Early Onset Familial Alzheimer Disease (EOFAD) Genetic Testing

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>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
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</thead>
<tbody>
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<td>PSEN1 Sequencing</td>
<td>81405</td>
</tr>
<tr>
<td>PSEN1 Deletion/Duplication</td>
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<tr>
<td>PSEN1 Known Familial Mutation</td>
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<tr>
<td>APP Sequencing</td>
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<td>APP Deletion/Duplication</td>
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<td>APP Known Familial Mutation</td>
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<tr>
<td>PSEN2 Sequencing</td>
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<tr>
<td>PSEN2 Known Familial Mutation</td>
<td>81403</td>
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</tbody>
</table>

What is early onset Alzheimer disease

Definition

Alzheimer disease (AD) is characterized by adult onset, progressive dementia with cerebral cortical atrophy and beta amyloid plaque formation. Common findings include memory loss, confusion, speech issues, hallucinations, and personality and behavioral changes such as poor judgment, agitation, and withdrawal. Symptoms of Alzheimer disease usually start after 60-65 years old.

- Of all people with Alzheimer disease, about 25% have at least two affected relatives (called “familial Alzheimer disease”). Most familial Alzheimer disease is late-onset, but in about 5% of cases symptoms start at an unusually young age (called “early onset familial Alzheimer disease” or EOFAD).
- EOFAD is suspected when:
  - More than one family member has Alzheimer disease.
  - Symptoms consistently start before 65 and often before 55.
Genetics

- Table 1 below summarizes three subtypes of EAFOD. While not clinically distinguishable, the underlying genetic cause differs. Among families with EOFAD, 40-80% will have a detectable mutation in the APP, PSEN1, or PSEN2 gene. Therefore, some families with EOFAD will not have an identifiable mutation by current testing. There may be other disease causing genes that have not been identified to date.

- EOFAD is inherited in an autosomal dominant fashion. Therefore, some families with EOFAD will not have an identifiable mutation by current testing. There may be other disease causing genes that have not been identified to date.

- A person who is found to have a mutation in one of the genes known to cause EOFAD has a 50% chance to pass the mutation to his/her children.

- Most people with EOFAD have an affected parent. In cases where there appears to be no parent affected, most people have a second degree relative with the condition. De novo (new) mutations are possible. However, they have not been reported in EOFAD.

- The presence of a mutation in the PSEN1 gene has complete penetrance by the age of 65, meaning that when a mutation is present symptoms present by this age. Mutations in PSEN2 have a penetrance of approximately 95%. The penetrance of APP is unknown.

Table 1

<table>
<thead>
<tr>
<th>EOFAD type D</th>
<th>Gene</th>
<th>Proportion of EOFAD cases</th>
<th>Average age of onset</th>
<th>Likelihood of symptoms with a mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>APP</td>
<td>No more than 10% to 15%</td>
<td>40's to 50's (occasionally 60s)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Type 3</td>
<td>PSEN1</td>
<td>30% to 70%</td>
<td>40 to early 50's</td>
<td>~100% by 65</td>
</tr>
<tr>
<td>Type 4</td>
<td>PSEN2</td>
<td>Less than 5%</td>
<td>40 to 75</td>
<td>~95% by 80s</td>
</tr>
</tbody>
</table>

Test information

- EOFAD is clinically diagnosed based on family history and age of onset. Genetic testing can confirm a clinical diagnosis in symptomatic individuals. Positive results also allow reliable presymptomatic predictive testing for at-risk family members. Sequence analysis is necessary for acceptable detection rates. Experts suggest that testing should start with PSEN1 sequencing and deletion/duplication analysis, as PSEN1 is the most commonly involved gene.
• Sequence analysis is available for each gene individually or as panel. In addition to sequencing, APP gene testing includes specialized deletion/duplication studies that explain a small percentage of cases.\(^1\)

• APP gene duplication FISH studies may be available as a separate test, but this test alone has limited clinical application.

• Once the disease-causing mutation is identified, predictive testing of adult first-degree relatives (primarily siblings and adult offspring) may be considered. The detection rate for a known familial mutation is greater than 99%. Because of the implications of predictive testing, “Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction.” \(^1\)

Guidelines and evidence

• The Amyloid Imaging Task Force, Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer’s Association (2013) reference genetic testing in their recommendations:\(^4\)
  - “The use of amyloid PET in lieu of genotyping for suspected autosomal dominant mutation carriers is considered inappropriate. The optimal clinical evaluation in these cases is careful collection of a family history, followed (if appropriate) by genetic counseling prior to and after genetic testing for known mutations. Future use of amyloid PET in autosomal dominant mutation carriers could include determination of whether the amyloid deposition phase of their illness has begun. In the setting of a complete clinical evaluation, including serial neuropsychological testing, this information may be useful in identifying one disease-related milestone that, along with the genetic information, aids decision making.”

• A 2012 expert-authored review states that:\(^1\)
  - “EOFAD is diagnosed in families with multiple affected individuals with mean age of onset before 65 years and/or with a documented disease-causing mutation in one of the genes known to be associated with EOFAD.”
  - “Establishing the diagnosis in a proband requires molecular genetic testing to identify a disease-causing mutation in one of the three genes known to be associated with EOFAD.”
  - “Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutation in the family.”

• American College of Medical Genetics and The National Society of Genetic Counselors (2011): \(^5\)
o “Testing for genes associated with early-onset autosomal dominant AD should be offered in the following situations:”
  ▪ “A symptomatic individual with EOAD in the setting of a family history of dementia or in the setting of an unknown family history (e.g., adoption).”
  ▪ “Autosomal dominant family history of dementia with one or more cases of EOAD.”
  ▪ “A relative with a mutation consistent with EOAD).”

• The European Federation of Neurological Societies (2010)\(^6\) Alzheimer's diagnosis and management guidelines address genetic testing: “Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia.” (No evidence level assigned.) They add, “Testing of patients with familial dementia and of unaffected at-risk-relatives should be accompanied by neurogenetic counseling and undertaken only after full consent and by specialist centres. Pre-symptomatic testing may be performed in at risk member of family-carrying mutation. It is recommended that the Huntington’s disease protocol is followed for pre-symptomatic testing.”

Criteria

PSEN1, PSEN2, or APP known familial mutation testing

• Clinical Consultation:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous genetic testing of PSEN1, PSEN2, or APP, and
  o PSEN1, PSEN2, or APP mutation identified in a 1\(^{st}\) or 2\(^{nd}\) degree biological relative, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Dementia diagnosed ≤65 years of age, OR

• Predictive Testing
  o Age 18 years or older, and
  o No previous genetic testing of PSEN1, PSEN2, or APP, and
  o PSEN1, PSEN2, or APP mutation identified in 1\(^{st}\) or 2\(^{nd}\) degree biological relative
PSEN1 full sequence and deletion/duplication analysis

- Clinical Consultation:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Testing:
  - No previous PSEN1 sequencing or deletion/duplication analysis, and
  - No known PSEN1, PSEN2, or APP mutation in the family, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Dementia diagnosed ≤65 years of age, and
  - Family history of dementia in 1\textsuperscript{st} or 2\textsuperscript{nd} degree relative

APP sequence and deletion/duplication analysis

- Criteria for PSEN1 analysis are met, AND
- No previous genetic testing for APP, AND
- No mutations detected in PSEN1 analysis

PSEN2 full sequence analysis

- Criteria for PSEN1 analysis are met, AND
- No previous genetic testing for PSEN2, AND
- No mutations detected in PSEN1 or APP analysis

References


