Genetic Testing for Alzheimer's Disease

Effective: June 1, 2025

Next Review: February 2026
Last Review: April 2025

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

I. Genetic testing for variants in presenilin genes (*PSEN*) or amyloid-beta precursor protein gene (*APP*) associated with autosomal dominant Alzheimer's disease may be considered **medically necessary** for an asymptomatic individual when either of the following criteria are met:

   A. Targeted genetic testing for a known familial variant when the individual has a first- or second-degree relative (see Policy Guidelines) with a known familial variant AND the results of testing will be used to inform reproductive decision-making; OR

   B. The individual has a family history of dementia consistent with autosomal dominant Alzheimer's disease (three or more affected members in two generations) for whom the genetic status of the affected family members is unavailable, AND the results of testing will be used to inform reproductive decision-making.

II. Genetic testing for risk assessment or in the evaluation of dementia or Alzheimer's disease is considered **investigational** for all other indications and when Criterion I is not met**.** 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.

LIST OF INFORMATION NEEDED FOR REVIEW

First-degree relatives are parents, siblings, and children of an individual; second-degree *relatives* are grandparents, aunts, uncles, nieces, nephews, grandchildren.

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No.81
3. Biochemical Markers of Alzheimer's Disease, Laboratory, Policy No. 22
4. Aduhelm, aducanumab, Medication Policy No. dru740

BACKGROUND

Alzheimer's disease (AD) is the most common form of dementia. In 2020, as many as 5.8 million Americans were living with AD, and by 2060 this number is projected to rise to 14 million.[1] Although scientist 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 VARIANTS

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 three genes have been identified in affected families: amyloid-beta precursor protein gene (*APP*), presenilin 1 (*PSEN1*) gene, and presenilin 2 (*PSEN*2) gene. *APP* and *PSEN1* pathogenic variants have 100% penetrance absent death from other causes, while *PSEN*2 has 95% penetrance. A variety of variants within these genes has been associated with AD; variants in *PSEN1* appear to be the most common. While only 3%–5% of all patients with AD have early onset disease, pathogenic variants have been identified in up to 70% or more of these patients. Identifiable genetic variants 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 *PSEN*2 variants 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. Pathogenic variants in *PSEN1* and *PSEN*2 are specific for AD; *APP* variants are also found in cerebral hemorrhagic amyloidosis of the Dutch type, a disease in which dementia and brain amyloid plaques are uncommon

The apolipoprotein E (*APOE*) lipoprotein is a carrier of cholesterol produced in the liver and brain glial cells. The *APOE* gene has three alleles—ε2, 3, and 4—with the ε3 allele being the most common. Individuals carry two *APOE* alleles. The presence of at least one ε4 allele is associated with a 1.2- to 3-fold increased risk of AD depending on the ethnic group. The correlation between *APOE* and AD in African-American, Hispanic populations is not as strong as is seen in white populations, despite higher rates of AD than white populations in both groups.[2] Among those homozygous for ε4 (about 2% of the population), the risk of AD is higher than for those heterozygous for ε4. The mean age of onset of AD is about 68 years for ε4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no ε4 alleles. About half of patients with sporadic AD carry an ε4 allele. However, not all patients with the allele develop AD. The ε4 allele represents a risk factor for AD rather than a disease-causing variant. In the absence of *APOE* testing, first-degree relatives of an individual with sporadic or familial AD are estimated to have a two- to four-fold greater risk of developing AD than the general population.[3] There is evidence of possible interactions between ε4 alleles, other risk factors for AD (e.g., risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, and diabetes[4]), 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.

Studies have also identified rs75932628-T, a rare functional substitution for R47H of *TREM2*, as a heterozygous risk variant for late-onset AD.[5, 6] 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* ε4 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.[7] 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).

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-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[8] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

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 variant that is present or in excluding a variant 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.

This evidence review focuses on clinical validity and utility.

GENETIC TESTING FOR LATE-ONSET ALZHEIMER DISEASE

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.[9]

Naj (2014) published a genome-wide association study of multiple genetic loci in late-onset AD.[10] 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 nine loci combined contributed 2.2% of the variation. Each additional copy of the *APOE* ε4 allele reduced age of onset by 2.45 years.

