Kansas City

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Genetic Testing for Alzheimer Disease

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Genetic Testing for Alzheimer Disease when it is determined to be medically necessary because the criteria shown below are met.

Genetic testing may be excluded in some contracts. Verify benefits prior to review for Medical Necessity.

When Policy Topic is covered

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 the following criteria are met:

- The individual has a close relative (ie, first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease AND
- Results of testing will inform reproductive decision making.

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 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.

When Policy Topic is not covered

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 ε4 allele (*APOE*) or triggering receptor expressed on myeloid cells 2 (*TREM2)*.

Considerations

Genetic testing for Alzheimer disease (AD) may be offered along with analysis of cerebral spinal fluid (CSF) levels of the tau protein and amyloid-β peptide 1-42 (see evidence review 2.04.14). This group of tests may be collectively referred to as the ADmark™ Profile, offered by Athena Diagnostics.

Testing Strategy

The 2011 guidelines from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors recommended that genetic testing for early-onset, autosomal dominant AD should only occur in the context of genetic counseling with support by someone expert in the area. In asymptomatic patients, a testing protocol based on the 1994 International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea guidelines has been recommended. Consultation of the Alzheimer Disease & Frontotemporal Dementia Mutation Database has also been recommended before disclosure of genetic test results.

A family history of autosomal dominant AD is suggested by 3 affected members in 2 generations. In individuals at risk of early-onset, autosomal dominant AD, ideally, an affected family member should be tested first to identify the familial variant. If no affected family member is available for testing and an asymptomatic individual remains interested in testing to inform reproductive decision making, then in-depth sequencing of the 3 genes (*APP*, *PSEN1*, *PSEN2*) associated with autosomal dominant AD may be indicated.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see 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.

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic and at risk for developing late-onset Alzheimer disease	Interventions of interest are: • Genetic testing	Comparators of interest are: • Standard clinical management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Change in disease status • Health status measures • Quality of life
Individuals: • Who are asymptomatic, at risk for developing early-onset Alzheimer disease, and have a known familial variant	Interventions of interest are: • Targeted familial variant testing	Comparators of interest are: • Standard clinical management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Change in disease status • Change in reproductive decision making • Health status measures • Quality of life
Individuals: • Who are asymptomatic, at risk for developing	Interventions of interest are: • Genetic testing	Comparators of interest are: • Standard clinical management	Relevant outcomes include: • Test accuracy • Test validity • Change in disease status

early-onset Alzheimer disease, and have no known familial variant		without genetic testing	• Change in reproductive decision making • Health status measures • Quality of life

Summary

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

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

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have a known familial variant who receive targeted genetic testing, the evidence includes studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision making, health status measures, and quality of life. Variants in the presenilin 1 and 2 (*PSEN1* and *PSEN2*) and amyloid-beta precursor protein (*APP*) genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be nearly certain when a familial pathogenic variant has previously been identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, 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, 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, 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.

Background

Alzheimer Disease

Alzheimer disease (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 (ie, 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: 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 ε4 allele (*APOE*E4*) 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 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 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, other risk factors for AD (eg, 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*E*4 allele, although it occurs less frequently.

Diagnosis

The diagnosis of AD is divided into 3 categories: possible, probable, and definite AD.[6] A diagnosis of definite AD requires postmortem confirmation of AD pathology, documenting the presence of extracellular β-amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. As a result, a diagnosis of definite AD cannot be made during life, and the diagnosis of probable or possible AD is made on clinical grounds.[7] Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. Criteria for diagnosis of probable AD have been developed by the National Institute on Aging and the Alzheimer's Association.[6] These criteria require evidence of a specific pattern of cognitive impairment, a typical clinical course, and exclusion of other potential etiologies, as follows:

- Cognitive impairment
  - Cognitive impairment established by history from the patient and a knowledgeable informant, plus objective assessment by bedside mental status examination or neuropsychological testing
  - Cognitive impairment involving a minimum of 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 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 disease, 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 (eg, sudden onset) or atypical progression. A diagnosis of possible AD is also made when there is another potentially causative systemic or neurologic disorder that is not thought to be the primary etiology of dementia.

Mild cognitive impairment (MCI) is a precursor of AD in many instances. MCI may be diagnosed when there is a change in cognition, but insufficient 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 (eg, neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings.[6] Other diagnostic tests for AD include

cerebrospinal fluid levels of tau protein or APP, as well as positron emission tomography amyloid imaging.

