Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Genetic Testing for Alzheimer's Disease

Description/Background

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

AD is commonly associated with a family history; 40% of patients with AD have a least one 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. AD within families of these patients may show an autosomal dominant pattern of inheritance. Pathogenic variants in 3 genes have been identified in affected families: amyloid-beta precursor protein gene (*APP*), presenilin 1 (*PSEN1*) gene, and the presenilin 2 (*PSEN2*) gene. *APP* and *PSEN1* variants have 100% penetrance absent death from other causes, while *PSEN2* has 95% penetrance. A variety of variants within these genes has 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 up to 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* variants in the rare patient with early onset AD has been investigated as an aid in diagnosis in patients presenting with symptoms suggestive of AD, or a technique for risk assessment in asymptomatic patients with a family history of AD. 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 epsilon 4 (≈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 an 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 variants. 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, 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 of 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* epsilon 4 allele, although it occurs less frequently.

Diagnosis

The diagnosis of AD is divided into three categories: possible, probable, and definite AD.[6] A diagnosis of definite AD requires postmortem confirmation of AD pathology, documenting the presence of extracellular beta 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 patient and a knowledgeable informant, plus objective assessment by bedside mental status examination or neuropsychological testing
  - Cognitive impairment involving a minimum of two of the following domains:
    - Impaired ability to acquire and remember new information
    - Impaired reasoning and handling of complex tasks, poor judgment
    - Impaired visuospatial abilities
    - Impaired language functions
    - Changes in personality, behavior, or comportment
  - Initial and most prominent cognitive deficits are one of the following:
    - Amnestic presentation

        - Nonamnestic presentations, either a language presentation with prominent word-finding deficits; a visuospatial presentation with visual cognitive defects; or a dysexecutive presentation with prominent impairment of reasoning, judgment, and/or problem solving.
- Clinical course
  - Insidious onset
  - Clear-cut history of worsening over time
  - Interference with 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 disease, including substantial cerebrovascular disease or dementia with Lewy bodies.
  - Lack of prominent features of variant frontotemporal dementia or primary progressive aphasia.
  - No medication use 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 (MCI) is a precursor of AD in many instances. MCI may be diagnosed when there is a change in cognition, but not sufficient impairment for the diagnosis of dementia.[8] Features of MCI are evidence of impairment in one or more cognitive domains, and preservation of independence in functional abilities. In some patients, MCI may be a predementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, and 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 (CSF) fluid levels of tau protein or beta-amyloid precursor protein, as well as positron emission tomography (PET) amyloid imaging. The CSF tests are considered separately in the policy "Biochemical Markers for Alzheimer's disease."

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.

Medical Policy Statement

Genetic testing for a known familial variant in the presenilin genes (*PSEN*) or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant early-onset Alzheimer disease in an asymptomatic individual to determine future risk of disease is considered established ***only*** for those individuals meeting patient selection criteria and who are seeking preconception genetic counseling. It may be considered a useful option when criteria are met.

Genetic testing for variants in presenilin genes (*PSEN*) or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant Alzheimer disease in an asymptomatic individual to determine future risk of disease is established for individuals who meet patient selection criteria ***and*** who are seeking preconception genetic counseling. It may be considered a useful option when criteria are met.

Genetic testing for the apolipoprotein E (*APOE)* gene to guide initiation or management of an amyloid-beta targeting therapy is experimental/investigational. There is insufficient evidence that the results of testing have been shown to improve clinical health outcomes.
Genetic testing for confirming a diagnosis of Alzheimer's disease or determining the risk assessment of developing AD when family planning is not an issue is experimental /investigational. There is insufficient evidence that the results of testing have been shown to improve clinical health outcomes.

Inclusionary and Exclusionary Guidelines

Inclusions:

- Targeted genetic testing for known familial variant in the presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease is established when all the following criteria are met:
  - 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

  AND
  - Results of testing will inform reproductive decision making.