Lambert (2013) published a large meta-analysis of GWAS of susceptibility loci for late-onset AD in 17,008 AD cases and 37,154 controls of European ancestry.[11] Nineteen loci had genome-wide significance in addition to the *APOE* locus. The researchers confirmed several genes already reported to be associated with AD (*ABCA7*, *BIN1*, *CD33*, *CLU*, *CR1*, *CD2AP*, *EPHA1*, *MS4A6A–MS4A4E*, *PICALM*). New loci located included *HLA-DRB5–HLA-DRB1*, *PTK2B*, *SORL1*, and *SLC24A4-RIN3*.

Susceptibility Testing at the Apolipoprotein E Gene

Many studies have examined the association between the apolipoprotein ε4 allele (*APOE*E4*) and AD. The Rotterdam and Framingham studies are both examples of large observational studies demonstrating the association. The Rotterdam Study was a prospective cohort study in the city of Rotterdam, the Netherlands, with main objectives of investigating risk factors of cardiovascular, neurologic, ophthalmologic, and endocrine diseases in the elderly.[12] In a sample of 6,852 participants, carriers of a single ε4 allele had a relative risk (RR) of developing AD approximately double that of ε3/ε3 carriers. Carriers of the two ε4 alleles had a relative risk of developing dementia approximately eight times that of ε3/ε3 carriers. The Framingham Heart Study was a longitudinal cohort study initiated in 1948 in Framingham, Massachusetts, to identify common risk factors for cardiovascular disease.[13] In 1,030 participants, the relative risk for developing AD was 3.7 (95% confidence interval [CI] 1.9 to 7.5) for carriers of a single ε4 allele and 30.1 (95% CI 10.7 to 84.4) for carriers with two ε4 alleles compared to those without an ε4 allele. 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.[14]

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.[15]

The association of *APOE* genotype with response to AD therapy has been examined. Exploratory analyses of pooled safety data from two phase 3 trials of the FDA-approved amyloid-beta targeting therapy aducanumab indicate that APOE ε4 carrier status is associated with a higher incidence of amyloid-related imaging abnormalities (ARIA).[16-18] Specifically, the incidence of ARIA-edema was 43% versus 20%, in APOE ε4 carriers and non-carriers receiving a 10 mg/kg dose of aducanumab, respectively. The overall incidence of any ARIA ranged from 36-41% in the treatment group compared to 10.3% in the placebo group. The clinical effects of ARIA range from asymptomatic to severe. Although the majority of patients were asymptomatic or had symptoms such as headache, confusion, or dizziness that resolved with temporary stoppage of the drug, 6.2% of participants receiving the high dose of aducanumab discontinued the drug due to ARIA compared to 0.6% in the placebo arm.

The majority of ARIA-edema radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. Among patients treated with a planned dose of aducanumab 10 mg/kg who had ARIA-edema, the maximum radiographic severity was mild in 30%, moderate in 58%, and severe in 13% of patients (refer to prescribing label for classification of severity of ARIA). Resolution occurred in 68% of ARIA-edema patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection. Ten percent of all patients who received aducanumab 10 mg/kg had more than 1 episode of ARIA-edema. Radiographic severity and symptomatic status were similar for APOE ε4 carriers and non-carriers.

Aducanumab dosing management decisions in the trials were based on clinical symptom severity and ARIA severity on MRI.[17] After radiographic resolution of ARIA-edema or stabilization of ARIA-hemorrhage and resolution of symptoms (if present), participants could resume dosing at the same dose and titration schedule. Limited follow-up data are available for the safety analysis because the phase 3 trials were stopped prematurely for futility.

The USA-1 Study group found *APOE* genotype did not predict therapeutic response.[19] Rigaud (2002) followed 117 individuals with AD over 36 weeks in an open-label trial of donepezil; 80 (68%) completed the trial.[20] 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

Korvatska (2015) published results from a retrospective study of genetic and pathologic studies that included 131 families (751 individuals) with late-onset AD (LOAD) between 1985 and 2014.[21] The authors found 12 of the 16 patients with AD in the LOAD123 family carried R47H. Eleven patients with dementia had apolipoprotein ε 4 (*APOE4*) and *R47H* genotypes. R47H carriers demonstrated a shortened disease duration (mean [SD] 6.7 [2.8] vs. 11.1 [6.6] years, two-tailed t test; p =0.04) and more frequent α-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, two-tailed t test p=0.005 and vs. 0.465 [0.32] for AD, p=0.02; in frontal cortex gray matter: 0.006 [0.004] for *R47H*_AD vs. 0.016 [0.01] for AD, p=0.04, and vs. 0.033 [0.013] for control individuals, p<0.001). 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 < 0.01).

