MP 2.04.09 | Genetic Testing for Familial Alzheimer’s Disease

Medical Policy

Section | Medicine
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Return to Medical Policy Index

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Description

Alzheimer’s disease (AD) is the most common cause of dementia in elderly patients. Early-onset AD is much less common, but can occur in non-elderly individuals. For late-onset AD, there is a component of risk that runs in families, suggesting the contribution of genetic factors. Early onset Alzheimer’s has a stronger component of family risk, with clustering in families, thus suggesting an inherited genetic mutation.

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

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 about 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. (2) 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 (APP), presenilin 1 (PSEN1) gene, and presenilin 2 (PSEN2) gene. APP and PSEN1 mutations have 100% penetrance absent death from other causes, while PSEN2 has 95% penetrance. A variety of mutations within these genes has been associated with AD; mutations in 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 APP, PSEN1, or PSEN2 mutations in the rare patient with early onset AD have been investigated as an aid in diagnosis in patients presenting with symptoms suggestive of AD, or a technique for risk assessment in asymptomatic patients with a family history of AD. Mutations in PSEN1 and PSEN2 are specific for AD; APP mutations are also found in cerebral hemorrhagic amyloidosis of the Dutch type, a disease in which dementia and brain amyloid plaques are uncommon.

The diagnosis of Alzheimer’s disease (AD) is divided into three categories: possible, probable, and definite AD. (4) 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. (5) 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. (4) 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 two 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. (4) 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. (6) 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. (4) 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. 2.04.14. PET amyloid imaging is considered in policy No. 6.01.55 on Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer’s Disease.

Policy

Genetic testing for the diagnosis or risk assessment of Alzheimer’s disease is considered investigational. Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 allele, presenilin genes, or amyloid precursor gene.
Policy Guidelines

Genetic testing for Alzheimer’s disease may be offered along with cerebral spinal fluid (CSF) levels of the Tau protein and AB-42 peptide (see separate policy No. 2.04.14). This group of tests may be collectively referred to as the ADmark™ Profile, offered by Athena Diagnostics (Worcester, Mass.).

Effective in 2013, there is CPT coding to more specifically report PSEN and APP testing.

CPT code 81405 includes:

*PSEN1 (presenilin 1) (eg, Alzheimer disease), full gene sequence.*

CPT code 81406 includes:


Effective in 2012, there is CPT coding to more specifically report APOE testing.

CPT code 81401 includes:

*APOE (apolipoprotein E) (e.g., hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (e.g., *2, *3, *4).*

Prior to 2013, the following series of CPT codes were identified by Athena Diagnostics as those used to identify the multiple laboratory steps in testing for apolipoprotein epsilon (APOE) alleles or mutations in the presenilin genes. Some codes would have been used more than once in an individual test.

**APOE**

83891: Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type

83892: ; enzymatic digestion, each enzyme treatment

83894: ; separation by gel electrophoresis (e.g., agarose, polyacrylamide), each nucleic acid preparation

83898: ; amplification, target, each nucleic acid sequence

83912: ; interpretation and report

**Mutations of presenilin genes**

83891: Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type

83898: ; amplification, target, each nucleic acid sequence

83902: ; reverse transcription
83904: ; mutation identification by sequencing, single segment, each segment

83912: ; interpretation and report

Prior to 2013, there was also a CPT genetic testing code modifier that is specific to APOE and should be appended to the above codes for APOE testing – 7A - APOE, commonly called apolipoprotein E (cardiovascular disease or Alzheimer's disease).

A HCPCS code specific to APOE epsilon 4 allele testing became effective July 1, 2003 – S3852: DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer’s disease.

