APOE Variant Analysis for Alzheimer Disease Testing

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APOE variant analysis for Alzheimer disease (AD) testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure codes
APOE genotyping	81401 S3852

Criteria

Requests for APOE allele analysis for Alzheimer disease (AD) are reviewed using the following criteria.

Criteria

APOE allele analysis for the purpose of diagnosing or predicting risk for AD is not medically necessary.

Other Considerations

For information on APOE variant analysis to determine eligibility for targeted treatment of AD, please refer to the guideline *Pharmacogenomic Testing for Drug Toxicity and Response* as this testing is not addressed here.

What is Alzheimer disease?

Alzheimer disease (AD) is characterized by an adult-onset, progressive dementia with cerebral cortical atrophy, beta amyloid plaque formation, and intraneuronal neurofibrillary tangles.[1]

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Prevalence

The general population lifetime risk of AD is about 10%. First-degree relatives, siblings or offspring of a single person in the family with AD have a 20-25% lifetime risk.[1] Approximately 95% of all AD is late-onset (age>60-65 years), and 5% is early-onset (age <60-65 years).[1]

Familial AD

Familial AD (3 or more affected individuals in a family) accounts for approximately 25% of all AD, including late and early-onset.[1]

Late-onset familial AD: Approximately 15-25% of people with AD, developing symptoms after 60-65 years of age.[1] Late-onset familial AD is believed to have complex inheritance with multiple susceptibility genes and environmental factors playing a role.[1]

Early-onset familial AD (EOFAD): Less than 2% of people with AD, developing symptoms before 60-65 years of age.[1] EOFAD is an autosomal dominant inherited disorder caused by different genes than those that may predispose to late-onset AD.[1]

Symptoms

Common findings include memory loss, confusion, speech issues, hallucinations, and personality and behavioral changes such as poor judgment, agitation, and withdrawal.[1,2] Symptoms of AD usually start after 60-65 years of age.[1]

Cause

Variants in the APOE gene may confer an increased risk for late-onset familial AD.[1] There are three major allelic variants of APOE: e2, e3, and e4.

APOE e4 allele

When present in the heterozygous state (APOE e3/e4) or the homozygous state (APOE e4/e4), the APOE e4 allele increases the risk for late-onset AD, but is not sufficient to cause disease.[1]

APOE e4 is not necessary to develop AD and having no copies of e4 does not rule out the disease.[1,3] APOE e4 appears to cause susceptibility to AD, but the reason is unclear.[1,4]

Diagnosis

Genetic testing of the APOE gene can determine which variants an individual has but cannot predict if an individual will develop AD.[5] The diagnosis of AD relies on clinical assessment, which may include mental status testing, examinations, and diagnostic tests.[1,6]

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Management

There is no cure for AD. However, some medications may help with symptoms such as memory loss and confusion. One treatment approved by the Food and Drug Administration in 2023, called lecanemab (Leqembi®), appears to confer a higher risk for side effects in individuals who carry an APOE e4 allele(s).[7] There are also non-drug treatments for Alzheimer's disease that are used with the goals of maintaining or improving cognitive function, overall quality of life and engagement, and the ability to perform activities of daily living.[5] Non-drug treatments include physical activity, memory and orientation exercises, and music- and art-based therapies.[5]

Survival

In individuals aged 65 years or older with AD, the average survival is four to eight years after the diagnosis is made, yet some individuals live as long as 20 years.[5]

Test information

Testing for APOE alleles is available clinically.

APOE allele clinical testing

Many laboratories in the U.S. directly test for the three major allelic variants (e2, e3, e4) to assist diagnosis or predict risk of Alzheimer disease.

Guidelines and evidence

American College of Medical Genetics and Genomics and National Society of Genetic Counselors

The American College of Medical Genetics and Genomics (ACMG, 2011; reaffirmed 2018) and the National Society of Genetic Counselors (NSGC, 2011; reaffirmed 2016) stated:

- "Genetic testing for susceptibility loci (e.g., APOE) is not clinically recommended due to limited clinical utility and poor predictive value."[4]
- "Because the ε4 allele is neither necessary nor sufficient to cause AD, there have been numerous consensus statements and articles that have recommended against using APOE genotyping for predicting AD risk."[4]

European Federation of Neurological Societies

The European Federation of Neurological Societies (EFNS, 2010) stated:

- "The ApoE e4 allele is the only genetic factor consistently implicated in late-onset AD, but it is neither necessary nor sufficient for development of the disease. Hence, there is no evidence to suggest ApoE testing is useful in a diagnostic setting."[3]

National Institute on Aging

The National Institute on Aging (NIA, 2024) Alzheimer's Association Working Group stated:

- "…[T]he presence of risk alleles does not indicate with certainty the presence or severity of ADNPC [AD neuropathologic change] in an individual at a given point in time. … We therefore regard risk alleles as a risk factor for AD, not diagnostic of or a stage of AD."[6]

The National Institute on Aging (NIA,1996) Alzheimer's Association Working Group stated:

- "Insofar as patients with AD are more likely to have an APOE-e4 allele than are patients with other forms of dementia or individuals without dementia, physicians may choose to use APOE genotyping as an adjunct to other diagnostic tests for AD."[8]
- "Since genotyping cannot provide certainty about the presence or absence of AD, it should not be used as the sole diagnostic test."[8]
- "The use of APOE genotyping to predict future risk of AD in symptom-free individuals is not recommended at this time."[8]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for APOE variant analysis for Alzheimer disease will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[9] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

References

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