Jonsson (2013) evaluated 3,550 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*).[5] 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.

Guerriero (2013) also found a strong association of the *R47H TREM2* variant with AD (p=0.001).[6] 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

Chao (2008) published results from the Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) study, which was designed to examine consequences of AD risk assessment by

APOE genotyping.[22] 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). There is insufficient evidence to conclude that these short-term behavioral changes would alter clinical outcomes. Green (2009) examined anxiety, depression, and test-related distress at six weeks, six months, and one year in the 162 participants randomized in REVEAL.[23] There were no significant differences between the group that received the results of *APOE* testing and the group that did not in changes in anxiety or depression overall or in the subgroup of participants with the *APOE* ε4 allele. However, the ε4 negative participants had significantly lower test-related distress than ε4 positive participants (p=0.01).

Christensen (2016) examined disclosing associations between *APOE* genotype and AD risk alone versus AD and coronary artery disease (CAD) risk in an equivalence trial from the REVEAL group.[24] Two hundred ninety participants were randomized to receive AD risk disclosure alone or AD+CAD risk disclosure. The 257 participants who received their genetic information were included in analyses. Mean anxiety, depression, and test-related distress scores were below cutoffs for mood disorders at all time points in both disclosure groups and were similar to baseline levels. At the 12-month follow-up, both anxiety (measured by the Beck Anxiety Index) and depression (measured by the Center for Epidemiologic Studies Depression Scale) fell within the equivalence margin indicating no difference between disclosure groups. Among participants with an ε4 allele, distress (measured by Impact of Event Scale) was lower at 12 months in AD+CAD group than in the AD-only group (difference -4.8, 95% CI -8.6 to -1.0, p=0.031). AD+CAD participants also reported more health behavior changes than AD-alone participants, regardless of APOE genotype.

There is a lack of interventions that can delay or mitigate late-onset AD. There is no evidence that early intervention for asymptomatic variant carriers can delay or mitigate future disease. Furthermore, there are many actions patients may take following knowledge of a pathogenic variant. 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.

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 other AD-associated variants 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. The REVEAL studies have found short-term changes in behaviors following disclosure of *APOE* genetic testing results in high-risk adults with little increase in anxiety or depression overall, although with possible increase in distress among ε4 allele carriers. It is unclear whether these changes in behaviors would improve clinical outcomes or whether there are long-term effects on psychological outcomes among ε4 carriers. Therefore, clinical utility has not been demonstrated for these tests.

GENETIC TESTING FOR EARLY-ONSET FAMILIAL ALZHEIMER'S DISEASE

Clinical Validity

In the scenario of targeted testing of individuals with a known familial pathogenic variant, due to nearly complete penetrance of pathogenic variants, an identified carrier will almost certainly develop the disease unless dying at an age preceding disease onset. Therefore, the clinical validity is nearly certain.

In the scenario of genetic testing of individuals with a family history consistent with autosomal dominant early-onset AD but in whom a pathogenic variant has not been found, the testing yield is less certain. Genetic testing for presenilin 1 (*PSEN1*) is estimated to detect disease-causing variants in 30% to 60% of individuals with familial early-onset AD,[25, 26] although estimates vary A number of variants 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. Variants in amyloid-beta precursor protein (*APP*) and presenilin 2 (*PSEN2*) genes account for another 10% to 20% of cases.

Genetic yields may vary by population. Giau (2019) reported on 200 patients with clinically diagnosed early-onset AD from Thailand, Malaysia, the Philippines, and Korea who were genetically screened between 2009 and 2018.[27] Thirty-two (16%) patients carried pathogenic *APP* (8/32 [25%]), *PSEN1* (19/32 [59%]), or *PSEN2* (5/32 [16%]) variants. However, this analysis included possible and probable pathogenic variants in addition to those classified as definite. Overall, approximately 84% (p=0.01) of autosomal dominant pedigrees in the tested Asian population were genetically unexplained. Clinical and phenotypic expressivity is variable. A report by Ryan (2016) indicates that individuals with a *PSEN1* variants may have a significantly younger age of onset than individuals with an *APP* variant (mean age [SD] 43.6 years [7.2] vs. 50.4 years [5.2], respectively, p<0.0001).[28] However, the presence of *PSEN1*, *PSEN2*, or *APP* variants is not useful in predicting age of onset (although age of onset is usually similar in affected family members), severity, type of symptoms, or rate of progression in asymptomatic individuals.