Effective 1/1/07, there is also a HCPCS code specific to testing for presenilin-1 mutations: S3855: Genetic testing for detection of mutations in the presenilin-1 gene

Rationale

**Susceptibility Testing at the Apolipoprotein E (APOE) Gene**

The policy regarding apolipoprotein epsilon (APOE) genotyping derives from a 1999 TEC Assessment (7) that offered the following conclusions and observations:

- Several consensus statements regarding APOE genotyping have been published, which conclude that APOE genotyping in asymptomatic patients, as a technique of risk assessment, is not recommended. Statements regarding its use as a diagnostic test in symptomatic patients are mixed. In 1998, the American College of Medical Genetics/American Society of Human Genetic Working Group on APOE and Alzheimer’s Disease stated, “Studies to date indicate that the APOE genotype alone does not provide sufficient sensitivity or specificity to allow genotyping to be used as a diagnostic test. In 1997, a national study group supported by the National Institutes of Health (NIH) and composed of Alzheimer's disease (AD) geneticists, policy experts, and ethicists, stated “The use of APOE genetic testing as a diagnostic adjunct in patients already presenting with dementia may prove useful but it remains under investigation.” In contrast, a report by the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease stated that APOE genotyping can add “confidence to the clinical diagnosis of AD…” but “…the sensitivity and specificity of the epsilon 4 allele alone are low, indicating that this measure cannot be used as the sole diagnostic test for AD.”

- Considering the published data regarding the sensitivity and specificity of APOE genotyping, the TEC Assessment concluded that the addition of APOE genetic testing does not improve the sensitivity of clinical criteria and only marginally improves the specificity of clinical criteria for the diagnosis of AD. In addition, APOE genetic testing would not alter recommended diagnostic testing for other treatable causes of dementia.

Subsequent to the TEC Assessment advances in genetic understanding of AD have been considerable (8) with associations between late-onset AD and more than 20 non-APOE genes suggested. However, relevant literature through August 2012 does not provide evidence supporting clinical utility or benefit from genetic testing for AD.
Tsuang et al (9) prospectively evaluated APOE testing for AD diagnosis in a community-based case series of older patients presenting with memory complaints but no previous diagnosis of dementia. Of 1,028 potential cases, 970 were evaluated; of these, 425 died and 132 were autopsied; of the 132, 71% were confirmed to have AD. The sensitivity and specificity of APOE epsilon 4 alone were poor, yielding positive and negative predictive values of 83% and 41% compared to 81% and 56%, all respectively, for clinical diagnosis alone. Using a criterion of positive clinical diagnosis or APOE epsilon 4 resulted in positive and negative predictive values of 79% and 70%. A criterion of positive clinical diagnosis and APOE epsilon 4 improved positive predictive value to 88% but at the expense of negative predictive value (40%). Eleven individuals had an epsilon 4 allele without neuropathologically confirmed AD. While APOE epsilon 4 increases disease susceptibility, it is associated with only approximately 50% of Alzheimer’s cases.

The effect of APOE genotype on response to AD therapy has also been examined. The USA-1 Study group found APOE genotype did not predict therapeutic response. (10) Rigaud et al followed 117 individuals with AD over 36 weeks in an open-label trial of donepezil; 80 (68%) completed the trial. (11) They found no statistically significant effect of APOE genotype on change in cognition (assessed by ADAS-Cog). However, the study was not designed to examine predictive therapeutic response, and there were baseline cognitive differences according to APOE genotype. There is currently insufficient information to make treatment decisions based on APOE subtype.

The REVEAL study was designed to examine consequences of AD risk assessment by APOE genotyping. (12) Of 289 eligible participants 162 were randomized (mean age, 52.8 years; 73% female; average education, 16.7 years) to either risk assessment based on APOE testing and family history (n=111) or family history alone (n=51). During a 1-year follow-up, those undergoing APOE testing with a high-risk genotype were more likely than low-risk or ungenotyped individuals to take more vitamins (40% vs. 24% and 30%, respectively), change diet (20% vs. 11% and 7%, respectively), or change exercise behaviors (8% vs. 4% and 5%, respectively). While in this well-educated sample of women there were some behavior changes, none can be considered a meaningful surrogate endpoint.