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. Lab tests listed in Tables 1 and 3 are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

This evidence review was created in July 1999 and has been updated regularly with searches of the MEDLINE database. The most recent update was performed through February 5, 2018.

The review was informed by a TEC Assessment (1999).[9]

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance 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 patients who are asymptomatic and at risk for developing late-onset Alzheimer disease (AD) is potentially to inform management decisions such as early treatment or behavioral changes. Asymptomatic patients at risk of late-onset AD are not generally treated with medical therapy but may choose to make behavioral changes associated with reduced risk of AD.

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

The following PICOTS were used to select literature to inform this review.

Patients
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
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 United States are provided on the Genetic Testing Registry website of the National Center for Biotechnology Information.[10] Table 1 lists examples of commercially available genetic panels for AD.

Table 1. Examples of Commercially Available Genetic Panels for Late-Onset Alzheimer Disease

Laboratory	Panel Name	No. of Genes Tested	Testing Methods
Fulgent Genetics	Parkinson-Alzheimer-Dementia NGS Panel	37	NGS
Knight Diagnostic Laboratories	Dementia	21	Sequence analysis of the entire coding region
PreventionGenetics	Dementia Sequencing Panel	13	Deletion/duplication analysis; sequence analysis of entire coding region; targeted variant analysis

NGS: next-generation sequencing.

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

Outcomes
The general outcomes of interest are change in disease status, health status measures, and quality of life. 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 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 2. Outcomes of Interest for Individuals With Symptomatic Late-Onset Alzheimer Disease

Outcomes	Details
Change in disease	Incidence or time to Alzheimer disease onset; changes in cognitive

status	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

Timing
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.

Setting
Asymptomatic patients are likely to be managed in primary care. Genetic testing for variants associated with late-onset AD is complex. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

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 both to predicting a future condition or to predicting a response to therapy.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of

specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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 examples of large observational studies demonstrating the association. The Rotterdam Study was a prospective cohort study in the city of Rotterdam, the Netherlands, with main objectives of investigating risk factors of cardiovascular, neurologic, ophthalmologic, and endocrine diseases in the elderly.[11] In a sample of 6852 participants, carriers of a single 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.[12] In 1030 participants, the relative risk for developing AD was 3.7 (95% confidence interval [CI], 1.9 to 7.5) for carriers of a single 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.[13]

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

Naj et al (2014) published a genome-wide association study (GWAS) of multiple genetic loci in late-onset AD.[14] 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*E4* allele reduced the 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.[15] Nineteen loci had genome-wide significance in addition to the *APOE* locus. The researchers confirmed several genes already reported to be associated with AD (*ABCA7*, *BIN1*, *CD33*, *CLU*, *CR1*, *CD2AP*, *EPHA1*, *MS4A6A–MS4A4E*, *PICALM*). New loci located included *HLA-DRB5–HLA-DRB1, PTK2B, SORL1,* and *SLC24A4-RIN3*.

Jonsson et al (2013) evaluated 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; $p=1.13\times10^{-8}$). In the control population of 8888 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; $p=3.42\times10^{-10}$). 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; $p=7.39\times10^{-6}$). The decrease *in TREM2* frequency in cognitively intact elderly patients supports findings associating *TREM2* with increasing risk of AD. Guerriero et al (2013) also found a strong association between the *TREM2* R47H variant and AD (p=0.001).[5] Using 3 imputed datasets of GWAS, meta-analysis found a significant association between the variant and AD (p=0.002). The authors further reported direct genotyping of R47H in 1994 AD patients and 4062 controls, which detected a highly significant association between the variant and AD (OR=5.05; 95% CI, 2.77 to 9.16; $p=9.0\times10^{-9}$).

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 as reported by Chao et al (2008) was designed to examine the consequences of AD risk assessment by *APOE* genotyping.[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*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 vs 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 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 plus CAD group than in the AD-only group (difference, -4.8; 95% CI, -8.6 to -1.0; p=0.031). AD plus CAD participants also reported more health behavior changes than AD-alone participants, regardless of *APOE* genotype.