- Genetic testing for variants in presenilin genes (*PSEN*) or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant early-onset Alzheimer disease is

established in an asymptomatic individual to determine future risk of disease when the following criteria are met:

- 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

AND

- Results of testing will inform reproductive decision making

Genetic counseling by appropriately trained individuals is strongly encouraged to be done in conjunction with the genetic testing for Alzheimer's disease when the above criteria are met.

Exclusions:

- Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered experimental/investigational in all other situations. Genetic testing includes, but is not limited to, testing for the apolipoprotein E ε4 allele (*APOE*) or triggering receptor expressed on myeloid cells 2 (*TREM2)*.
- Genetic testing for the apolipoprotein E (*APOE)* gene to guide initiation or management of an amyloid-beta targeting therapy.
- Genetic testing for *APP*, *PSEN* and *E (APOE)* is experimental/investigational in situations that do not meet the above criteria.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes (for preconception testing purposes only):

81401 81405 81406

Other codes (investigational, not medically necessary, etc.):

S3852

Rationale

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 benefits and harms is 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 **PICOs** were 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 family history of AD or dementia.

Interventions
Genetic testing can be performed on a number of candidate genes, individually or collectively. Lists of genes associated with AD and testing laboratories in the United States are provided on the Genetic Testing Registry website of the National Center for Biotechnology Information.[9]

Comparators
The comparator of interest is standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are change in disease status, health status measures, and quality of life (QOL). Specific outcomes in each of these categories are listed in Table 2. 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 AD are initiated that prevent or slow progression of cognitive decline. Improvement in health status measures is also important.

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 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

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for Alzheimer disease, 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 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 adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer either to predicting a future condition or to 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 ε4 allele (*APOE*E4*) and AD. The Rotterdam and Framingham studies are both 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 (RR) 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 to those without an ε4 allele. The association between the *APOE*E4* 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.

In 2014, Naj et al 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 polymorphisms at 10 loci significantly associated with risk of late-onset AD. Analysis confirmed the association of *APOE* with an earlier age of onset and found significant associations for *CR1*, *BIN1*, and *PICALM*. *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*E4* allele reduced age of onset by 2.45 years.

Lambert et al (2013) published a large meta-analysis of GWAS 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 with only 1 marker, the T allele of rs75932628 (excluding the *APOE* locus and the A673T variant in *APP11*).[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 was found to confer a risk of AD of 0.63% (odds ratio [OR], 2.26; 95% confidence interval [CI], 1.71 to 2.98; $p=1.13x10^{-8}$). In the control population of 8888 patients 85 years of age or older without a diagnosis of AD, *TREM2* frequency was 0.46% (OR=2.92; 95% CI, 2.09 to 4.09; $p=3.42x10^{-10}$). In 1236 cognitively intact controls age 85 or older, the frequency of *TREM2* decreased even further to 0.31% (OR=4.66; 95% CI, 2.38 to 9.14; $p=7.39 x10^{-6}$). The decrease *in TREM2* frequency in elderly patients who are cognitively intact supports the findings associating *TREM2* with increasing risk of AD. Guerriero et al (2013) also found a strong association of the R47H *TREM2* variant with AD (p=0.001).[5] Using 3 imputed data sets of genome-wide association AD studies, a meta-analysis found a significant association with the variant and disease (p=0.002). The authors further reported direct genotyping of R47H in 1994 AD patients and 4062 controls and found a highly significant association with AD (OR=5.05; 95% CI, 2.77 to 9.16; $p=9.0x10^{-9}$).

