Medical Policy Manual

Genetic Testing, Policy No. 01

Genetic Testing for Familial Alzheimer's Disease

Effective: March 1, 2017

Next Review: February 2018
Last Review: February 2017

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Genetic testing has been investigated as an aid in the diagnosis of patients presenting with symptoms suggestive of Alzheimer's disease (AD), or as a technique for risk assessment in asymptomatic patients with a family history of AD.

MEDICAL POLICY CRITERIA

Genetic testing for risk assessment or in the evaluation of dementia or Alzheimer's disease is considered investigational. Genetic testing includes, but is not limited to, testing for the apolipoprotein E (APOE) epsilon 4 allele, presenilin (PSEN) genes, amyloid precursor protein (APP) gene, or triggering receptor expressed on myeloid cells 2 (TREM2) gene.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Biochemical Markers of Alzheimer's Disease, Laboratory, Policy No. 22
Alzheimer’s disease (AD) is the most common form of dementia. In 2013, as many as 5 million Americans were living with AD, and by 2050 this number is projected to rise to 14 million.[1] Although scientists don’t fully understand the cause of AD, it is diagnosed based on a clinical-neuropathologic assessment, and age and a family history are the best known risk factors. The symptoms of AD most commonly appear after the age of 60, known as late-onset AD; however, AD can be found in younger people, known as early-onset AD. Researchers believe genetics may play a role in the development of AD in patients who have a family history, or in the risk assessment or management of asymptomatic patients with a family history of AD.

GENETIC MUTATIONS

Individuals with early onset familial AD (i.e., before age 65, 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 apolipoprotein E (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.

SUSCEPTIBILITY POLYMORPHISM AT THE APOLIPOPROTEIN E GENE

The apolipoprotein E (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.

**SUSCEPTIBILITY TESTING AT THE TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS 2 (TREM2) GENE**

Recent studies identified rs75932628-T, a rare functional substitution for R47H of TREM2, as a heterozygous risk variant for late-onset AD.\[^4,5\] 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.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings.\[^6\] Other proposed diagnostic tests for AD include cerebrospinal (CSF) fluid levels of Tau protein or beta-amyloid precursor protein. These CSF tests are addressed in a separate medical policy (see Cross References below).

**GENETIC COUNSELING**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling could assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**REGULATORY STATUS**

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. The 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 (CLIA). The laboratory offering the service must be licensed by CLIA for high
Validation of the clinical use of any genetic test focuses on three main principles:

- The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
- The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
- The clinical utility of the test, which describes how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

GENETIC TESTING FOR LATE-ONSET ALZHEIMER DISEASE

Analytic Validity

There is a lack of published evidence on the analytic validity of genetic testing for late-onset familial Alzheimer disease (AD). Analytic validity is expected to be high when current methods of sequencing are performed (i.e., Sanger sequencing and/or next-generation sequencing).

Clinical Validity

The advances in genetic understanding of AD have been considerable, with associations between late-onset AD and more than 20 non-APOE genes suggested.[7]

In 2014, Naj et al published a genome-wide association study of multiple genetic loci in late-onset AD.[8] Genetic data from 9,162 Caucasian participants with AD from the Alzheimer Disease Genetics Consortium were assessed for polymorphisms at 10 loci significantly associated with risk of late-onset AD. Analysis confirmed the association of APOE with an earlier age of onset and found significant associations for CR1, BIN1, and PICALM. APOE contributed 3.7% of the variation in age of onset and the other 9 loci combined contributed 2.2% of the variation. Each additional copy of the APOE ε4 allele reduced age of onset by 2.45 years.

Susceptibility Testing at the Apolipoprotein E Gene

The association of the APOE ε4 allele with AD is significant; however, APOE genotyping does not have high specificity or sensitivity, and is of little value in the predictive testing of asymptomatic individuals.[9]

The American College of Medical Genetics and Genomics has concluded that APOE genotyping for AD risk prediction has limited clinical utility and poor predictive value.[10]

The association of APOE genotype with response to AD therapy has been examined. The USA-1 Study group found APOE genotype did not predict therapeutic response.[11] Rigaud et al. followed 117 individuals with AD over 36 weeks in an open-label trial of donepezil; 80 (68%)
completed the trial.\[12\] They found no statistically significant effect of APOE genotype on change in cognition (assessed by Cognitive subscale of the Alzheimer’s Disease Assessment Scale). 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.

