Medical Policy
Genetic Testing for Familial Alzheimer’s Diseases

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 580
BCBSA Reference Number: 2.04.13

Related Policies
- Biochemical Markers of Alzheimer’s Disease, #581
- Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer’s Disease, #903

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Genetic testing for the diagnosis or risk assessment of Alzheimer’s disease is INVESTIGATIONAL.

Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 allele, presenilin genes, amyloid precursor gene, or TREM2.

Prior Authorization Information

<table>
<thead>
<tr>
<th>Authorization Information</th>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Commercial PPO and Indemnity</th>
<th>Medicare HMO BlueSM</th>
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CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.
CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (eg, 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)</td>
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<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
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<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
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HCPCS Codes

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<th>HCPCS codes:</th>
<th>Code Description</th>
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<tr>
<td>S3852</td>
<td>DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease</td>
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<td>S3855</td>
<td>Genetic testing for detection of mutations in the presenilin - 1 gene</td>
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Description
Alzheimer’s disease (AD) is the most common cause of dementia in elderly patients. Early onset AD is much less common, but can occur in non-elderly individuals. For late-onset AD, there is a component of risk that runs in families, suggesting the contribution of genetic factors. Early onset Alzheimer’s has a stronger component of family risk, with clustering in families, thus suggesting an inherited genetic mutation.

Background
Alzheimer’s 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 mutations in chromosomes 1, 14, and 21 have been associated with early onset familial AD. (1)

Susceptibility Polymorphism at the Apolipoprotein E (APOE) Gene
The APOE lipoprotein is a carrier of cholesterol produced in the liver and brain glial cells. The APOE gene has 3 alleles—epsilon 2, 3, and 4—with the epsilon 3 allele being the most common. Individuals carry 2 APOE alleles. The presence of at least 1 epsilon 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 (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 at about age 68 years for epsilon 4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no epsilon 4 alleles. About half of patients with sporadic AD carry an epsilon 4 allele. However, not all patients with the allele develop AD. The epsilon 4 allele represents a risk factor for AD rather than a disease-causing mutation. 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 epsilon 4 alleles, other risk factors for AD [e.g., risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, and 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 polymorphisms in other genes that may increase the risk of AD.

Genetic Mutations
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 mutations in 3 genes have been identified in affected families: amyloid-beta precursor protein gene (APP), presenilin 1 (PSEN1) gene, and presenilin 2 (PSEN2) gene. APP and PSEN1 mutations have 100% penetrance absent death from other causes, while PSEN2 has 95%
penetrance. A variety of mutations within these genes has been associated with AD; mutations in PSEN1 appear to be the most common. While only 3–5% of all patients with AD have early onset disease, pathogenic mutations have been identified in up to 70% or more of these patients. Identifiable genetic mutations are, therefore, rare causes of AD.

Testing for the APOE 4 allele among patients with late-onset AD and for APP, PSEN1, or PSEN2 mutations 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. Mutations in PSEN1 and PSEN2 are specific for AD; APP mutations are also found in cerebral hemorrhagic amyloidosis of the Dutch type, a disease in which dementia and brain amyloid plaques are uncommon.

Susceptibility Testing at the Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) Gene
Recent studies identified rs75932628-T, a rare functional substitution for R47H of TREM2, as a heterozygous risk variant for late-onset AD. (4, 5) On chromosome 6p21.1, at position 47 (R47H), the T allele of rs75932628, encodes a histidine substitute for arginine in the gene that encodes TREM2.

TREM2 is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. TREM2 may serve a protective role in the brain by suppressing inflammation and clearing it of cell debris, amyloids and toxic products. A decrease in the function of TREM2 would allow inflammation in the brain to increase and may be a factor in the development of AD. The effect size of the TREM2 variant confers a risk of AD that is similar to the APOE epsilon 4 allele, although it occurs less frequently.

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

- **Cognitive impairment**
  - Cognitive impairment established by history from patient and a knowledgeable informant, plus objective assessment by bedside mental status examination or neuropsychological testing
  - Cognitive impairment involving a minimum of 2 of the following domains:
    - Impaired ability to acquire and remember new information
    - Impaired reasoning and handling of complex tasks, poor judgment
    - Impaired visuospatial abilities
    - Impaired language functions
    - Changes in personality, behavior, or comportment
- **Initial and most prominent cognitive deficits are one of the following:**
  - Amnestic presentation
  - Nonamnestic presentations, either a language presentation with prominent word-finding deficits; a visuospatial presentation with visual cognitive defects; or a dysexecutive presentation with prominent impairment of reasoning, judgment, and/or problem solving.
- **Clinical course**
  - Insidious onset
  - Clear-cut history of worsening over time
  - Interference with ability to function at work or usual activities
  - Decline from previous level of functioning and performing
- **Exclusion of other disorders**
Cognitive decline not explained by delirium or major psychiatric disorder
No evidence of other active neurologic disease, including substantial cerebrovascular disease or dementia with Lewy bodies.
Lack of prominent features of variant frontotemporal dementia or primary progressive aphasia.
No medication use with substantial effects on cognition.

A diagnosis of possible AD dementia is made when the patient meets most of the AD criteria, but has an atypical course or an etiologically mixed presentation. (6) This may consist of an atypical onset (e.g., sudden onset) or atypical progression. A diagnosis of possible AD is also made when there is another potentially causative systemic or neurologic disorder that is not thought to be the primary etiology of dementia.

Mild cognitive impairment (MCI) is a precursor of AD in many instances. MCI may be diagnosed when there is a change in cognition, but not sufficient impairment for the diagnosis of dementia. (8) Features of MCI are evidence of impairment in one or more cognitive domains, and preservation of independence in functional abilities. In some patients, MCI may be a predementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, and neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings. (6) Other diagnostic tests for AD include cerebrospinal (CSF) fluid levels of tau protein or beta-amyloid precursor protein, as well as positron emission tomography (PET) amyloid imaging. The CSF tests are considered separately in policy No. 2.04.14. PET amyloid imaging is considered in policy No. 6.01.55 on Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer's Disease.

Summary
Many genes, including APOE and TREM2, have been associated with late-onset Alzheimer’s disease (AD). However, the sensitivity and specificity of these genes is low or unknown for diagnosing AD, and genetic testing has not been shown to add value to the diagnosis of AD made clinically. For individuals with early onset AD, mutations in the PSEN1 and APP genes are found in a substantial number of patients. However, there is no direct or indirect evidence to establish that clinical outcomes are improved as a result of genetic testing for these mutations.

Therefore, the current evidence does not support genetic testing for AD. The lack of effective methods to prevent the onset of AD or to target AD treatments based on genetic characteristics limits the clinical benefit for such genetic testing. The low sensitivity and specificity of APOE testing for indicating which individuals will progress to AD or as a diagnostic tool, as well as the high likelihood that other genetic findings may affect progression, lend further support to this conclusion. The association of TREM2 and AD has only recently been identified and its clinical utility is unknown. Therefore, genetic testing for AD is considered investigational.

Policy History

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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines
References