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

There are no randomized controlled trials 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 was designed to examine consequences of AD risk assessment by *APOE* genotyping.[16] Of 289 eligible participants 162 were randomized (mean age, 52.8 years; 73% female; average education, 16.7 years) to either risk assessment based on *APOE* testing and 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 ungenotyped individuals to take more vitamins (40% vs. 24% and 30%, respectively), change diet (20% vs. 11% and 7%, respectively), or change exercise behaviors (8% vs. 4% and 5%, 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] 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 in the subgroup of participants with the *APOE*E4* allele. However, the ε4 negative participants had significantly lower test-related distress than ε4 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.[18] Two hundred ninety participants were randomized to receive AD risk disclosure alone or AD+CAD risk disclosure. The 257 participants who received their genetic information were included in 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 an ε4 allele, distress (measured by Impact of Event Scale) was lower at 12 months in AD+CAD group than in the AD-only group (difference, -4.8; 95% CI, -8.6 to -1.0; p=0.031). AD+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 variant carriers can delay or mitigate future disease. There are many actions patients may 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, thus demonstrating some degree of clinical validity. However, the clinical sensitivity and specificity of *APOE ε4* is poor, and there is a lack of evidence on the clinical sensitivity and specificity of other genes.[19]

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 Familial AD 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 **PICOs** were 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 *APP*, *PSEN1*, or *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 change in disease status, health status measures, QOL, 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 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.

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, the 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 30–60% of individuals with familial early-onset AD.[20,21] A number of variants scattered throughout the presenilin 1 (*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 amyloid-beta precursor protein (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=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 age of onset (although it is usually similar to age of onset 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 one 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 one 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

There are no randomized controlled trials 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 in 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 early identification of patients at risk leads to interventions to delay or mitigate clinical disease, then clinical utility will 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, 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 assess 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 disease. 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 AD
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 in 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, clinical utility for the purposes of reproductive decision making has not 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 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.

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), 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

Exploratory analyses of pooled safety data from 2 phase 3 trials of the FDA-approved amyloid-beta targeting therapy aducanumab indicate that *APOE* ε4 carrier status is associated with a higher incidence of amyloid-related imaging abnormalities (ARIA).[26-28] 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 to5% (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]

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 for genetic testing in individuals who are asymptomatic and at risk for developing AD includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy, test validity, change in disease status, and health status measures. Many genes, including apolipoprotein E (*APOE*), *CR1*, *BIN1*, *PICALM*, and *TREM2*, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing for indicating which individuals will progress to AD is low, and numerous other factors can affect progression. Overall, genetic testing has not been shown to add value to the diagnosis of AD made clinically. The current lack of effective

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

For individuals who are asymptomatic and at risk for developing early-onset, autosomal dominant AD with a known familial variant who receive targeted genetic testing for a known familial variant the evidence includes studies on gene associations and test accuracy. Variants in the presenilin 1/2 (*PSEN1/2*) 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 been previously identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions regarding the benefit of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, clinical utility for the purposes of reproductive decision-making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic and at risk for developing early-onset, autosomal dominant AD whose familial variant is unknown who receive genetic testing the evidence includes studies on gene associations and test accuracy. Variants in the presenilin 1/2 (*PSEN1/2*) 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 reasonably certain when a variant found in the variant database of pathogenic *PSEN1/2,* and *APP* variants is identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions regarding the benefit of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, clinical utility for the purposes of reproductive decision-making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

Ongoing and Unpublished Clinical Trials

Some currently 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)	3000	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 (recruiting)
NCT04241068[a]	Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (Aducanumab) in Subjects with Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205 (EMBARK)	1696	Feb 2025 (ongoing)
NCT04770220[a]	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Efficacy, Safety and Biomarker Effects of ALZ-801 in Subjects with Early Alzheimer's Disease and APOE4/4 Genotype	300	Jul 2025 (recruiting)
NCT00869817	Dominantly Inherited Alzheimer Network (DIAN)	700	Jul 2025 (recruiting)
NCT04680013	Genetic Studies in Familial Dementia	20,000	Nov 2025 (recruiting)
NCT03657732	A Multi-center Longitudinal Cohort Study of Familial Alzheimer's Disease in China (CFAN)	40,000	Jan 2038 (recruiting)
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
NCT01998841a	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	Dec 2022
NCT03876314	The Effect of Physical Activity on Cognition Relative to APOE Genotype (PAAD-2)	240	Mar 2023

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

SUPPLEMENTAL INFORMATION

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.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics lists genetic testing for *APOE* alleles as one 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 later-onset AD, the most common cause of dementia. These recommendations stated that "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."

