Genetic Testing for Familial Alzheimer’s Disease

Policy # 00204
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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for the diagnosis or risk assessment of Alzheimer disease (AD) to be investigational.*

Note: Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 allele (APOE), presenilin genes (PSEN), amyloid-beta precursor protein (APP), or triggering receptor expressed on myeloid cells 2 (TREM2).

Background/Overview
Alzheimer disease is commonly associated with a family history; 40% of patients with AD have at least 1 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.

Susceptibility Polymorphism at the Apolipoprotein E 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 at about age 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. There is evidence of possible interactions between epsilon 4 alleles, other risk factors for AD (eg, risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, diabetes), 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 (ie, 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: APP gene, 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
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Genes have been associated with AD; mutations in PSEN1 appear to be the most common. While only 3% to 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 of patients presenting with symptoms suggestive of AD, or as 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.

Susceptibility Testing at the Triggering Receptor Expressed on Myeloid Cells 2 Gene
Recent studies identified rs75932628-T, a rare functional substitution for R47H of triggering receptor expressed on myeloid cells 2 (TREM2), as a heterozygous risk variant for late-onset AD. On chromosome 6p21.1, at position 47 (R47H), the T allele of rs75932628, encodes a histidine substitute for arginine in the gene that encodes TREM2.

TREM2 is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. TREM2 may serve a protective role in the brain by suppressing inflammation and clearing it of cell debris, amyloids, and toxic products. A decrease in the function of TREM2 would allow inflammation in the brain to increase and may be a factor in the development of AD. The effect size of the TREM2 variant confers a risk of AD that is similar to the APOE epsilon 4 allele, although it occurs less frequently.

Diagnosis of AD
The diagnosis of AD is divided into 3 categories: possible, probable, and definite AD. 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. 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. 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 2 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
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- 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. 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. Features of MCI are evidence of impairment in 1 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, 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. Other diagnostic tests for AD include CSF levels of tau protein or beta amyloid precursor protein, as well as PET amyloid imaging.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
No U.S. FDA-cleared genotyping tests were found. FDA has not regulated these tests to date. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.
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Centers for Medicare and Medicaid Services (CMS)  
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source  
Susceptibility Testing at the Apolipoprotein E Gene  
The policy regarding APOE genotyping derives from a 1999 TEC Assessment 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 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 and composed of 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, with associations between late-onset AD and more than 20 non-APOE genes suggested. However, relevant literature does not provide evidence supporting clinical utility or benefit from genetic testing for AD.

Tsuang et al 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 1028 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 (PPV) and negative predictive values (NPV) of 83% and 41% compared with 81% and 56%, all respectively, for clinical diagnosis alone. Using a criterion of positive clinical diagnosis or APOE epsilon 4 resulted in PPVs and NPVs of 79% and 70%, respectively. A criterion of positive clinical diagnosis and APOE epsilon 4 improved PPV to 88% but at the expense of NPV (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 AD cases.
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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. Rigaud et al followed 117 individuals with AD over 36 weeks in an open-label trial of donepezil; 80 (68%) completed the trial. 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. 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 untested 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 end point.

Genetic Testing for Early-Onset Familial AD

Genetic testing for PSEN1 detects 30% to 60% of familial early-onset AD. A number of mutations have been reported scattered throughout the 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 Society15 suggested that “predictive or diagnostic genetic testing for highly penetrant mutations (eg, APP, PSEN1, PSEN2) 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 (ie, those with MCI 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 MCI have not demonstrated benefit in reducing progression to AD.

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.
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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-test genetic counseling. Finally, it should be noted that pharmacologic therapy for AD should be based on the patient’s symptomatology rather than testing results.

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.

Mihaescu et al cite a proposed framework by Khoury et al for the continuum of translational research that is required to move genomics research findings in AD 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 et al conclude that genetic testing for AD 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.

Susceptibility Testing at the Triggering Receptor Expressed on Myeloid Cells 2 Gene

Jonsson et al evaluated 3550 subjects with AD and found a genome-wide association with only 1 marker, the T allele of rs75932628 (excluding the APOE locus and the A673T variant in APP11). The frequency of rs75932628 TREM2 was then tested in a general population of 110,050 Icelanders of all ages and found to confer a risk of AD of 0.63% (odds ratio [OR], 2.26; 95% confidence interval [CI], 1.71 to 2.98; p=1.13 x 10⁻⁶). In the control population of 8888 patients 85 years of age or older without a diagnosis of AD, TREM2 frequency was 0.46% (OR=2.92; 95% CI, 2.09 to 4.09; p=3.42 x 10⁻¹⁰). In 1236 cognitively intact controls age 85 or older, the frequency of TREM2 decreased even further to 0.31% (OR=4.66; 95% CI, 2.38 to 9.14; p=7.39 x 10⁻⁶). The decrease in TREM2 frequency in elderly patients who are cognitively intact supports the findings associating TREM2 with increasing risk of AD.

Guerriero et al also found a strong association of the R47H TREM2 variant with AD (p=0.001). Using 3 imputed data sets of genome-wide association AD studies, a meta-analysis found a significant association
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with the variant and disease (p=0.002). The authors further reported direct genotyping of R47H in 1994 AD patients, and 4062 controls found a highly significant association with AD (OR=5.05; 95% CI, 2.77 to 9.16; p=9.0 x10^{-9}).

No studies were identified that address how the use of the TREM2 rs75932628-T variant might be incorporated into clinical practice.

Ongoing and Unpublished Clinical Trials
An online search of ClinicalTrials.gov on August 20, 2014, identified several clinical trials on APOE, APP, PSEN1, and other gene mutation testing and the clinical manifestations in patients with genetic traits suspected to be associated with AD. No studies on TREM2 were identified.

Summary of Evidence
Many genes, including APOE and triggering receptor expressed on myeloid cells 2 (TREM2), have been associated with late-onset AD. However, the sensitivity and specificity of these genes is low or unknown 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. The association of TREM2 and AD has only recently been identified and its clinical utility is unknown. Therefore, genetic testing for AD is considered investigational.

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