (p=.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.[18,] 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 ε4 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=.031). AD plus CAD participants also reported more health behavior changes than AD-alone participants, regardless of *APOE* genotype.

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* ε4 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* ε4 allele is poor,[19,] and there is a lack of evidence on the clinical sensitivity and specificity of other genes.

It is 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 ε4 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 ε4 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 individuals 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 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.

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,[20,21,] 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.[22,] 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=.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.[23,]

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.[24,]

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. Additionally, 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.[25,]

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 affected 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. It is not clear how a change in the management of asymptomatic patients with these genes would improve outcomes. Outside of 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.

Genetic Testing for Management of Amyloid-Beta Targeting Therapy

Clinical Context and Test Purpose

The purpose of genetic testing in individuals with mild cognitive impairment or mild dementia associated with AD who are considering or are currently being treated with an FDA-approved amyloid-beta targeting therapy is to inform management decisions such as initiation, discontinuation, or continuation of therapy.

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

Populations

The relevant population of interest is individuals with mild cognitive impairment or mild dementia associated with AD who are being considered for or are currently being treated with an FDA-approved amyloid-beta targeting therapy (e.g., lecanemab and donanemab).

Interventions

The intervention of interest is genetic testing, used in addition to clinical diagnosis or assessment of cognitive and functional response to therapy, to inform amyloid-beta targeting therapy management decisions (e.g., initiation, discontinuation, or continuation of therapy).

Comparators

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

Outcomes

The general outcomes of interest are symptoms, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related morbidity and mortality.

The outcome of primary interest would be changes in treatment decision-making that result in beneficial improvements in health status measures, such as the Clinical Dementia Rating-Sum of Boxes (CDR-SB), Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory-10 (NPI-10), Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale (ADAS-Cog 13), Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI), Alzheimer's Disease Composite Score (ADCOMS) and other AD-specific assessment scales.

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).

Exploratory analyses of pooled safety data from 2 phase 3 trials of a no longer marketed amyloid-beta targeting therapy, aducanumab, indicate that *APOE* ε4 carrier status is associated with a higher incidence of amyloid-related imaging abnormalities (ARIA).[26,27,28,] Specifically, the incidence of ARIA-edema was 43 % versus 20%, in *APOE* ε4 carriers and non-carriers receiving a 10 mg/kg dose of aducanumab, respectively. The overall incidence of any ARIA ranged from 36-41% in the treatment group compared to 10.3% in the placebo group. The clinical effects of ARIA range from asymptomatic to severe. Although the majority of patients were asymptomatic or had symptoms such as headache, confusion, or dizziness that resolved with temporary stoppage of the drug, 6.2% of participants receiving the high dose of aducanumab discontinued the drug due to ARIA compared to 0.6% in the placebo arm.

The majority of ARIA-edema radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. Among patients treated with a planned dose of aducanumab 10 mg/kg who had ARIA-edema, the maximum radiographic severity was mild in 30%, moderate in 58%, and severe in 13% of patients (refer to prescribing label for classification of severity of ARIA). Resolution occurred in 68% of ARIA-edema patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection. Ten percent of all patients who received aducanumab 10 mg/kg had more than 1 episode of ARIA-edema. Radiographic severity and symptomatic status were similar for *APOE* ε4 carriers and non-carriers.

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.[29,30,]

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.[31,]

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.[31,]

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 health outcomes of patients who are considering or currently undergoing treatment with amyloid-beta targeting therapy with and without genetic testing for *APOE* carrier status.

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 identification of patients who are at increased risk of ARIA related to treatment with amyloid-beta targeting therapy. Clinical utility may be demonstrated if testing leads to changes in treatment management decisions (e.g., initiation, discontinuation, or continuation of therapy) that leads to beneficial health outcomes.

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

Section Summary: Genetic Testing for Management of Amyloid-Beta Targeting Therapy

Randomized clinical trials of amyloid-beta targeting therapy for the treatment of mild cognitive impairment or mild dementia associated with Alzheimer disease demonstrated an increased incidence of ARIA following treatment with the amyloid-beta targeting therapy. For lecanemab, 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%, 1.7%, and 1.4%, respectively. Serious events of ARIA were reported in 3% of homozygotes compared to 1% of heterozygotes and noncarriers. Subgroup analyses suggested that the benefit of lecanemab might also be smaller in *APOE* ε4 homozygotes. Therefore, individuals considering treatment with an amyloid-beta targeting therapy need to be aware of *APOE* status in order to inform risk discussions. The boxed warnings in the FDA labels for lecanemab and donanemab states that testing for *APOE* ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.