A study by Cochran (2019) confirmed a high diagnostic yield in early-onset or atypical dementia.[29] Fifty percent (16/32) of patients tested harbored one or more genetic variants capable of explaining symptoms, including variants in *APP*. Nine of 32 patients (28%) had a variant defined as pathogenic or likely pathogenic whereas six had one or more variants with moderate penetrance. The authors noted this supports a potential oligogenic model for early-onset dementia.

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 variant carriers can delay or mitigate future disease. There are many actions patients may take following knowledge of a pathogenic variant: 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 variant status leads to beneficial changes in psychological outcomes. However, 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.[30]

When a known pathogenic variant is identified in a prospective parent, with reasonable certainty, disease will develop and there is a 50% risk of an affected offspring. When a pathogenic variant is detected in a prospective parent, the prospective parent can choose to refrain from having children or choose medically assisted reproduction during which preimplantation testing would allow a choice to avoid an affecting offspring. Identification of a pathogenic variant by genetic testing is more accurate than the alternative of obtaining a family history alone. Therefore, testing in the reproductive setting can improve health outcomes.

Section Summary

For those individuals who do have a family member with early-onset, familial AD, with a known pathogenic familial variant or a family pedigree consistent with autosomal dominant AD, testing a prospective parent when performed in conjunction with genetic counseling provides more accurate information to guide reproductive planning than family history alone. Therefore, the clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. There are currently no known preventive measures or treatments that can mitigate the effect of AD. It is not clear how change in the management of asymptomatic patients with these genes would improve outcomes. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants.

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.[15] 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 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 in 2011, which were reaffirmed in 2019:[3, 31]

- 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.
- 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:
    - 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*, *PSEN*2, 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.

SUMMARY

There is enough research to show that *PSEN* and *APP* genetic testing for autosomal dominant Alzheimer's disease can help individuals at risk for this disorder to make reproductive decisions. Therefore, this genetic testing may be considered medically necessary when policy criteria are met.

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 when policy criteria are not met, including risk assessment or to aid in the diagnosis of Alzheimer's disease, is considered investigational.

REFERENCES

1. Centers for Disease Control and Prevention Healthy Aging: Alzheimer's Disease. [cited 2/28/2025]. 'Available from:' https://www.cdc.gov/aging/aginginfo/alzheimers.htm.
2. Rubin L, Ingram LA, Resciniti NV, et al. Genetic Risk Factors for Alzheimer's Disease in Racial/Ethnic Minority Populations in the U.S.: A Scoping Review. *Front Public Health.* 2021;9:784958. PMID: 35004586
3. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med.* 2011;13(6):597-605. PMID: 21577118
4. Caselli RJ, Dueck AC, Locke DE, et al. Cerebrovascular risk factors and preclinical memory decline in healthy APOE epsilon4 homozygotes. *Neurology.* 2011;76(12):1078-84. PMID: 21325652
5. Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *The New England journal of medicine.* 2013;368(2):107-16. PMID: 23150908
6. Guerreiro R, Wojtas A, Bras J, et al. TREM2 variants in Alzheimer's disease. *The New England journal of medicine.* 2013;368(2):117-27. PMID: 23150934
7. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):263-9. PMID: 21514250
8. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. *Human mutation.* 2016;37(6):564-9. PMID: 26931183
9. Bertram L, Tanzi RE. Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. *Nat Rev Neurosci.* 2008;9(10):768-78. PMID: 18802446

