

(20413)

Medical Benefit		Effective Date: 10/01/17	Next Review Date: 03/19
Preauthorization	No	Review Dates: 07/07, 07/08, 05/09, 03/10, 03/11, 03/12, 03/13, 03/14, 03/15, 03/16, 03/17, 07/17, 03/18	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are asymptomatic and at risk for developing late-onset Alzheimer disease 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Change in disease status Health status measures Quality of life
Individuals: <ul style="list-style-type: none"> Who are asymptomatic, at risk for developing early-onset Alzheimer disease, and have a known familial variant 	Interventions of interest are: <ul style="list-style-type: none"> Targeted familial variant testing 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Change in disease status Change in reproductive decision making Health status measures Quality of life
Individuals: <ul style="list-style-type: none"> Who are asymptomatic, at risk for developing early-onset Alzheimer disease, and have no known familial variant 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical management without genetic testing 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Change in disease status Change in reproductive decision making Health status measures Quality of life

Description

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

Summary of Evidence

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

Policy

Targeted genetic testing for a known familial variant in the presenilin genes (*PSEN*) or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant early-onset Alzheimer disease 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 (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 PSEN or APP gene associated with autosomal dominant 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.

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

Policy Guidelines

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

Testing Strategy

The 2011 guidelines from the American College of Medical Genetics and Genomics (ACMG) and the National Society of Genetic Counselors recommended that genetic testing for early-onset, autosomal dominant 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 have been recommended. Consultation of the Alzheimer Disease & Frontotemporal Dementia Mutation Database has also recommended before disclosure of genetic test results.

A family history of autosomal dominant AD is suggested by three affected members in two 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 three genes (APP, PSEN1, PSEN2) associated with autosomal dominant AD may be indicated.

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) 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 protocol updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUMAN Genome Organization (HUGO).

ACMG and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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

Previous	Updated	Definition
		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

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

For Medicare Advantage genetic testing for APOE is unlikely to impact therapeutic decision-making, directly impact treatment, outcome and/or clinical management and is considered **not medically necessary**.

Background

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 (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 three 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. 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 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 have 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 three alleles— ϵ 2, 3, and 4—with the ϵ 3 allele being the most common. Individuals carry two *APOE* alleles. The presence of at least one ϵ 4 allele is associated with a 1.2- to 3-fold increased risk of AD, depending on the ethnic group. Among those homozygous for epsilon 4 (\approx 2% of the population), the risk of AD is higher than for those heterozygous for ϵ 4. Mean age of onset of AD is about age 68 years for ϵ 4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no ϵ 4 alleles. About half of patients with sporadic AD carry an ϵ 4 allele. However, not all patients with the allele develop AD. The ϵ 4 allele represents a risk factor for AD rather than a disease-associated variant. In the absence of *APOE* testing, first-degree relatives of an individual with sporadic or familial AD are estimated to have a two- to four-fold greater risk of developing AD than the general population.² There is evidence of possible interactions between ϵ 4 alleles, other risk factors for AD (e.g., risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, diabetes³), 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.

Recent studies have 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*E4* 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 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 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 comportsment
 - 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 prodementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings.⁶ Other diagnostic tests for AD include cerebrospinal fluid (CSF) levels of tau protein or APP, as well as positron emission tomography (PET) amyloid imaging.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Lab tests listed in Tables 1 and 2 are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Table 1. 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

Laboratory	Panel Name	No. of Genes Tested	Testing Methods
PreventionGenetics	Dementia Sequencing Panel	13	Deletion/duplication analysis; sequence analysis of entire coding region; targeted variant analysis

NGS: next-generation sequencing.

Table 2. 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	one each test	Deletion/duplication analysis; sequence analysis of entire coding region; targeted variant analysis

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

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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29. National Government Services, Inc. (Primary Geographic Jurisdiction - Illinois, New York - Entire State, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont, Wisconsin, Minnesota) Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 10/01/2017.