

MEDICAL POLICY



SUBJECT: GENETIC TESTING for FAMILIAL ALZHEIMER'S DISEASE	EFFECTIVE DATE: 12/20/01 REVISED DATE: 09/19/02, 07/17/03, 06/17/04, 06/16/05, 04/20/06, 02/15/07, 03/20/08, 05/28/09, 05/27/10, 05/19/11, 03/15/12, 03/21/13, 03/20/14, 03/19/15, 03/17/16, 03/16/17, 04/19/18
POLICY NUMBER: 2.02.16 CATEGORY: Laboratory Test	PAGE: 1 OF: 5
<ul style="list-style-type: none">• <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i>• <i>If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</i>• <i>If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</i>	

POLICY STATEMENT:

Based upon our criteria and the lack of peer-reviewed literature, genetic testing for familial Alzheimer's disease (including, but not limited to testing for the apolipoprotein E epsilon 4 allele, presenilin genes, or amyloid precursor gene) has not been medically proven to be effective and is considered **investigational** for all indications including, but not limited to:

- I. As a risk assessment tool in asymptomatic patients; and
- II. As a diagnostic test in symptomatic patients.

Refer to Corporate Medical Policy #2.02.03 regarding Genetic Testing for Specific Diseases.

Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.

Refer to Corporate Medical Policy #11.01.12 regarding Screening Tests.

POLICY GUIDELINES:

- I. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.
- II. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).
- III. Genetic testing is contract dependent. Please contact the Customer (Provider/Member) Services Department of your local plan to determine contract coverage.

DESCRIPTION:

Alzheimer's disease (AD) is the leading cause of dementia in the elderly, accounting for 50-75% of all cases of dementia. Alzheimer's disease can be associated with a family history (40% of patients with AD have at least one other afflicted first-degree relative) or idiopathic. More than 90% of AD occurs after age 65 years (late-onset AD) and is characterized by gradual onset and progressive and irreversible decline in cognitive function. There is also a less common early-onset form of AD, which appears before the age of 60 and is associated with a rapid decline and severe neurochemical and neuron-pathological changes. The estimated lifetime risk of AD in the general population is about 15%. Over 100 genes, particularly on chromosomes 9, 10, and 12 have been associated with late-onset AD; while mutations in chromosomes 1, 14, and 21 have been associated with early onset familial AD. Genetic testing has been investigated both in patients with probable AD and in asymptomatic family members.

Susceptibility Polymorphism at the Apolipoprotein E (APOE) Gene

The APOE lipoprotein gene is a carrier of cholesterol and is produced in the liver and brain glial cells. The APOE gene has three alleles - epsilon 2, 3, and 4 - with the epsilon 3 allele being the most common. Every person carries two APOE alleles. The presence of at least one epsilon 4 allele is associated with an increased risk of AD in the range of 1.2- to 3-

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fold, depending on the ethnic group. For those homozygous for epsilon 4 (about 2% of the population), the risk of AD is higher than for those heterozygous for epsilon 4. The mean age of onset of AD is about 68 years for epsilon 4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no epsilon 4 allele. It should be noted that the epsilon 4 allele represents a risk factor for AD rather than a disease-causing mutation.

Genetic Mutations

Patients with early-onset AD (e.g., before age 65 but as early as 30 years) are a small subset of patients. The families of these patients may show an autosomal dominant pattern of inheritance. Three genes have been identified by linkage analysis of affected families: amyloid-beta precursor protein gene (APP), presenilin 1 (PS1) gene, and presenilin 2 (PS2) gene. These genes have nearly 100% penetrance, absent death from other causes; however, rare cases of lack of penetrance in elderly individuals have been reported. A variety of mutations within these genes have been associated with AD; mutations in PS1 appear to be the most common. However, only 2% - 10% of all patients with AD have early onset AD, and genetic mutations have only been identified in 30% - 50% of these patients. Therefore, overall, identifiable genetic mutations are rare causes of AD.

RATIONALE:

Genetic testing for the APOE 4 allele in patients with late-onset AD and testing for APP, PS1, or PS2 mutations in the rare patient with early-onset AD have been investigated as an aid in diagnosis in patients presenting with symptoms suggestive of AD, or as a technique for risk assessment in asymptomatic patients with a family history of AD.

Currently, the clinical diagnosis of AD is established by the presence of a consistent history, and by excluding treatable causes of dementia. In 1988, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's and Related Disorders Association (ADRDA) developed clinical criteria for the diagnosis of AD. These organizations defined three diagnostic categories: possible, probable, and definite Alzheimer's disease. The diagnosis of definite AD requires a brain biopsy confirming the presence of characteristic neurofibrillary tangles. While definite AD is invariably only confirmed at autopsy, in approximately 85% of those with a diagnosis of probable AD, postmortem pathological findings are consistent.

The BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment regarding APOE Epsilon 4 testing and Alzheimer's disease concluded that there are insufficient studies to indicate that apolipoprotein E epsilon 4 allele (APOE) genotyping provides sufficient sensitivity or specificity to allow genotyping to be used as a diagnostic test in symptomatic individuals. There is no evidence to indicate that genetic testing would change the medical management of the symptomatic patient to improve outcomes. In addition, no published studies or consensus statements support APOE genotyping in asymptomatic individuals as a technique of risk assessment.

Genetic testing for early onset familial Alzheimer's disease (EOFAD) is clinically available for *PSEN1*, *PSEN2*, and *APP* mutations in clinical laboratories. Molecular genetic testing of the *PSEN1* gene detects approximately 30 - 70% of individuals with EOFAD, molecular genetic testing of the *PSEN2* gene detects fewer than 5% of individuals with EOFAD, and molecular genetic testing of the *APP* gene detects approximately 10 - 15% of individuals with EOFAD. Such testing is not useful in predicting age of onset, severity or rate of progression. A positive test in an at-risk individual with equivocal symptoms does not prove that the symptoms are related to the presence of the mutation. There is inadequate data regarding the role of genetic testing in asymptomatic at-risk individuals and no evidence regarding how test results may alter the medical management of risk. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know."

The Joint Practice Guidelines of the American College of Genetics and the National Society of Genetic Counselors (2011) do not recommend pediatric testing for Alzheimer's disease. 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. Direct to consumer testing of APOE is not advised. At least a three generation family history should be obtained with specific information regarding diagnosis of AD in affected family members along with age of onset and age of

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death. Specific recommendations are listed for symptomatic patients, for families in which an autosomal dominant AD gene mutation is a possibility, and for families in which autosomal dominant AD is unlikely.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

CPT:	81401	Molecular pathology procedure level 2 (includes <i>APOE (apolipoprotein E)</i> (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4)
	81405	Molecular pathology procedure level 6 (includes <i>PSEN1 (presenilin 1)</i> (eg, Alzheimer's disease), full gene sequence (E/I if used for genetic testing for familial Alzheimer's disease)
	81406	Molecular pathology procedure level 7 (includes <i>PSEN2 (presenilin 2[Alzheimer's disease 4])</i> (eg, Alzheimer's disease), full gene sequence (E/I if used for genetic testing for familial Alzheimer's disease) <i>Copyright © 2018 American Medical Association, Chicago, IL</i>

HCPCS: S3852 (E/I) DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

ICD10: G30.0-G30.9 Alzheimer's Disease (code range)

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KEY WORDS:

AD, Alzheimer's Disease, APOE epsilon 4, Dementia, EOAD, LOAD.

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CATEGORY: Laboratory Test	PAGE: 5 OF: 5

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=79&CtrctrSelected=298*1&Ctrctr=298&s=41&DocType=Active&bc=AggAAAIBAAAA&