Summary of Evidence

For individuals who are asymptomatic and at risk for developing late-onset Alzheimer disease (AD) who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy and validity, change in disease

status, health status measures, and quality of life. Many genes, including *APOE*, *CR1*, *BIN1*, *PICALM*, and *TREM2*, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing for indicating which individuals will progress to AD is low, and numerous other factors can affect progression. Overall, genetic testing has not been shown to add value to the diagnosis of AD made clinically. The current lack of effective methods to prevent the onset of AD limits the clinical benefit for genetic testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals with a clinical diagnosis of mild cognitive impairment or mild dementia associated with AD who are considering initiation or discontinuation of an FDA-approved amyloid-beta targeting therapy who receive genetic testing, the evidence includes randomized clinical trials. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related morbidity and mortality. The incidence of asymptomatic, symptomatic and serious amyloid-related imaging abnormalities (ARIA) following treatment with the amyloid-beta targeting therapiesis significantly higher in *APOE* ε4 homozygotes compared to heterozygotes and noncarriers. The boxed warnings in the FDA labels for approved amyloid-beta targeting therapies states that testing for *APOE* ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA..The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Clinical Input From Physician Specialty Societies And Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers,

input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

Clinical input was sought to help determine whether the use of genetic testing for those for individuals with early AD who are considering initiation or discontinuation of an FDA-approved amyloid-beta targeting therapy would provide a clinically meaningful improvement in net health outcome. In response to requests, clinical input was received from 3 respondents; 1 physician-level response identified through a specialty society; 2 physician-level responses (joint response) identified through an academic medical center.

For individuals with early AD who are considering initiation or discontinuation of an FDA-approved amyloid-beta targeting therapy who receive genetic testing, clinical input supports this use provides a clinically meaningful improvement in net health outcome with the criteria described.

Further details from clinical input are included in the Appendix.

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.[32,] 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 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:[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 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:[33,]

- 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:[34,]

- 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.[35,] The guidelines state that *APOE* genotyping should not be used to diagnose Alzheimer 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)	10,000	Jul 2026 (recruiting)
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	Oct 2027
NCT03876314	The Effect of Physical Activity on Cognition Relative to APOE Genotype (PAAD-2)	240	Dec 2023
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	Aug 2024
NCT04770220[a]	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Efficacy, Safety and Biomarker Effects of ALZ-801 in Subjects With Early Alzheimer's Disease and APOE4/4 Genotype	300	Jun 2024
NCT00869817	Dominantly Inherited Alzheimer Network (DIAN)	700	Jul 2025
NCT04680013	Genetic Studies in Familial Dementia	20,000	Nov 2025
NCT03657732	A Multi-center Longitudinal Cohort Study of Familial Alzheimer's Disease in China (CFAN)	40,000	Jan 2038
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
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	Aug 2023

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

Appendix 1

2024 Clinical Input

Objective

Clinical input was sought to help determine whether the use of genetic testing for those for individuals with early AD who are considering initiation or discontinuation of an FDA-approved amyloid-beta targeting therapy would provide a clinically meaningful improvement in net health outcome.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Cliatt Brown, Christine J, MD; Behavioral Neurology, identified by University of Utah
- Sorweid, Michelle K., DO, MPH, Geriatrics, identified by University of Utah
- Anonymous**, MD, PhD, Behavioral Neurology and Neurology, identified by American Academy of Neurology (AAN)

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.
** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the clinical input process provide review, input, and feedback on topics being evaluated. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the opinion published by BCBSA or any Blue Plan.