**Susceptibility Testing at the Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) Gene**

In 2015, Korvatska et al. published results from a retrospective study of genetic and pathologic studies that included 131 families (751 individuals) with late-onset AD (LOAD) between 1985 to 2014.\[13\] The authors found 12 of the 16 patients with AD in the LOAD123 family carried R47H. Eleven patients with dementia had apolipoprotein E 4 (APOE4) and R47H genotypes. R47H carriers demonstrated a shortened disease duration (mean [SD], 6.7 [2.8] vs 11.1 [6.6] years; 2-tailed t test; \( P = .04 \)) and more frequent \( \alpha \)-synucleinopathy. The panmicroglial marker ionized calcium-binding adapter molecule 1 was decreased in all AD cases and the decrease was most pronounced in R47H carriers (mean [SD], in the hilus: 0.114 [0.13] for R47H_AD vs 0.574 [0.26] for control individuals; 2-tailed t test; \( P = .005 \) and vs 0.465 [0.32] for AD; \( P = .02 \); in frontal cortex gray matter: 0.006 [0.004] for R47H_AD vs 0.016 [0.01] for AD; \( P = .04 \) and vs 0.033 [0.013] for control individuals; \( P < .001 \)). Major histocompatibility complex class II, a marker of microglial activation, was increased in all patients with AD (AD: 2.5, R47H_AD: 2.7, and control: 1.0; \( P < .01 \)).

In 2013, Jonsson et al. evaluated 3550 subjects with AD and found a genome-wide association with only one marker, the T allele of rs75932628 (excluding the APOE locus and the A673T variant in APP).\[4\] The frequency of TREM2 rs75932628 was then tested in a general population of 110,050 Icelanders of all ages and was found to confer a risk of AD of 0.63% (odds ratio [OR], 2.26; 95% confidence interval [CI], 1.71 to 2.98; \( p=1.13x10^{-8} \)). In the control population of 8,888 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; \( p=3.42x10^{-10} \)). In 1,236 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; \( p=7.39x10^{-6} \)). The decrease in TREM2 frequency in elderly patients who are cognitively intact supports the findings associating TREM2 with increasing risk of AD.

Also in 2013, Guerriero et al. also found a strong association of the R47H TREM2 variant with AD (\( p=0.001 \)).\[5\] Using three imputed data sets of genome-wide association AD studies, a meta-analysis found a significant association with the variant and disease (\( p=0.002 \)). The authors further reported direct genotyping of R47H in 1994 AD patients and 4062 controls, and found a highly significant association with AD (OR=5.05; 95% CI, 2.77 to 9.16; \( p=9.0x10^{-9} \)).

**Clinical Utility**

In 2008, Chao et al. published results from the REVEAL study, which was designed to examine consequences of AD risk assessment by APOE genotyping.\[14\] 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 one-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.

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

There is a lack of interventions that can delay or mitigate late-onset AD. There is no evidence that early intervention for asymptomatic mutation carriers can delay or mitigate future disease. Furthermore, there are many actions patients may take following knowledge of a mutation. Changes in lifestyle factors (e.g., diet, exercise) or the incorporation of “brain training” exercises can be made, but there is no evidence that these interventions impact clinical disease.

Reproductive planning may be affected as well, but it is unclear whether outcomes would be improved. Testing for a disease that will not manifest for many decades includes uncertainty about whether treatments for AD will be available at that future time point. This leads to uncertainties about whether current reproductive interventions will reduce the future incidence or severity of disease.

Section Summary

Both the APOE gene and the triggering receptor gene have shown strong statistical associations with AD, thus demonstrating some degree of clinical validity. However, the clinical sensitivity and specificity of APOE ε4 is poor, and there is a lack of evidence on the clinical sensitivity and specificity of the triggering receptor gene. Furthermore, no studies were identified that address how the use of the APOE or TREM2 variant might be incorporated into clinical practice and it is not clear how management of patients with these genes would change in a way that improves outcomes. Therefore, clinical utility has not been demonstrated for these tests.

GENETIC TESTING FOR EARLY-ONSET FAMILIAL ALZHEIMER’S DISEASE

Analytic Validity

There is a lack of published evidence on the analytic validity of genetic testing for early-onset familial AD. Analytic validity is expected to be high when current methods of sequencing are performed, (ie Sanger sequencing and/or next-generation sequencing).

Clinical Validity

Genetic testing for presenilin 1 (PSEN1) detects 30% to 60% of familial early-onset AD. A number of mutations scattered throughout the PSEN1 gene have been reported, 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 amyloid-beta precursor protein
(APP) and presenilin 2 (PSEN2) genes account for only a small fraction of cases; it is likely that other causative genes will be discovered.

The nearly complete penetrance of a PSEN1 disease–associated mutation would change the probability of developing familial AD in an unaffected family member from 50% to either 0% or 100%. However, there is evidence that clinical expressivity is variable. A 2016 report by Ryan et al. indicates that individuals with a PSEN1 mutations may have a significantly younger age of onset than individuals with an APP mutation (mean age 43.6 years [SD 7.2] vs 50.4 years [SD 5.2], respectively, p<0·0001).\[15\]

Finally, it is not uncommon to discover previously unreported PSEN1 mutations in an individual. Without additional family information, they may reflect mutations not associated with disease, or new causative mutations restricted to a single family (i.e. 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.