**Genetic Testing for Early Onset Familial AD**

Genetic testing for PSEN1 detects 30–60% of familial early onset AD. A number of mutations have been reported scattered throughout the presenilin 1 (PSEN1) gene, requiring sequencing of the entire gene when the first affected member of a family with an autosomal dominant pattern of AD inheritance is tested. Mutations in APP and PSEN2 genes account for only a small fraction of cases; it is likely that other causative genes will be discovered.

In 1998, the Alzheimer Disease Working Group of the Stanford Program in Genomics, Ethics, and Society (13) suggested that “predictive or diagnostic genetic testing for highly penetrant mutations (e.g., APP [amyloid-beta precursor protein], PSEN1, PSEN2 [presenilin 2]) may be appropriate for individuals from families with a clear autosomal dominant pattern of inheritance, particularly those with a family history of early onset of symptoms.” Such families generally have 3 affected members in 2 generations. In the case of diagnostic testing of clearly symptomatic individuals, testing would do little to change diagnostic confidence; however, it might assist excluding other causes of early onset dementia, as potentially treatable contributory causes would still require exploring. In cases of early detection of questionably symptomatic individuals (i.e., those with mild cognitive impairment, mutation identification might secure a diagnosis and
lead to early treatment. The possibility that earlier diagnosis might lead to improved outcomes, while plausible, is not based on current evidence. Pharmacologic interventions for mild cognitive impairment have not demonstrated benefit in reducing progression to AD. (14)

The nearly complete penetrance of a PSEN1 disease-associated mutation would change the probability of developing AD in an unaffected family member from 50% to either 0% or 100%. Testing for PSEN1 mutations is not useful in predicting age of onset (although it is usually similar to age of onset in affected family members), severity, type of symptoms, or rate of progression in asymptomatic individuals. However, identification of asymptomatic, young adult carriers could allow for reproductive planning. Identification of both symptomatic and asymptomatic carriers could also allow for other types of life planning in advance of incapacitating disease.

It is not uncommon to discover previously unreported PSEN1 mutations in an individual, and without additional family information, these may reflect mutations not associated with disease, or new causative mutations restricted to a single family (private mutation). Thus, interpretation of test results of asymptomatic individuals without identification of a mutation in affected family members may be inconclusive in a significant proportion of patients. Should testing be undertaken, affected family members should be tested first or in conjunction with unaffected family members. When no mutation can be identified in affected family members with a clear autosomal dominant pattern of disease inheritance, the family can be referred to a research program for additional study. Any testing should be performed only in the context of adequate pre- and post-testing genetic counseling. Finally, it should be noted that pharmacologic therapy for Alzheimer’s disease should be based on the patient’s symptomatology rather than testing results.

GeneTests.org (available online at: www.genetests.org) notes availability of testing for PSEN1, PSEN2, and APP through a number of laboratories.

A systematic review on the psychological and behavioral impact of genetic testing for AD found few studies on the impact of testing for early onset familial AD. The existing studies generally have small sample sizes and retrospective designs, and the research was conducted in different countries, which may limit the generalizability of the findings. (15)

Mihaescu et al. (16) cite a proposed framework by Khoury and colleagues (17) for the continuum of translational research that is required to move genomics research findings in Alzheimer’s disease to clinical and public health applications that benefit population health…The 4 phases of translation research include: 1) translation of basic genomics research into a potential health care application; 2) evaluation of the application for the development of evidence-based guidelines; 3) evaluation of the implementation and use of the application in health care practice; and 4) evaluation of the achieved population health impact.

Mihaescu and colleagues conclude that genetic testing for Alzheimer’s disease is still in the first phase. At this point, the sensitivity and specificity of APOE for detecting individuals at risk of developing AD is too low. For those from families with early onset, familial AD, there are currently no known preventive measures or treatments that can mitigate the effect of the disease.