There is a lack of interventions that can delay or mitigate late-onset AD. There is no evidence that early intervention for asymptomatic disease-associated variant carriers can delay or mitigate future disease. There are many actions patients can take following knowledge of a disease-associated variant. Changes in lifestyle factors (eg, 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*E4* 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*E4* allele is poor, and there is a lack of evidence on the clinical sensitivity and specificity of other genes.

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

Genetic Testing for Early-Onset AD with and without a known familial variant

Clinical Context and Test Purpose

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

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

The following PICOTS were used to select literature to inform this review.

Patients

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. Table 3 provides examples of commercially available genetic panels that include the early-onset, autosomal dominant variants.

Table 3. Examples of Commercially Available Genetic Panels for Early-Onset Alzheimer Disease

Laboratory	Panel Name	No. of Genes Tested	Testing Method
PreventionGenetics	Alzheimer Disease, Familial, Sequencing Panel	3	CGH, NGS, bidirectional Sanger sequence analysis
Athena Diagnostics	ADmark® Early Onset Alzheimer's Evaluation	3	Bidirectional Sanger sequence analysis
Fulgent Genetics	Early Onset Familial Alzheimer Disease NGS Panel	3	Deletion/duplication analysis; sequence analysis of entire coding region
PreventionGenetics	Alzheimer's Disease, Familial via the APP Gene, Exons 16 and 17; Familial via the PSEN1 Gene; Familial via the PSEN2 Gene	1 each test	Deletion/duplication analysis; sequence analysis of entire coding region;

	targeted variant analysis

CGH: comparative genomic hybridization; NGS: next-generation sequencing.

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, 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 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.

Timing

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

Setting

Asymptomatic patients are likely to be managed in primary care. Reproductive decision making is a complex psychological process. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes. The American College of Medical Genetics and Genomics and the National Society of Genetic Counselors guidelines have recommended that genetic testing for early-onset, autosomal dominant AD should only occur in the context of genetic counseling with support by someone expert in the area.[2] In asymptomatic patients, a testing protocol based on the 1994 International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea guidelines has also been recommended.[19]

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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 presenilin 1 (*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 amyloid-beta precursor protein (*APP*) and presenilin 2 (*PSEN2*) genes account for another 10% to 20% of cases.

The Human Genome Variation Society maintains a catalog of identified pathogenic variants called the Alzheimer Disease & Frontotemporal Dementia Mutation Database.[22] A pathogenic association (clinical validity) between variants and disease has been demonstrated for identified variants through the presence in related probands with nearly complete penetrance. Most of the *PSEN1*, *PSEN2*, and *APP* variants reported in the database (>200) are identified as pathogenic—over half by multiple studies.

Clinical expressivity is variable, ie, 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.

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 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 clinical utility would be established. Identification of asymptomatic, young adult carriers could impact reproductive planning. And clinical utility may be demonstrated if testing leads to informed reproductive planning that improves outcomes. Alternatively, 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 of 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.[23]

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 (eg, 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 the variant database.

For those from families with early-onset, familial AD, when a pathogenic familial variant is known or when the family pedigree is consistent with autosomal dominant AD but the affected family members have not been tested to determine

the familial variant, testing a prospective parent when performed in conjunction with genetic counseling provides more accurate information to guide reproductive planning than family history alone. Therefore, the clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. There are currently no known preventive measures or treatments that can mitigate the effect of AD. It is not clear how a change in the management of asymptomatic patients with these genes would improve outcomes. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants.

Summary of Evidence

For individuals who are asymptomatic and at risk for developing late-onset AD who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, and quality of life. Many genes, including *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, 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, 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, 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, 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.

Supplemental Information

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics et al

The American College of Medical Genetics and Genomics has listed genetic testing for apolipoprotein E (*APOE*) alleles as 1 of 5 recommendations in the Choosing Wisely initiative.[24] 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."

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 (available online at: www.molgen.ua.ac.be/ADMutations/) 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."

American Academy of Neurology

In 2001, the American Academy of Neurology made the following guideline recommendations[25]:

- 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.

These guidelines are being updated as of February 2018.

European Federation of Neurological Sciences
In 2010, the European Federation of Neurological Sciences made the following recommendations for genetic testing (level of evidence not reported)[26]:

- "Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia."
- "Testing of patients with familial dementia and of unaffected at-risk-relatives should be accompanied by neurogenetic counseling and undertaken only after full consent and by specialist centers. Pre-symptomatic testing may be performed in at-risk members of family-carrying mutation. It is recommended that the Huntington's disease protocol is followed for pre-symptomatic testing."
- "Routine Apo E genotyping is not recommended."

