Medical Policy
Genetic Testing for Alzheimer Disease

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Policy Number: 580
BCBSA Reference Number: 2.04.13
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease, #581
Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer Disease, #903

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

Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered INVESTIGATIONAL. Genetic testing includes, but is not limited to, testing for the apolipoprotein E á4 allele (APOE), presenilin genes (PSEN), amyloid-beta precursor protein (APP), or triggering receptor expressed on myeloid cells 2 (TREM2).

Genetic testing for Alzheimer disease in individuals with dementia is considered INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
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<th>Medicare HMO Blue&lt;sup&gt;SM&lt;/sup&gt;</th>
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<tr>
<th>Medicare PPO Blue&lt;sup&gt;SM&lt;/sup&gt;</th>
<th>No</th>
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**CPT Codes / HCPCS Codes / ICD Codes**

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.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

According to the policy statement above, the following CPT codes are considered investigational for the conditions listed for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<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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<tr>
<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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</table>

The following HCPCS codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### HCPCS Codes

<table>
<thead>
<tr>
<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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**Description**

Alzheimer disease (AD) is commonly associated with a family history; 40% of patients with AD have at least 1 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.

**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. 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 (\textit{APP}), presenilin 1 (\textit{PSEN1}) gene, and presenilin 2 (\textit{PSEN2}) gene. \textit{APP} and \textit{PSEN1} mutations have 100% penetrance absent death from other causes, while \textit{PSEN2} has 95% penetrance. A variety of mutations within these genes has been associated with AD; mutations in \textit{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 \textit{APP}, \textit{PSEN1}, or \textit{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 \textit{PSEN1} and \textit{PSEN2} are specific for AD; \textit{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 (\textit{TREM2}) Gene
Recent studies identified rs75932628-T, a rare functional substitution for R47H of \textit{TREM2}, as a heterozygous risk variant for late-onset AD. On chromosome 6p21.1, at position 47 (R47H), the T allele of rs75932628, encodes a histidine substitute for arginine in the gene that encodes \textit{TREM2}.

\textit{TREM2} is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. \textit{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 \textit{TREM2} would allow inflammation in the brain to increase and may be a factor in the development of AD. The effect size of the \textit{TREM2} variant confers a risk of AD that is similar to the \textit{APOE} epsilon 4 allele, although it occurs less frequently.

Diagnosis of AD
The diagnosis of Alzheimer’s disease (AD) is divided into three categories: possible, probable, and definite AD. 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. 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. 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. 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. 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. 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. 581. PET amyloid imaging is considered in policy No. 903 (Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer Disease).

**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 mutation.

The evidence for genetic testing in individuals who are asymptomatic and at risk for developing AD includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy, test validity, change in disease status, and health status measures. 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. For individuals with early-onset AD, mutations in the presenilin 1 (PSEN1) and amyloid-beta precursor protein (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. 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.

### Policy History

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<th>Date</th>
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<td>5/2016</td>
<td>Genetic testing for Alzheimer disease in individuals with dementia is considered investigational. Effective 5/1/2016.</td>
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<tr>
<td>7/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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<td>1/2015</td>
<td>Clarified coding information.</td>
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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