**Clinical Utility**

The potential clinical utility of testing is in early identification of asymptomatic patients who are at risk for developing early-onset AD. Genetic testing, will in most cases, lead to better risk stratification, distinguishing patients who will develop the disease from those who will not. If early identification of patients at risk leads to interventions to delay or mitigate clinical disease, then clinical utility would be established. Identification of asymptomatic, young adult carriers could impact reproductive planning. And clinical utility may be demonstrated if testing leads to informed reproductive planning that improves outcomes. However, there is no evidence that early intervention for asymptomatic mutation carriers can delay or mitigate future disease. There are many actions patients may take following knowledge of a mutation: changes in lifestyle factors (e.g., diet, exercise) and incorporation of “brain training” exercises; but there is no evidence that these interventions impact clinical disease.

Alternatively, clinical utility could be demonstrated if knowledge of mutation status leads to beneficial changes in psychological outcomes. However, asystematic 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.[16]

Reproductive planning may be affected as well, but it is unclear whether outcomes would be improved. Testing for a disease that will not manifest for more than several decades includes uncertainty about whether treatments for AD will be available. This leads to uncertainties about whether reproductive interventions now will reduce the future incidence or severity of disease.

Mihaescu et al. cite the framework proposed by Khoury et al. for the continuum of translational research that is required to move genomics research findings in AD into clinical and public health applications to benefit population health.\[17,18\] The four 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. The authors concluded that genetic testing for AD is still in the first phase.

Section Summary

A substantial percentage of patients with early-onset AD will have a pathogenic mutation; however, up to 40% will test negative. Therefore, the clinical sensitivity is suboptimal. The mutations are also found in some individuals who do not have a family history of familial AD, but the false-positive rate and clinical specificity is not well-defined.

For those individuals who do have a family member with early-onset, familial AD, there are currently no known preventive measures or treatments that can mitigate the effect of the disease. It is not clear how management of asymptomatic patients with these genes would change in a way that improves outcomes. Therefore, clinical utility has not been demonstrated for these tests.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS

The American College of Medical Genetics and Genomics lists genetic testing for APOE alleles as one of five recommendations in the Choosing Wisely initiative.[10] The recommendation is “Don’t order APOE genetic testing as a predictive test for Alzheimer disease.” The stated rationale is that APOE is a susceptibility gene for later-onset AD, the most common cause of dementia. These recommendations stated that “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, and the APOE genotyping for AD risk prediction has limited clinical utility and poor predictive value.”

AMERICAN ACADEMY OF NEUROLOGY

The American Academy of Neurology made the following recommendations:[19]

• Routine use of APOE genotyping in patients with suspected AD is not recommended at this time; and
• There are no other genetic markers recommended for routine use in the diagnosis of AD.

AMERICAN COLLEGE OF GENETICS AND NATIONAL SOCIETY OF GENETIC COUNSELORS

The American College of Genetics and the National Society of Genetic Counselors issued the following joint practice guidelines:[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.
  o Symptomatic patients: Genetic counseling for symptomatic patients should be performed in the presence of the individual’s legal guardian or family member.
  o Asymptomatic patients: A protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington’s Chorea Guidelines is recommended.
• Direct-to-consumer 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:
  o The lifetime risk of AD in the general population is approximately 10–12% in a 75–80 year lifespan.
  o The effect(s) of ethnicity on risk is still unclear.
  o 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:
  o 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).
  o Autosomal dominant family history of dementia with one or more cases of EOAD.
  o 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.
  o 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.
  o 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.

**SUMMARY**

There is not enough research to show that genetic testing for late- or early-onset Alzheimer's disease can improve health outcomes, including for those with a family history of Alzheimer's disease. Therefore genetic testing for the risk assessment or to aid in the diagnosis of Alzheimer's disease is considered investigational.

**REFERENCES**

12. Rigaud, AS, Traykov, L, Latour, F, Couderc, R, Moulin, F, Forette, F. Presence or absence of at least one epsilon 4 allele and gender are not predictive for the response


### CODES

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81401</td>
<td>Molecular pathology procedure, Level 1</td>
</tr>
<tr>
<td></td>
<td>81405</td>
<td>Molecular pathology procedure, Level 6</td>
</tr>
<tr>
<td></td>
<td>81406</td>
<td>Molecular pathology procedure, Level 7</td>
</tr>
<tr>
<td></td>
<td>88363</td>
<td>Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S3852</td>
<td>DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease</td>
</tr>
</tbody>
</table>

*Date of Origin: January 2011*