10. Naj AC, Jun G, Reitz C, et al. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. *JAMA Neurol.* 2014;71:1394-404. PMID: 25199842
11. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature genetics.* 2013;45(12):1452-8. PMID: 24162737
12. Slooter AJ, Cruts M, Hofman A, et al. The impact of APOE on myocardial infarction, stroke, and dementia: the Rotterdam Study. *Neurology.* 2004;62(7):1196-8. PMID: 15079025
13. Myers RH, Schaefer EJ, Wilson PW, et al. Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study. *Neurology.* 1996;46(3):673-7. PMID: 8618665
14. Bird TD. Alzheimer Disease Overview. In: MP Adam, DB Everman, GM Mirzaa, et al., eds. GeneReviews(®). Seattle (WA): Copyright © 1993-2023, University of Washington, Seattle. [updated 2018 Dec 20], 1993.
15. Summary of Recent Activities of The American College of Medical Genetics and Genomics [cited 2/28/2025]. 'Available from:' https://www.genome.gov/Pages/About/NACHGR/February2017AgendaDocuments/ACMG_NACHGR_Feb_%202017.pdf.
16. Biogen. Highlights of Prescribing Information: ADUHELM (aducanumab-avwa) injection, for intravenous use. [cited 2/16/2024]. 'Available from:' https://biogencdn.com/us/aduhelm-pi.pdf.
17. Burkett P CS, Umans K, et al. Considerations for the Real-World Management of ARIA from the Aducanumab Phase 3 Studies EMERGE and ENGAGE. Poster presented at: Alzheimer's Association International Conference; July 2021; Denver, Colorado.:
18. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients With Early Alzheimer Disease. *JAMA Neurol.* 2022;79(1):13-21. PMID: 34807243
19. Raskind MA, Peskind ER, Wessel T, et al. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology.* 2000;54(12):2261-8. PMID: 10881250
20. Rigaud AS, Traykov L, Latour F, et al. Presence or absence of at least one epsilon 4 allele and gender are not predictive for the response to donepezil treatment in Alzheimer's disease. *Pharmacogenetics.* 2002;12(5):415-20. PMID: 12142731
21. Korvatska O, Leverenz JB, Jayadev S, et al. R47H Variant of TREM2 Associated With Alzheimer Disease in a Large Late-Onset Family: Clinical, Genetic, and Neuropathological Study. *JAMA Neurol.* 2015;72:920-7. PMID: 26076170
22. Chao S, Roberts JS, Marteau TM, et al. Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. *Alzheimer disease and associated disorders.* 2008;22(1):94-7. PMID: 18317253
23. Green RC, Roberts JS, Cupples LA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. *The New England journal of medicine.* 2009;361(3):245-54. PMID: 19605829
24. Christensen KD, Roberts JS, Whitehouse PJ, et al. Disclosing Pleiotropic Effects During Genetic Risk Assessment for Alzheimer Disease: A Randomized Trial. *Annals of internal medicine.* 2016;164(3):155-63. PMID: 26810768
25. Kowalska A, Wender M, Florczak J, et al. Molecular genetics of Alzheimer's disease: presenilin 1 gene analysis in a cohort of patients from the Poznan region. *Journal of applied genetics.* 2003;44(2):231-4. PMID: 12817569

26. Janssen JC, Beck JA, Campbell TA, et al. Early onset familial Alzheimer's disease: Mutation frequency in 31 families. *Neurology.* 2003;60(2):235-9. PMID: 12552037
27. Giau VV, Bagyinszky E, Youn YC, et al. APP, PSEN1, and PSEN2 Mutations in Asian Patients with Early-Onset Alzheimer Disease. *International journal of molecular sciences.* 2019;20(19). PMID: 31557888
28. Ryan NS, Nicholas JM, Weston PS, et al. Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. *The Lancet Neurology.* 2016;15(13):1326-35. PMID: 27777022
29. Cochran JN, McKinley EC, Cochran M, et al. Genome sequencing for early-onset or atypical dementia: high diagnostic yield and frequent observation of multiple contributory alleles. *Cold Spring Harbor molecular case studies.* 2019;5(6). PMID: 31836585
30. Rahman B, Meiser B, Sachdev P, et al. To know or not to know: an update of the literature on the psychological and behavioral impact of genetic testing for Alzheimer disease risk. *Genetic testing and molecular biomarkers.* 2012;16(8):935-42. PMID: 22731638
31. Goldman JS, Hahn SE, Catania JW, et al. ADDENDUM: Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med.* 2019;21(10):2404. PMID: 31217590

CODES

Codes	Number	Description
CPT	81401	Molecular pathology procedure, Level 1
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
HCPCS	S3852	DNA analysis for *APOE* epsilon 4 allele for susceptibility to Alzheimer’s disease

Date of Origin: *January 2011*