MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Genetic Testing for Familial Alzheimer's Disease**
Policy Number	**2.02.16**
Category	**Technology Assessment**
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Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program(DSNP) 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.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, genetic testing for familial Alzheimer's disease (including, but not limited to testing for the apolipoprotein E (APOE) epsilon 4 allele, presenilin genes (PSEN1 and PSEN2), or amyloid precursor gene (APP)) has not been medically proven to be effective and, therefore, is considered **investigational** for all indications including, but not limited to:
   A. As a risk assessment tool in asymptomatic patients; and
   B. As a diagnostic test in symptomatic patients.

Refer to Corporate Medical Policy #2.02.03 Genetic Testing for Inherited Disorders

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

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 or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Supporting documentation required:

The following factors will be considered when determining the medical appropriateness of a genetic test:

A. There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.
B. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.
C. The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).
D. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.
E. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any panel testing. If targeted testing has not been performed, rationale as to why panel testing is medically necessary should be documented.

DESCRIPTION

Alzheimer's disease (AD) is the leading cause of dementia in the elderly, accounting for 50 to75% of all cases of dementia. AD 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-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 (APP) gene, 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% to 10% of all patients with AD have early onset AD, and genetic mutations have only been identified in 30% to 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 for APP, PS1, or PS2 mutations 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.

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 in 1988, since then great

advancements in understanding Alzheimer's Disease process have occurred. Dubois et al. (2007) researched criteria for the diagnosis of AD, revising the NINCDS-ADRDA criteria. The proposed criteria move away from the traditional two-step approach (degree of functional disability and specifying its cause), they aimed to define the clinical, biochemical, structural and metabolic presence of AD, their usefulness will be determined in future studies.

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 to 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 to 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 are 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 Medical Genetics and the National Society of Genetic Counselors (2011) do not recommend pediatric testing for AD. Genetic testing for AD should only occur in the context of genetic counseling (in-person or through video conference) and support by someone with expertise in this area. 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 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. An addendum was made to the guidelines, changing the word "mutation" to "pathological variant," when discussing pathologic variants to autosomal dominant early-onset AD. The guidelines no longer meet the criteria for an evidence-based practice guideline by the American College of Medical Genetics and Genomics (ACMG) or National Society of Genetic Counselors (NSGC), NSGC reclassified this document as a Practice Resource in 2016, and ACMG is also classifying it as a Practice Resource as of this reaffirmation.

CODES

- *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 Codes

Code	Description
81401	Molecular pathology procedure level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat). (Includes *APOE (apolipoprotein E)* (e.g., hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (e.g., *2, *3, *4)
81405*	Molecular pathology procedure level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis). (Includes *PSEN1 (presenilin 1)* (e.g., Alzheimer's disease), full gene sequence) *(E/I if used for genetic testing for familial Alzheimer's disease)

Code	Description
81406*	Molecular pathology procedure level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons). (Includes *PSEN2 (presenilin 2[Alzheimer's disease 4])* (e.g., Alzheimer's disease), full gene sequence) *(E/I if used for genetic testing for familial Alzheimer's disease)
0346U **(E/I)**	Beta amyloid, AB40 and AB42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma (Includes QUEST AD-Detect, Beta-Amyloid 42/40 ratio, Quest Diagnostics)
0412U **(E/I)**	Beta amyloid, Aβ42/40 ratio, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and qualitative ApoE isoform-specific proteotyping, plasma combined with age, algorithm reported as presence or absence of brain amyloid pathology. (Includes PrecivityAD blood test) *Effective 10/01/23*

HCPCS Codes

Code	Description
S3852 **(E/I)**	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

ICD10 Codes

Code	Description
G30.0-G30.9	Alzheimer's Disease (code range)

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*Key Article

KEY WORDS

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

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures (L35000). Please refer to the following LCD website for Medicare Members: [https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000&ver=140&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AAQAAAIAIAAA&=] accessed 02/27/24.

There is currently a Local Coverage Article (LCA) for Molecular Pathology Procedures (A56199). Please refer to the following LCD website for Medicare Members: [https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56199&ver=99&LCDId=35000&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AAQAAAIAIAAAAAAA&=] accessed 02/27/24.