APOE Variant Analysis for Alzheimer Disease Testing

Introduction

APOE variant analysis for Alzheimer disease 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.

<table>
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<th>Procedure addressed by this guideline</th>
<th>Procedure codes</th>
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<td>APOE Genotyping</td>
<td>81401</td>
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What is Alzheimer disease

Definition

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

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.\(^2\)

Familial AD

Of all people with AD, about 25% have at least two affected people in the family. This is referred to as familial AD.\(^2\)

Approximately 95% of people with familial AD develop symptoms after 65.\(^2\) This is called late-onset familial AD. Late-onset familial AD is believed to have complex inheritance with multiple susceptibility genes and environmental factors playing a role.\(^2\)

In about 5% of familial cases, symptoms consistently start before 65.\(^2\) This is called early onset familial Alzheimer disease (EOFAD). 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.\(^2\)\(^3\)

Onset

Symptoms of AD usually start after 60-65 years old.\(^2\)

APOE variants

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.\(^2\)

APOE e4 is not necessary to develop AD and having no copies of e4 does not rule out the disease.\(^2\)\(^4\) APOE e4 appears to cause susceptibility to AD, but the reason is unclear.\(^2\)\(^5\)

Test information

Introduction

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

Introduction

This section includes relevant guidelines and evidence pertaining to APOE allele analysis for AD.

**Choosing Wisely/American College of Medical Genetics and Genomics (2015)**

"Don't order APOE genetic testing as a predictive test for Alzheimer disease. APOE is a susceptibility gene for later-onset Alzheimer disease (AD), the most common cause of dementia. The presence of an ε4 allele is neither necessary nor sufficient to cause AD."
The relative risk conferred by the ε4 allele is confounded by the presence of other risk alleles, gender, environment and possibly ethnicity. APOE genotyping for AD risk prediction has limited clinical utility and poor predictive value."  

The American College of Medical Genetics and The National Society of Genetic Counselors (2011)

“Genetic testing for susceptibility loci (e.g., APOE) is not clinically recommended due to limited clinical utility and poor predictive value.”

“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.”

European Federation of Neurological Societies (2010)

“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.”


“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.”

“Since genotyping cannot provide certainty about the presence or absence of AD, it should not be used as the sole diagnostic test.”

“The use of APOE genotyping to predict future risk of AD in symptom-free individuals is not recommended at this time.”

Criteria

Introduction

Requests for APOE allele analysis for AD are reviewed using these criteria.

Criteria

• This test is considered investigational and/or experimental
  o Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical
management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

- In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility

References

Introduction

These references are cited in this guideline.