Summary
Many genes, including APOE, have been associated with late-onset AD. However, the sensitivity and specificity of these genes is low for diagnosing AD, and 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 PSEN1 and 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.

Therefore, the current evidence does not support genetic testing for AD. The lack of effective methods to prevent the onset of AD or to target AD treatments based on genetic characteristics limits the clinical benefit for such genetic testing. The low sensitivity and specificity of APOE testing for indicating which individuals will progress to AD or as a diagnostic tool, as well as the high likelihood that other genetic findings may affect progression, lend further support to this conclusion. Therefore, genetic testing for AD is considered investigational.

Guidelines

American Academy of Neurology (18)

- Routine use of APOE genotyping in patients with suspected AD is not recommended at this time (Guideline).
- There are no other genetic markers recommended for routine use in the diagnosis of AD (Guideline).

This guideline is currently being updated (available online at: http://www.aan.com/practice/guideline/index.cfm?fuseaction=home.welcome&Topics=15&keywords=&Submit=Search+Guidelines).

European Federation of Neurological Sciences (EFNS) (19)

Recommendations: genetic testing (level of evidence not reported)

Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. 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. Presymptomatic testing may be performed in at-risk members of family-carrying mutation. It is recommended that the Huntington’s disease protocol is followed for pre-symptomatic testing.

Routine Apo E genotyping is not recommended.

Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD) (20)

Predictive genetic testing for asymptomatic “at risk” individuals with an apparent autosomal dominant inheritance, and a family-specific mutation has been identified:

1. With appropriate pre- and post-testing counseling, predictive genetic testing (PGT) can be offered to “at-risk” individuals (Grade B, Level 2**). Examples:
   a. First-degree relatives of an affected individual with the mutation (e.g., children and siblings);
b. First cousins of an affected individual if the common ancestors (parents who were siblings) died before the average age of onset of dementia in the family;

c. Nieces and nephews of affected individuals whose parent (sibling of the affected individual) died well before the average age of onset of dementia in the family;

d. PGT in minors is not generally offered in Canada, but occasionally may be considered on a case-by-case basis by the relevant medical ethics committee(s);

e. Individuals who are not “at risk” for the inherited disease do not require testing.

2. In young persons (60 years or younger) presenting with an early onset dementia, it is sometimes worthwhile to test for the most common mutations based on the “best estimate” diagnosis (e.g., in early onset AD, one might test for the most common mutations in PS1, APP). (Grade B, Level 2**) If a mutation is identified, it would have direct implications for offspring of the individual (if a de novo mutation is assumed). Conversely, it would also be important to test other family members such as parents and siblings for possible non-penetrance of a mutation.

Genetic screening with APOE genotype in asymptomatic individuals in the general population is not recommended because of the low specificity and sensitivity. (Grade E, Level 2**)

Genetic testing with APOE genotype is not recommended for the purpose of diagnosing AD because the positive and negative predictive values are low. (Grade E, Level 2**)

The 2012 Canadian Consensus Conference on Dementia was held in May 2012. The results have not been released to date (available online at:http://www.healthplexus.net/article/2012-canadian-consensus-conference-dementia).

**CCCDTD Evidence Ratings

Grade (B) There is fair evidence to support this maneuver.

Grade (E) There is good evidence to recommend against this procedure.

Level 2: (1) Evidence obtained from well-designed controlled trial without randomization, or (2) Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one center, or (3) Evidence obtained from comparisons between times or places with or without intervention. Dramatic results in uncontrolled experiments are included in this category.

Joint Practice Guidelines of the American College of Genetics and the National Society of Genetic Counselors (2)

- Pediatric testing for AD should not occur. Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation.

- Genetic testing for AD should only occur in the context of genetic counseling (in person or through videoconference) and support by someone with expertise in this area.

  - Symptomatic patients: Genetic counseling for symptomatic patients should be performed in the presence of the individual’s legal guardian or family member.
Asymptomatic patients: A protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington’s Chorea Guidelines is recommended.

