Genetic Testing for Familial Alzheimer Disease

Description

Alzheimer 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 has a stronger component of family risk, with clustering in families, thus suggesting an inherited genetic mutation.

Background

Alzheimer 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 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 [eg, 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.
Individuals with early onset familial AD (ie, 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 (\textit{APP}), presenilin 1 (\textit{PSEN1}) gene, and presenilin 2 (\textit{PSEN2}) gene. \textit{APP} and \textit{PSEN1} mutations have 100% penetrance absent death from other causes, while \textit{PSEN2} has 95% penetrance. A variety of mutations within these genes has been associated with AD; mutations in \textit{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 \textit{APP}, \textit{PSEN1}, or \textit{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 \textit{PSEN1} and \textit{PSEN2} are specific for AD; \textit{APP} mutations are also found in cerebral hemorrhagic amyloidosis of the Dutch type, a disease in which dementia and brain amyloid plaques are uncommon.

\textbf{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 triggering receptor expressed on myeloid cells 2 (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 \textit{TREM2}.

\textit{TREM2} is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. \textit{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 \textit{TREM2} would allow inflammation in the brain to increase and may be a factor in the development of AD. The effect size of the \textit{TREM2} variant confers a risk of AD that is similar to the \textit{APOE} epsilon 4 allele, although it occurs less frequently.

\textbf{Diagnosis of AD}

The diagnosis of Alzheimer disease (AD) is divided into three categories: possible, probable, and definite AD. (6) 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. (7) 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. (6) 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
- 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. (6) This may consist of an atypical onset (eg, 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. (8) 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 (eg, 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. (6) 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 Disease.

**Regulatory Status**

No U.S. Food and Drug Administration (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.

**Related Policies**

2.04.14 Biochemical Markers of Alzheimer Disease  
6.01.55 Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer Disease

**Policy**

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Genetic testing for the diagnosis or risk assessment of Alzheimer disease is considered not medically necessary.

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).

**Policy Guidelines**

Genetic testing for Alzheimer 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.).

**Rationale**

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

Apolipoprotein epsilon (APOE) genotyping for testing of familial Alzheimer disease derives from a 1999 Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) Assessment (9) that offers 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 (NIH) 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 (10) 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 (11) 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 and negative predictive values of 83% and 41% compared to 81% and 56% 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. (12) Rigaud et al followed 117 individuals with AD over 36 weeks in an open-label trial of donepezil; 80 (68%) completed the trial. (13) 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. (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 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% to 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 (15) suggested that “predictive or diagnostic genetic testing for highly penetrant mutations (e.g., APP [amyloid-beta precursor protein], PSEN1, PSEN2 [presenlin2]) 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 three affected members in two 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. (16)

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

GeneTests.org (www.genetests.org) notes availability of testing for \textit{PSEN1}, \textit{PSEN2}, and \textit{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. (17)

Mihaescu et al (18) cite a proposed framework by Khoury et al (19) for the continuum of translational research that is required to move genomics research findings in Alzheimer 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 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.

\textbf{Susceptibility Testing at the Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) Gene}

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 APP11). (4) The frequency of rs75932628 (triggering receptor expressed on myeloid cells 2[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; $p=1.13\times10^{-8}$). In the control population of 8888 patients 85 years of age or older without a diagnosis of AD, \textit{TREM2} frequency was 0.46\% (OR= 2.92; 95\% CI, 2.09 to 4.09; $p=3.42\times10^{-10}$). In 1236 cognitively intact controls age 85 or older, the frequency of \textit{TREM2} decreased even further to 0.31\% (OR=4.66, 95\% CI, 2.38 to 9.14; $p=7.39\times10^{-6}$). The decrease in \textit{TREM2} frequency in elderly patients who are cognitively intact supports the findings associating \textit{TREM2} with increasing risk of AD.

Guerriero et al also found a strong association of the R47H \textit{TREM2} variant with AD ($p=0.001$). (5) Using 3 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 1,994 AD patients, and 4,062 controls found a highly significant association with AD (OR= 5.05; 95\% CI, 2.77 to 9.16; $p=9.0\times10^{-9}$).
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

A search of online site clinicaltrials.gov in August, 2014 identified a number of 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.

Practice Guidelines and Position Statements

American Academy of Neurology (20)

- 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 as of July 1, 2014.

European Federation of Neurological Sciences (21)

- 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.

Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia

The 2012 Canadian Consensus Conference on Treatment of Dementia (CCCDTD) was held in May 2012 to update the third consensus guidelines referenced below. Previous recommendations were endorsed if there weren’t any changes in the literature. Full articles written by CCCTD workgroups providing complete background information for the consensus conference are available online at: http://www.healthplexus.net/article/2012-canadian-consensus-conference-dementia.

A summary of consensus recommendations from the CCCDTD4 was published by Gauthier et al in 2012. (22) It is noted in the summary that: “Despite a large number of important advances, the CCCDTD4 concluded that fundamental changes in dementia diagnosis and management have not yet arrived.” The 2012 CCCDTD4 summary recommends:

“Testing and longitudinal follow-up of asymptomatic individuals or patients with subjective cognitive impairments not meeting MCI [mild cognitive impairment] criteria, or at-risk individuals
Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia (23)

The third CCCDTD conference recommended the following predictive genetic testing for asymptomatic “at risk” an individual 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 (eg, 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 (eg, 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**)

**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 (eg, 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 \textit{PSEN1}, \textit{PSEN2}, or \textit{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.

Summary

Many genes, including \textit{APOE} and \textit{TREM2}, have been associated with late-onset Alzheimer disease (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 \textit{PSEN1} and \textit{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 \textit{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 \textit{TREM2} and AD has only recently been identified and its clinical utility is unknown. Therefore, genetic testing for AD is considered \textbf{not medically necessary}.

\textbf{U.S. Preventive Services Task Force Recommendations}

Genetic testing for Alzheimer disease is not a preventive service.

\textbf{National Medicare Coverage}

There is no national coverage determination (NCD).

\textbf{References}


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<td>June 2012</td>
<td>New Policy</td>
<td>Policy updated with literature review. Multiple references added, others reordered or removed. TREM2 added to not medically necessary policy statement.</td>
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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 5, 2014 and is effective January 15, 2015.

Signature on File

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