Ratings

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.
** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Respondent Profile

	Specialty Society				
#	**Name of Organization**		**Clinical Specialty**		
1	American Academy of Neurology		Neurology		
	Physician				
#	**Name**	**Degree**	**Institutional Affiliation**	**Clinical Specialty**	**Board Certification and Fellowship Training**
1	Anonymous	MD, PHD	Anonymous	Behavioral Neurology	Neurology
Identified by University of Utah					
2	Cliatt Brown, Christine J.;	MD	University of Utah	Behavioral Neurology	Neurology
3	Sorweid, Michelle K.	DO, MPH	University of Utah	Geriatrics	Behavioral Neurology & Neuropsychiatry

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	No		Yes	I am a member of a work group at the American Academy of Neurology regarding anti amyloid therapies. I also have served on an advisory board for Eisai and am a member of the Eisai Speaker's bureau	Yes	I have received compensation for my participation on an advisory board and the Speaker's bureau for Eisai.	No	
2	No		No		No		No	
3	No		No		No		No	

#	Conflict of Interest Policy Statement
1	N/A
2	N/A
3	N/A

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response. NR = not reported

Responses

Note that the request for clinical input included questions related to several policies. Questions 1 through 3 were related to policy 5.01.38 and more details on those responses can be found in the Appendix of 5.01.38.

Question 4: 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.

a) Is genetic testing for the apolipoprotein E (APOE) gene to guide initiation or management of a U.S. Food and Drug Administration-approved amyloid-beta targeting therapy (eg, lecanemab) in individuals with mild cognitive impairment or mild dementia associated with Alzheimer disease clinically appropriate?

#	Indications	YES / NO	Comment
1	Indication 1, testing to guide treatement with lecanemab	Yes	YES please let us support the coverage for ApoE testing. I had to do two “peer” to peers for [redacted] recently for ApoE testing and the internist and gynecologist they gave me as peers didn’t have any idea what lecanemab even did. (And then denied the test anyways)

#	Indications	YES / NO	Comment
2, 3 (joint response)	Indication 1, testing to guide treatement with lecanemab	Yes	NA

b) Should use of lecanemab be limited to individuals who are NOT APOE ε4 homozygotes?

#	Indications	YES / NO	
1	Indication 1, testing to guide treatement with lecanemab	No	NO, lecanemab use should NOT be limited to individuals who are not E4 homozygotes, particularly since they are at highest risk of AD. I agree that more research is needed to figure out what happens in these individuals and their risks but the opportunity for treatment should not be withheld.
2, 3 (joint response)	Indication 1, testing to guide treatement with lecanemab	No	The drug was clearly studied in those who are APOE ε4 homozygotes. The decision on whether to proceed should be left to the prescribing physician and the patient with an extensive risks/benefits discussion. Consideration can be given to additional monitoring (extra MRI after 52 weeks of therapy) for those who are APOE ε4 carriers or homozygotes as suggested by Cummings, et al. Additional caution should be used to avoid anticoagulants and perhaps also antiplatelets in those who are APOE ε4 homozygotes or carriers, but this should be determined by the physician a

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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
- Provider 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

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
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
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.
12/01/2021	Policy statement, guidelines and literature updated.
03/01/2022	Coding update.
03/01/2022	Coding update.
12/01/2022	Annual review. No change to policy statement. Literature review updated.
03/01/2023	Coding update.
12/01/2023	Annual review. No change to policy statement. Policy guidelines updated
10/01/2025	Policy reactivated. Previously archived from 06/01/2024 to 09/30/2025.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare 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 of California, are: (a) consistent with Blue Shield of California 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 member; 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 or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments,

suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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: 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 member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
Reactivated Policy Policy Statement: N/A	Genetic Testing for Alzheimer Disease 2.04.13 Policy Statement: I. Targeted genetic testing for a known familial variant in the presenilin (PSEN) genes or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when **all** of the following criteria are met: A. 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 (see Policy Guidelines) B. Results of testing will inform reproductive decision making II. Genetic testing for variants in presenilin (PSEN) genes or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when **all** of the following criteria are met: A. 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 B. Results of testing will inform reproductive decision making III. Genetic testing for the apolipoprotein E (*APOE)* gene to guide initiation or management of a U.S. Food and Drug Administration-approved amyloid-beta targeting therapy may be considered **medically necessary** in individuals with mild cognitive impairment or mild dementia associated with Alzheimer disease. IV. Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered **investigational** in all other

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
	situations. Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 (*APOE* ε4) allele or triggering receptor expressed on myeloid cells 2 (*TREM2)*.