The College, jointly with the National Society of Genetic Counselors, issued the following practice guidelines (2011)[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 videoconference) 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:[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 recommendations for the diagnosis of dementia[34]:

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

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 apolipoprotein E genotyping should not be used to diagnose Alzheimer's disease.

Government Regulations
National/Local:

There is no national or local coverage determination on this topic. In the absence of an LCD, coverage decisions are left to the discretion of local Medicare carriers.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Biochemical Markers of Alzheimer's Disease

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/21/03	7/21/03	7/7/03	Joint policy for Biochemical Markers of Alzheimer's Disease established
10/6/03	10/6/03	10/14/03	Joint policy for Genetic Testing for Familial Alzheimer's Disease established
2/26/05	2/26/05	1/14/05	Routine maintenance for Genetic Testing for Alzheimer's Disease (changed title from Genetic Testing for Familial Alzheimer's Disease
2/27/05	2/27/05	1/14/05	Routine maintenance for Biochemical Markers of Alzheimer's Disease policy
1/1/07	1/18/07	10/20/06	Biochemical Markers of Alzheimer's Disease and Genetic Testing for Alzheimer's Disease combined into one policy, Genetic Testing and Biochemical Markers for Alzheimer's Disease.
9/1/07	7/3/07	8/29/07	Routine maintenance of combined policy
1/1/09	10/13/08	12/30/08	Routine maintenance of combined policy; policy retired.
5/1/12	2/21/12	2/21/12	Combined policy pulled out of retirement to clarify coverage guidelines; references updated. Policy enhanced to mirror BCBSA policy. Added codes 83520 and 83912 to policy for coding urinary and CSF biomarker testing.
11/1/13	8/22/13	8/27/13	Combined policy split out into two policies to mirror the BCBSA policies Biochemical Markers of Alzheimer's Disease and Genetic Testing for Familial Alzheimer's Disease. This policy speaks to genetic testing only.

Next Review Date: The combined policy, Genetic Testing and Biochemical Markers for Alzheimer's Disease will no longer be reviewed. Please reference individual policies.

Joint BCBSM/BCN Medical Policy History

1/1/14	10/17/13	10/25/13	Separate policy, "Genetic Testing for Familial Alzheimer's Disease" established.
7/1/15	4/24/15	5/8/15	Routine maintenance. No change in policy status.
7/1/16	4/19/16	4/19/16	Routine policy maintenance.
7/1/17	5/4/17	5/3/17	Routine policy maintenance. No change in policy status. Removed "familial" from title. Policy now mirrors BCBSA policy. Moved S3852 to non-covered code section.
7/1/18	4/17/18	4/17/18	Routine policy maintenance. No change in policy status.
7/1/19	4/16/19		Routine policy maintenance, no change in policy status.
7/1/20	4/14/20		Routine policy maintenance. No change in policy status.
7/1/21	4/20/21		Routine policy maintenance. Added references 27-29. No change in policy status.
7/1/22	4/19/22		Routine policy maintenance, removed reference #24 and #25, replaced with NICE guidelines. No change in policy status.
7/1/23	4/26/23		• Added code 0346U as E/I • Added section on APOE testing to rationale section • Added "Genetic testing to guide initiation or management of a U.S. Food and Drug Administration-approved amyloid-beta targeting therapy (e.g., aducanumab) is considered investigational. Genetic testing includes but is not limited to, testing for the APOE epsilon 4 allele." • Added information on ARIA • Vendor managed: N/A (ds)
7/1/24	4/16/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
3/1/25	12/17/24		Code 0346U deleted, effective 1/1/25. Vendor managed: N/A (ds)
7/1/25	4/22/25		Routine policy maintenance. Rationale updated, references 29-31 added. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2026

Pre-Consolidation Medical Policy History for Genetic Testing for Alzheimer Disease

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: 7/16/99	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR ALZHEIMER DISEASE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Per policy
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.