# Early Onset Familial Alzheimer Disease Genetic Testing

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### Introduction

Early onset familial Alzheimer disease (EOFAD) genetic 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.

| Procedures addressed by this guideline | Procedure codes |
|---|---|
| APP deletion/duplication | 81479 |
| APP known familial mutation | 81403 |
| APP sequencing | 81406 |
| EOFAD multigene panel | 81479 |
| PSEN1 deletion/duplication | 81479 |
| PSEN1 known familial mutation | 81403 |
| PSEN1 sequencing | 81405 |
| PSEN2 known familial mutation | 81403 |
| PSEN2 sequencing | 81406 |

## Criteria

### Introduction

Requests for early onset familial Alzheimer disease (EOFAD) testing are reviewed using the following criteria.

### PSEN1, PSEN2, or APP Known Familial Mutation Testing

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



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- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, and
  - PSEN1, PSEN2, or APP mutation identified in a 1st or 2nd degree biological relative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Dementia diagnosed ≤65 years of age, OR
- Predictive Testing:
  - Age 18 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**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 1st or 2nd degree relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**APP Full Sequence and Deletion/Duplication Analysis**

- Criteria for PSEN1 analysis are met, AND
- No previous APP sequencing or deletion/duplication analysis, AND
- PSEN1 sequencing and deletion/duplication analysis were performed, and no mutations were detected, AND
- No mutations detected in PSEN2 sequencing, if performed.

**PSEN2 Full Sequence Analysis**

- Criteria for PSEN1 analysis are met, AND
- No previous PSEN2 sequencing analysis, AND

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- PSEN1 sequencing and deletion/duplication analysis were performed, and no mutations were detected, AND
- No mutations detected in APP sequencing, if performed.

**Multigene Panel (PSEN1, APP, and PSEN2 ONLY)**

- Clinical Consultation:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous testing for EOFAD, and
  - No known PSEN1, PSEN2, or APP mutation in the family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Dementia diagnosed less than or equal to 65 years of age, and
  - Family history of dementia in 1st or 2nd degree relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

## Billing and Reimbursement

### Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

When otherwise reimbursable, the following limitations apply:

- When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81479*).
- When use of a panel code is not possible, each billed component procedure will be assessed independently.
- In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

- When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement in a tiered fashion:
    - PSEN1
    - APP
    - PSEN2

**Note** *The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

## What is early onset familial Alzheimer disease?

### Definition

Alzheimer disease (AD) is characterized by 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%.

#### Familial AD

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

Most familial AD is late-onset, but in less than 2% of cases, symptoms start at an unusually young age (called “early onset familial Alzheimer disease” or EOFAD).[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 old; however, symptoms of EOFAD begin at 65 years or younger.[1]

EOFAD is suspected when:[1]

- More than one family member has AD; and
- Symptoms occur before the age of 65.

### Cause

There are three subtypes of EOFAD.[1]

- While not clinically distinguishable, the underlying genetic cause differs. Among families with EOFAD, 60-80% will have a detectable mutation in the APP, PSEN1, or PSEN2 gene.[1] 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.
- 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.[1,2]
- Reduced penetrance of EOFAD-associated mutations has been described.

Table 1: Subtypes of EOFAD[1]

| Gene | Proportion of EOFAD cases | Average age of onset |
|---|---|---|
| APP | 10-15% | 40s to 50s (occasionally 60s) |
| PSEN1 | 20-70% | 40s to early 50s |
| PSEN2 | ~5% | 40 to 75 |

## Inheritance

EOFAD is an autosomal dominant disorder.

### Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

## Diagnosis

The diagnosis of AD relies on clinical assessment, which may include mental status testing, neurological examinations, diagnostic tests, and brain imaging.[3] Genetic testing of APP, PSEN1, or PSEN2 is another tool to establish the diagnosis in individuals with early onset AD and a positive family history. In asymptomatic individuals with a mutation in one of these genes, there is an increased likelihood they will develop EOFAD however reduced penetrance has been documented.[1]

Because of the implications of predictive testing, pretest genetic counseling should include limitations of predictive testing and potential consequences with regard to health, life, and disability insurance coverage; employment and educational

discrimination; and changes in social and family dynamics.[1] Predictive testing is considered inappropriate for asymptomatic minors who are at risk for adult-onset conditions if there is not an early treatment option expected to have a beneficial effect on the disease morbidity and mortality.[1]

### Management

There is no cure for AD however some medications may help with symptoms such as memory loss and confusion. 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.[3] Non-drug treatments include physical activity, memory and orientation exercises, and music- and art-based therapies.

### Survival

The survival for individuals with EOFAD is unknown due to the rarity of the condition and a paucity of longitudinal studies. In individuals with late-onset AD diagnosed at age 65 or older, the average survival is four to eight years after the diagnosis is made but can be as long as 20 years.[3] EOFAD is believed to have a more aggressive disease course that late-onset AD with faster progression.[1]

## Test information

### Introduction

Testing for EOFAD may include known familial mutation analysis, next generation sequencing, deletion/duplication analysis, and/or multigene panel testing.

### Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

### Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Given the significant overlap in clinical manifestations and age of onset in AD, a multigene panel that includes PSEN 1/2 and APP, rather than single gene testing, is most likely to identify the genetic cause but also limit identification of variants of uncertain significance.[1]

### Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

### Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

## 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:[4]

- "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 pathogenic variant consistent with EOAD (currently PSEN 1/2 or APP)."





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### Amyloid Imaging Taskforce, Society of Nuclear Medicine and Molecular Imaging, and Alzheimer's Association

The Amyloid Imaging Taskforce (AIT, 2013), Society of Nuclear Medicine and Molecular Imaging (SNMMI, 2013), and the Alzheimer's Association referenced genetic testing in their recommendations:[5]

- "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."

### European Federation of Neurological Societies

The European Federation of Neurological Societies (EFNS, 2010) Alzheimer's diagnosis and management guidelines addressed genetic testing:[6]

- "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 centers. 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."

### Selected Relevant Publications

A 2018 expert-authored review stated:[1]

- "Establishing a specific genetic cause of Alzheimer disease (AD): Can aid in discussions of prognosis (which are beyond the scope of this GeneReview) and genetic counseling (Section 4); Usually involves a medical history, physical examination, and laboratory testing to exclude disorders included in the differential diagnosis (see Section 1), family history, and genomic/genetic testing."
- "Because familial AD and nonfamilial AD appear to have the same clinical and pathologic phenotypes, they can only be distinguished by family history and/or by molecular genetic testing."
- "Because of the significant overlap in clinical manifestations and age of onset in AD, single-gene testing (i.e., sequence analysis, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended."

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- "Predictive testing for asymptomatic adults at risk for APP-, PSEN1-, or PSEN2-related EOFAD is possible if the pathogenic variant has been identified in an affected family member."

**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 early onset familial Alzheimer disease testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

## References


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