Canadian Consensus Conference on Diagnosis and Treatment of Dementia

Fourth Canadian Consensus Conference
The Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD4), held in 2012, updated guidelines from the third consensus conference, referenced next. Previous recommendations were endorsed if there were no changes in the literature.

A summary of consensus recommendations from the CCCDTD4 was published by Gauthier et al (2012).[27] It was noted that: "Despite a large number of important advances, the CCCDTD4 concluded that fundamental changes in dementia diagnosis and management have not yet arrived." The CCCDTD4 summary recommended:

> "Testing and longitudinal follow-up of asymptomatic individuals or patients with subjective cognitive impairments not meeting MCI [mild cognitive impairment] criteria, or at-risk individuals (e.g., gene mutation carriers, family history of AD, *APOE* epsilon 4) should be restricted to research."

Third Canadian Consensus
The CCCDTD recommended the following[28]:

> "Predictive genetic testing for asymptomatic 'at-risk' individuals with an apparent autosomal dominant inheritance and a family-specific mutation that has been identified

1. With appropriate pre- and post-testing counseling, predictive genetic testing (PGT) can be offered to 'at-risk' individuals (Grade B, Level 2). Examples:
   a) First-degree relatives of an affected individual with the mutation (e.g., children and siblings);
   b) First cousins of an affected individual if the common ancestors (parents who were siblings) died before the average age of onset of dementia in the family;
   c) Nieces and nephews of affected individuals whose parent (sibling of the affected individual) died well before the average age of onset of dementia in the family;
   d) PGT in minors is not generally offered in Canada, but occasionally may be considered on a case-by-case basis by the relevant medical ethics committee(s);
   e) Individuals who are not 'at risk' for the inherited disease do not require testing.
2. In young persons (60 years or younger) presenting with an early onset dementia, it is sometimes worthwhile to test for the most common mutations based on the 'best estimate' diagnosis (e.g., in early onset AD, one might test for the most common mutations in PS1, APP). (Grade B, Level 2) If a mutation is identified, it would have direct implications for offspring of the individual (if a de novo mutation is assumed). Conversely, it would also be important to test other family members such as parents and siblings for possible non-penetrance of a mutation.
7. Genetic screening with APOE genotype in asymptomatic individuals in the general population is not recommended because of the low specificity and sensitivity. (Grade E, Level 2)
8. Genetic testing with APOE genotype is not recommended for the purpose of diagnosing AD because the positive and negative predictive values are low. (Grade E, Level 2)"

CCCDTD used the following evidence ratings for the Third Canadian Consensus: grade (B) is fair evidence to support this maneuver; grade (E) is good evidence to recommend against this procedure; level 2 evidence is that obtained from (1) well-designed controlled trial without randomization or (2) well-designed cohort or case-control analytic studies, preferably from more than one center or (3) comparisons between times or places with or without intervention. Dramatic results in uncontrolled experiments are included in this category.

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 unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00064870	National Cell Repository for Alzheimer's Disease (NCRAD)	3000	Jul 2021
NCT00064870	National Cell Repository for Alzheimer's Disease (NCRAD)	3000	Jul 2021
NCT02564692	Alzheimer's Prevention Registry GeneMatch Program	500,000	Dec 2030
NCT01760005	A Phase II/III Randomized, Double-Blind, Placebo-Controlled Multi-Center Study of 2 Potential Disease Modifying Therapies in Individuals at Risk for and With Dominantly Inherited Alzheimer's Disease	210	Dec 2023

NCT: national clinical trial.

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Billing Coding/Physician Documentation Information

81401	Molecular pathology procedure, Level 2 (i.e., 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	
81406	Molecular pathology procedure, Level 7 (i.e, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to

Alzheimer's disease

	ICD-10 Codes
F03	Dementia code range
G30.0-G30.9	Alzheimer's disease code range
G31.1	Senile degeneration of brain, not elsewhere classified
R41.0	Disorientation, unspecified
R41.81	Age-related cognitive decline
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management
Z82.0	Family history of epilepsy and other diseases of the nervous system (Conditions classifiable to G00-G99)

Additional Policy Key Words

N/A

Policy Implementation/Update Information

11/1/2018 New Policy. Considered Medically Necessary when criteria is met.