- DTC APOE testing is not advised.
- A ≥3-generation family history should be obtained, with specific attention to the age of onset of any neurologic and/or psychiatric symptoms, type of dementia and method of diagnosis, current ages, or ages at death (especially unaffected relatives), and causes of death. Medical records should be used to confirm AD diagnosis when feasible. The history of additional relatives may prove useful, especially in small families or those with a preponderance of early death that may mask a history of dementia.
- A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with EOAD [early-onset AD] or LOAD [late-onset AD] and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance.
- Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression.
- The following potential genetic contributions to AD should be reviewed:
  - The lifetime risk of AD in the general population is approximately 10–12% in a 75–80 year lifespan.
  - The effect(s) of ethnicity on risk is still unclear.
  - Although some genes are known, there are very likely others (susceptibility, deterministic, and protective) whose presence and effects are currently unknown.

For families in which an autosomal dominant AD gene mutation is a possibility:

- Discuss the risk of inheriting a mutation from a parent affected with autosomal dominant AD is 50%. In the absence of identifying a mutation in apparent autosomal dominant families, risk to offspring could be as high as 50% but may be less.
- 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 (currently PSEN1/2 or APP).
- The Alzheimer Disease & Frontotemporal Dementia Mutation Database should be consulted (available online at: www.molgen.ua.ac.be/ADMutations/) before disclosure of genetic test results, and specific genotypes should not be used to predict the phenotype in diagnostic or predictive testing.
  - Discuss the likelihood of identifying a mutation in PSEN1, PSEN2, or APP, noting that current experience indicates that this likelihood decreases with lower proportions of affected family members and/or older ages of onset.
Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains interested in testing despite counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), he/she should be counseled according to the recommended protocol. If the affected relative, or their next of kin, is uninterested in pursuing testing, the option of DNA banking should be discussed.

**Ongoing Clinical Trials**

There are a number of clinical trials on APOE testing and the clinical manifestations of AD among patients with APOE epsilon 4 (at online site: clinicaltrials.gov).

**References:**


<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>See Policy Guidelines</td>
<td></td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>Investigational for all codes</td>
<td></td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCPCS</td>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>S3852</td>
<td>DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer’s disease (effective July 1, 2003)</td>
</tr>
<tr>
<td></td>
<td>S3855</td>
<td>Genetic testing for detection of mutations in the presenilin-1 gene (effective Jan 1, 2007)</td>
</tr>
<tr>
<td>ICD-10-CM (effective 10/1/14)</td>
<td></td>
<td>Investigational for all codes</td>
</tr>
<tr>
<td>F03</td>
<td></td>
<td>Unspecified dementia</td>
</tr>
<tr>
<td>G30.0-G30.9</td>
<td></td>
<td>Alzheimer’s disease code range</td>
</tr>
<tr>
<td>G31.1</td>
<td></td>
<td>Senile degeneration of brain, not elsewhere classified</td>
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<tr>
<td>R41.0</td>
<td></td>
<td>Disorientation, unspecified</td>
</tr>
<tr>
<td>R41.81</td>
<td></td>
<td>Age-related cognitive decline</td>
</tr>
<tr>
<td>Z13.858</td>
<td></td>
<td>Encounter for screening for other nervous system disorders</td>
</tr>
<tr>
<td>ICD-10-PCS (effective 10/1/14)</td>
<td></td>
<td>Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.</td>
</tr>
</tbody>
</table>

**Type of Service**  Pathology/Laboratory  
**Place of Service**  Laboratory/Reference Laboratory

**Index**

Alzheimer’s Disease, Genetic Testing  
Apolipoprotein E (APOE), Genetic Testing for Alzheimer’s Disease  
Genetic Testing, Alzheimer’s Disease  
Presenilin, Genetic Testing for Alzheimer’s Disease